Surgical and Ablative Procedures for Venous Insufficiency and Varicose Veins

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➲ Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

Thermal and Non-Thermal Treatments for Venous Insufficiency and Varicose Veins

The initial and subsequent treatment of the Great Saphenous Veins (GSV), Small Saphenous Veins (SSV), and Accessory Veins with radiofrequency ablation, endovenous laser ablation, Stripping with Ligation and excision, endovenous foam Sclerotherapy, and/or cyanoacrylate-based adhesive are considered reconstructive and medically necessary when all of the following criteria are met:

- Individual must have one of the following Functional or Physical Impairments:
  - Skin ulceration; or
  - Documented episode(s) of frank bleeding of the Varicose Vein due to erosion of/or trauma to the skin; or
  - Documented superficial thrombophlebitis; or
  - Documented Venous Stasis Dermatitis causing Functional or Physical Impairment; or
  - Moderate to Severe Pain causing Functional or Physical Impairment
- Venous size:
  - The GSV must be three millimeters (mm) or greater when measured at the proximal thigh immediately below the saphenofemoral junction via Duplex Ultrasonography
  - The SSV or Accessory Veins must measure three mm or greater in diameter immediately below the appropriate junction via Duplex Ultrasonography
- Duplex ultrasound study performed in the standing or reverse Trendelenburg position, shows duration of reflux that meets the following parameters:

- Greater than or equal to 500 milliseconds (ms) for the GSV, SSV, or Accessory Veins

Note: Duplex ultrasound interpretations may describe this as moderate to severe reflux which will be acceptable.

Ablation of incompetent perforator veins using radiofrequency ablation or endovenous laser ablation is considered reconstructive and medically necessary when all of the following criteria are met:

- Evidence of perforator Venous Insufficiency measured by recent duplex ultrasound study performed in the standing or reverse Trendelenburg position; and
- Perforator vein size is 3.5 mm or greater; and
- Perforating vein reflux of 500 ms or greater; and
- Perforating vein lies beneath a healed or active venous stasis ulcer; and
- Not secondary to acute deep vein thrombosis

Ablation of incompetent perforator veins using endovenous foam Sclerotherapy, and/or cyanoacrylate-based adhesive is unproven and not medically necessary due to insufficient evidence of efficacy.

Ligation Procedures

The following procedure is proven and medically necessary:

- Ligation at the saphenofemoral junction, as a stand-alone procedure, when used to prevent the propagation of an active clot to the deep venous system in individuals with ascending superficial thrombophlebitis who fail or are intolerant of anticoagulation therapy

The following procedures are unproven and not medically necessary for treating Venous Reflux due to insufficient evidence of efficacy:

- Ligation of the GSV at the saphenofemoral junction, as a stand-alone procedure
- Ligation of the SSV at the saphenopopliteal junction, as a stand-alone procedure
- Ligation of the Accessory Veins, as a stand-alone procedure
- Ligation at the saphenofemoral junction, as an adjunct to radiofrequency ablation or endovenous laser ablation of the main saphenous veins

Sclerotherapy of Superficial Veins

- Refer to the Applicable Codes section for Sclerotherapy (i.e., liquid, foam, ultrasound-guided, endovenous chemical ablation, endovenous microfoam).
- Refer to the Benefit Considerations section for cosmetic Sclerotherapy.

Other Procedures

The following procedures are unproven and not medically necessary for treating Venous Reflux due to insufficient evidence of efficacy:

- Endovenous mechanochemical ablation (MOCA) of Varicose Veins
- Porcine bioprosthetic valve (e.g., VenoValve) implantation into the femoral vein for treatment of deep vein reflux associated with chronic Venous Insufficiency

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled Medical Records Documentation Used for Reviews.

Definitions

When applicable, refer to the member specific benefit plan document for definitions.

Accessory Vein: Accessory saphenous veins indicate a venous segment ascending parallel to the Great Saphenous Vein (GSV) and located more superficially above the saphenous fascia, both in the leg and in the thigh. These can include the anterior and posterior Great Saphenous Veins and the circumflex veins (anterior or posterior). Additionally, before the

Small Saphenous Vein (SSV) penetrates the muscular fascia, it may branch out a cranial extension, known as the vein of Giacomini, which goes upward to join the GSV (Lee et al., 2017).
Axial Reflux: Axial Reflux of the GSV is defined as uninterrupted retrograde venous flow from the groin to the upper calf. Axial Reflux in the SSV is defined as being from the knee to the ankle. Axial Reflux in the anterior accessory Great Saphenous Vein (AAGSV) and posterior accessory Great Saphenous Vein (PAGSV) is retrograde flow between two measurements, at least five centimeters (cm) apart (Gloviczki et al., 2023).

Duplex Ultrasonography: Noninvasive imaging that uses sound waves to assess blood flow through the vessels in legs. Combines a B mode scanner with built-in Doppler capability. B-mode imaging permits accurate placement of the pulsed Doppler sample volume, and the addition of color makes it easier to establish obstruction, turbulence, and the direction of venous and arterial flow (National Institutes for Health [NIH], 2023; Gloviczki et al., 2011).

Endovenous Ablation: A minimally invasive procedure that uses heat generated by radiofrequency or laser energy to seal off damaged veins (NHLBI, 2014; updated 2023).

Functional or Physical Impairment: A Functional or Physical or Physiological Impairment causes deviation from the normal function of a tissue or organ. This results in a significantly limited, impaired, or delayed capacity to move, coordinate actions, or perform physical activities and is exhibited by difficulties in one or more of the following areas: physical and motor tasks; independent movement; performing basic life functions (Medicare, 2023).

Great Saphenous Vein: A Superficial Vein that originates from the medial side of the dorsal pedal venous arch, ascends along the inside of the leg and thigh until it joins the common femoral vein at the saphenofemoral junction (Lee et al., 2017).

Ligation: Tying off a vein (NHLBI, 2014; updated 2023).

Moderate to Severe Pain: The Venous Clinical Severity Score (VCSS) describes Moderate Pain to be daily pain or other discomfort interfering with, but not preventing regular daily activities, and Severe Pain to be daily pain or discomfort that limits most regular daily activities (Vasquez et al., [American Venous Forum], 2010).

Sclerotherapy: The injection of liquid or foam chemicals into the vein to create a plug that seals it shut (NHLBI, 2014; updated 2023).

Small Saphenous Vein: A Superficial Vein that ascends along the posterior calf to join the popliteal vein in the popliteal fossa in most cases (De Maeseneer et al., 2022).

Superficial Vein: Veins located above the muscular fascia (Lee et al., 2017).

Telangiectasias/Spider Veins: Dilated small Superficial Veins measuring less than one millimeter (mm) in diameter and occurring predominantly in the lower extremities (Gloviczki et al., 2023).

Tributary Vein: Small Superficial Veins in the legs that run close to the skin within the superficial plane of the subcutaneous layer (Caggiati et al., 2024).

Varicose Veins: Varicose Veins are dilated subcutaneous tributaries greater than or equal to three mm in diameter and individuals with Varicose Veins belong to clinical stage, etiology, anatomy, pathology (CEAP) Class C2 (Gloviczki et al., 2023).

Venous Reflux/Insufficiency: Gloviczki et al. (2023) defines Venous Reflux as reversed blood flow in the veins. Abnormal (pathological reflux) times exceed different thresholds depending on the system of veins:
- Deep veins: one second (sec)
- Superficial Veins: 0.5 sec
- Perforator veins: 0.5 sec

Venous Stasis Dermatitis: A skin inflammation due to the chronic buildup of fluid (swelling) under the skin (MedlinePlus, 2022).

Venous Stripping: Surgical removal of Superficial Veins (NHLBI, 2014; updated 2023).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Coding Clarifications:

- Per AMA coding guidance for endovenous radiofrequency ablation (e.g., CPT code 36475), the initial incompetent vein treated may only be requested once per extremity. Endovenous radiofrequency ablation for treatment of subsequent incompetent veins in the same extremity as the initial vein treated (e.g., CPT code 36476), only one add-on code per extremity may be requested, regardless of the number of additional vein(s) treated (CPT Assistant, November 2016). Therefore, only one primary code may be requested for the initial vein treated, and only one add-on code per extremity may be requested for any subsequent vein(s) treated.
- **Sclerotherapy**:
  - Per AMA coding guidance, if the targeted vein is an extremity truncal vein and injection of non-compounded foam sclerosant with ultrasound guided compression maneuvers to guide dispersion of the injectate is performed, refer to CPT codes 36465 and 36466. (CPT Assistant, 2018)
  - CPT code 36468 for sclerosant treatment for Spider Veins/Telangiectasias is considered cosmetic; does not improve a Functional, Physical, or Physiological Impairment. (2019 Certificate of Coverage Amendment)
  - CPT codes 36470 and 36471 are covered for sclerotherapy (non-truncal, non-telangiectasia) up to three sessions per leg within a year.
    - More than three sessions per leg within a year is considered cosmetic; does not improve a Functional, Physical, or Physiological Impairment. Cosmetic Sclerotherapy is excluded. (2019 Certificate of Coverage Amendment)
    - A session is defined as one date of service in which Sclerotherapy (CPT codes 36470 and 36471) is performed.
    - A year is defined as a rolling 12 months (365 days).

CPT Code	Description
0744T	Insertion of bioprosthetic valve, open, femoral vein, including duplex ultrasound imaging guidance, when performed, including autogenous or nonautogenous patch graft (e.g., polyester, ePTFE, bovine pericardium), when performed
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	Injection(s) of sclerosant for spider veins (telangiectasia), limb or trunk
36470	Injection of sclerosant; single incompetent vein (other than telangiectasia)
36471	Injection of sclerosant; multiple incompetent veins (other than telangiectasia), 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; subsequent vein(s) 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

CPT Code	Description
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; subsequent vein(s) 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)
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
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

Description of Services

Varicose Veins are enlarged veins that are swollen and raised above the surface of the skin. They can be dark purple or blue and look twisted and bulging. Varicose Veins usually occur in the legs. Veins have one-way valves that help keep blood flowing towards the heart. When the valves become weak or damaged and do not close properly, blood can back up and pool in the veins causing them to get larger. The resulting condition is known as reflux. Varicose Veins may lead to complications such as pain, itching or burning, skin color changes around the veins, blood clots, or skin ulcers [National Heart, Lung, and Blood Institute (NHLBI), 2014; updated 2023].

Duplex ultrasound is considered the gold standard for diagnosis of superficial venous incompetence. The CEAP (clinical, etiology, anatomy, pathophysiology) classification system is used to describe the degree of varicosity. The “C” part of CEAP classification is more useful and practical in rating the severity of Varicose Veins:

- C0: No visible or palpable signs of venous disease
- C1: Telangiectasis (Spider Veins) or reticular veins
- C2: Varicose Veins [diameter of vein is > 3 millimeters (mm)]
- C3: Edema
- C4a: Pigmentation and eczema
- C4b: Lipodermatosclerosis and atrophie blanche
- C5: Healed venous ulcer
- C6: Active venous ulcer

[Lurie et al., American Venous Forum (AVF), 2020]

Preoperative venous duplex ultrasound is used to evaluate individuals for Venous Insufficiency symptoms or suspected deep vein thrombosis (DVT); it can provide a road map of vein anatomy similar to contrast venography, as well as essential hemodynamic information about the presence of proximal obstruction, vein valve function, and Venous Reflux (Lin et al., 2015).

Varicose Veins are treated with lifestyle changes and medical procedures done either to remove the veins or to close them. Endovenous Ablation therapy uses lasers or radiofrequency energy to create heat to close off a Varicose Vein. Vein Stripping and Ligation involves tying shut and removing the veins through small cuts in the skin (NHLBI, 2014; updated 2023).

Endovascular embolization using cyanoacrylate-based adhesive (e.g., VenaSeal™ Closure System) is a minimally invasive, non-thermal and non-sclerosant procedure that does not require tumescent anesthesia. The medical adhesive is

used to close the lower extremity superficial truncal veins in individuals with symptomatic Venous Reflux disease (Hayes, 2022; updated 2024).

Endovascular embolization using endovenous foam Sclerotherapy with polidocanol endovenous microfoam (PEM) [e.g., Varithena™ (Provensis Ltd.)], is a prescribed proprietary canister that generates a sterile, uniform, stable, low-nitrogen polidocanol 1% microfoam sclerosant intended for ultrasound-guided intravenous (IV) injection for treating venous incompetence and varicosities (Hayes, 2022). The aim of ultrasound-guided foam Sclerotherapy (UGFS) for Varicose Veins is to damage the endothelial surface of the vein causing scarring and leading to blockage of the treated Varicose Veins. Sclerosant, in the form of a foam, is intended to have good surface area contact with the vein walls [National Institute of Health and Care Excellence (NICE), 2013].

Endovenous mechanochemical ablation (e.g., ClariVein) uses a flexible, steerable, infusion catheter equipped with a rotatable dispersion wire. The wire tip causes minimal mechanical damage to the vessel lining, then a sclerosing agent is distributed to the treatment area. The process induces sclerosis of the vein, activating the clotting system and leading to vessel occlusion (Hayes, 2022; updated 2024).

A porcine bioprosthetic valve (e.g., VenoValve) is currently under investigation for treatment of deep vein reflux. The porcine aortic monocuspid valve leaflet attached to a nonexpandable stainless-steel frame is implanted into the femoral vein and the leaflet is designed to act as a functional valve. VenoValve is intended to be a permanent implant that decreases the risk of venous hypertension developing in the leg affected by chronic Venous Insufficiency by preventing the backflow of blood (Hayes, 2022; updated 2024).

Benefit Considerations

Coverage Limitations and Exclusions

The following procedures are excluded from coverage:

- Procedures that correct an anatomical congenital anomaly without improving or restoring physiologic function are considered cosmetic procedures and therefore excluded from coverage. The fact that a covered person may suffer psychological consequences or socially avoidant behavior as a result of an injury, sickness or congenital anomaly does not classify surgery (or other procedures done to relieve such consequences or behavior) as a reconstructive procedure.
- Any procedure that does not meet the criteria in the Coverage Rationale section.
- Treatments for Spider Veins and/or Telangiectasias are considered to be cosmetic and therefore excluded from coverage.
- Endovenous Ablation (radiofrequency and/or laser) of either reticular or Telangiectatic veins is not reconstructive and not medically necessary and therefore excluded from coverage.

Sclerotherapy Treatment of Veins

- Cosmetic Sclerotherapy is excluded.

Clinical Evidence

Jiang et al. (2024) conducted a systematic review and meta-analysis of pertinent literature on the treatment of lower extremity varicose veins using radiofrequency ablation (RFA) and laser ablation to compare the short-term and long-term outcomes of these treatments and identify which endovenous thermal ablation (EVTA) treatment is more effective. Occlusion rates of the great saphenous vein (GSV) and incidence of venous thrombotic events, which were assessed at the one-month and one-year follow-ups, were the primary endpoints. Nerve injury, recurrence of varicose veins, and postoperative pain and complications were secondary outcomes. Twenty-nine studies, comprised of 16 randomized controlled trials (RCTs) and 13 cohort studies, were included in the review. At one month, the occlusion rates of the GSV were 98.35% for RFA and 98.04% for laser ablation, whereas at one year, the rates were 93.13% for RFA and 94.18% for laser ablation. Subgroup analyses revealed that RFA had higher GSV occlusion rates at one year since 2016 (93.27% versus 91.24%; odds ratio [OR], 1.35; 95% confidence interval [CI], 1.0-1.83; p = .05). The incidence of postoperative venous thrombotic events was 0.78% for RFA and 0.87% for laser ablation at one month (OR, 1.46; 95% CI, 0.77-2.74; p = .24). Radiofrequency ablation showed a reduced risk of burns and ecchymosis (OR, 0.65; 95% CI, 0.48-0.87; p = .005), postprocedural pain (mean difference [MD], -0.85; 95% CI, -1.06 to -0.64; p < .001), recurrence of varicose veins (OR, 0.58; 95% CI, 0.36-0.92; p = .02), and paresthesia since 2016 (OR, 0.42; 95% CI, 0.19-0.91; p = .03), but an increased risk of skin pigmentation (OR, 1.75; 95% CI, 1.06-2.9; p = .03) compared with laser ablation therapy. The rate of phlebitis was similar between RFA and laser ablation (OR, 0.87; 95% CI, 0.33-2.27; p = .78). The authors concluded both RFA and

laser ablation are safe and effective treatments for lower extremity varicose veins and recent years have seen RFA achieve higher occlusion rates of treated GSVs and a reduction in postoperative complications compared to laser ablation. In these aspects of lower extremity varicose vein therapy, RFA appears to be superior to laser ablation. The authors recommended further RCTs are necessary to confirm these findings. Limitations included the retrospective nature of a few studies and primary and secondary outcomes were only assessed in some of studies, resulting in limited data. Woźniak et al., 2016, Lawaetz et al. 2017, and Vähäaho et al., 2019, which were previously cited in this policy are included in this review.

A Cochrane systematic review and meta-analysis performed by Cai et al. (2023) examined the effectiveness of superficial endovenous ablation for venous leg ulcers with regards to healing, recurrence, and quality of life (QOL). This review included two RCTs involving 506 participants, comparing endovenous ablative techniques combined with standard compression therapy to local standard of care which had to include compression therapy. At least one of the following primary outcomes related to ulcer healing needed to be evaluated: the percentage of ulcers healed within a specific period, the duration required for complete healing, changes in ulcer size, the rate of ulcer recurrence over a defined period or at a particular point, or the number of ulcer-free days. Secondary outcomes included patient-reported QOL, economic data, and any adverse events. There is high-certainty evidence that combined endovenous ablation and compression compared with compression therapy alone, or compression with deferred endovenous treatment, improves time to complete ulcer healing (pooled hazard ratio [HR] 1.41, 95% CI 1.36 to 1.47; I2 = 0%; two studies, 466 participants). There is moderate-certainty evidence that the proportion of ulcers healed at 90 days is probably higher with combined endovenous ablation and compression compared with compression therapy alone or compression with deferred endovenous treatment (risk ratio [RR] 1.14, 95% CI 1.00 to 1.30; I2 = 0%; two studies, 466 participants). There is low-certainty evidence showing an unclear effect on ulcer recurrence at one year in people with healed ulcers with combined endovenous treatment and compression when compared with compression alone or compression with deferred endovenous treatment (RR 0.29, 95% CI 0.03 to 2.48; I2 = 78%; two studies, 460 participants). There is also low-certainty evidence that the median number of ulcer-free days at one year may not differ (306 days versus 278 days) following combined endovenous treatment and compression when compared with compression and deferred endovenous treatment; (one study, 450 participants). There is low-certainty evidence of an unclear effect in rates of thromboembolism between groups (RR 2.02, 95% CI 0.51 to 7.97; I2 = 78%, two studies, 506 participants). The addition of endovenous ablation to compression is probably cost-effective at one year (99% probability at GBP 20,000/QALY; one study; moderate-certainty evidence). The authors concluded that endovenous ablation of superficial venous incompetence, when combined with compression, enhances leg ulcer healing compared to compression alone. The authors noted that further research is needed to determine the additional benefits of endovenous ablation for ulcers lasting more than six months and to identify the best method of endovenous ablation. Limitations included the majority of participants had an ulcer less than six months and only two studies met inclusion criteria.

Hamel-Desnos et al. (2023) conducted a multicenter RCT to compare endovenous laser ablation (EVLA) and ultrasound-guided foam sclerotherapy (UGFS) for treatment in participants with small saphenous vein (SSV) incompetence. One hundred and sixty-one participants were randomly selected to EVLA (n = 79) or UGFS (n = 82). The absence of SSV reflux (> 0.5 second) was the primary outcome, secondary outcomes were QOL scores and clinical scores. Assessments were performed at eight days, six months, and one, two, and three years. Only 3% of participants who received UGFS had the second (allowed) treatment and 86% of participants completed the three-year study. Forty-one and 19 tributary treatments (by sclerotherapy) were performed in 27 UGFS participants (33%) and 15 EVLA participants (19%), respectively. The complete absence of reflux at three years was significantly better after EVLA (86%) than after UGFS (56%). Two deep vein thromboses (DVTs), and one endovenous heat induced thrombosis occurred in the EVLA group. Seven DVTs were seen in the UGFS group, including two partial popliteal DVTs and five gastrocnemius vein thromboses (four asymptomatic and incidental on day eight screening). At three years, there was no difference between groups for the following: rate of visible varices (p = .87), revised Venous Clinical Severity Score (VCSS) (p = .28), and QOL (p = .59). Participant satisfaction scores were high in both groups. Symptoms were significantly improved in both groups. The authors note technical outcomes were better for EVLA than for UGFS, despite an allowance for a second UGFS treatment at six weeks for the foam group. Clinical scores were similarly improved in both groups; however, more participants had tributary treatment after UGFS, and more venous thromboembolism (VTE) events occurred after UGFS. The authors concluded this study supports EVLA as the first-choice treatment for SSV incompetence. Limitations included the trial was not powered to study factors such as influence of SSV diameters and polidocanol concentrations. Additionally, VTE prophylaxis and criteria for offering tributary treatment were left to the discretion of the investigator.

Giannopoulos et al. (2022) conducted a systematic review designed to compile and summarize the existing literature on minimally invasive treatments for saphenous and/or perforator vein disease, which leads to chronic venous insufficiency.

The review encompassed a total of 35 studies. Among these, 15 studies (n = 1677) focused on EVLA, either alone or in combination with sclerotherapy or microphlebectomy. Additionally, 12 studies (n = 1,477) examined RFA, with or without

sclerotherapy. Lastly, eight studies (n = 331) investigated the use of ultrasound-guided sclerotherapy as a standalone treatment. The primary outcome was the short-term anatomical success, defined as the complete occlusion of the treated varicosities. Secondary outcomes included periprocedural complications, such as postprocedural pain, paresthesia, wound infection at the access site, thrombophlebitis, DVT, induration, ecchymosis, skin necrosis, burns, or skin darkening. The study also evaluated long-term anatomical success and the ulcer healing rate. All techniques were found to be safe in terms of periprocedural adverse events, with only a few complications occurring in each group. Immediate procedural success (within 30 days) was 95% in the EVLA group, 91% in the RFA group, and 58% to 70% in the ultrasound-guided sclerotherapy group. At 12 months of follow-up, the occlusion rates were 89%, 77%, and 83% in the EVLA, RFA, and ultrasound-guided sclerotherapy groups, respectively. The 12-month pooled estimate of ulcer healing between the EVLA and RFA groups was similar, although no direct comparisons were performed. The authors concluded the use of percutaneous, minimally invasive techniques for treating pathological perforator veins revealed high success rates and a low incidence of periprocedural adverse events. Among the techniques studied, EVLA or RFA demonstrated the most favorable outcomes, although no direct comparisons between these methods were available. The authors suggested further research is necessary to confirm these findings and establish the most effective treatment approach for pathological perforator veins. The limitations identified included the inclusion of both single-arm and double-arm studies, and the absence of comparative prospective studies with standardized treatment protocols.

Brown et al. (2021) evaluated the both short- and long-term clinical outcomes, as well as patient-reported outcomes, among individuals (n = 4881) who underwent truncal endovenous ablation from 2015 to 2019 in the Vascular Quality Initiative. This study specifically compared outcomes between individuals with and without deep venous reflux. Notably, the researchers identified that 2,254 of these individuals exhibited combined deep and superficial venous reflux. The inclusion criteria consisted of individuals who underwent truncal vein ablation in the lower extremity using RFA or EVLA between 2015 and 2019. To minimize potential confounding factors, the study excluded individuals who had undergone sclerotherapy or phlebectomy, as well as those who received treatment for nontruncal veins. The median follow-up was 336.5 days. Individuals with deep reflux were less likely to be female (65.9% versus 69.9%; p = .003), more likely to be Caucasian (90.2% versus 86.5%; p = .003) and had no difference in body mass index (BMI) (30.6 ±7.5 versus 30.6 ±7.2; p = .904). Additionally, no difference was seen in rates of prior varicose vein treatments, number of pregnancies, or history of deep venous thrombosis; however, individuals without deep reflux were more likely to be on anticoagulation at the time of the procedure (10.9% versus 8.1%; p < .001). Individuals without deep reflux had slightly higher median preprocedural VCSS scores (eight [interquartile range (IQR), six to 10]) versus seven [IQR, six to 10]; p = .005) as well as postprocedural VCSS scores (five [IQR, three to seven] versus four [IQR, two to six]; p < .001). The median change in VCSS from before to after the procedure was lower for Individuals without deep reflux (three [IQR, 1.0-5.5] versus 3.5 [IQR, one to six]; p = .006). Total symptom score was higher for individuals without deep reflux both before (median, 14 [IQR, 10-19] versus median, 13.5 [IQR, 9.5-18]; p = .005) and postprocedurally (median, four [IQR, 1-9] versus median, 3.25 [IQR, one to seven]; p < .001), but no difference was seen in change in symptom score (median, eight [IQR, four to 13] versus median, nine [IQR, four to 13]; p = .172). Individuals with deep reflux had substantially higher rates of complications (10.4% versus 3.0%; p < .001), with a particular increase in proximal thrombus extension (3.1% versus 1.1%; p < .001). After controlling for confounding, this estimate of effect size for any complication increased (OR, 5.72; 95% CI, 2.21-14.81; p < .001). The authors found no significant difference in overall symptom improvement between individuals undergoing truncal endovenous ablation with concomitant deep venous reflux and those without. However, individuals with deep venous reflux did show a greater improvement in their VCSS. Despite this, these individuals experienced substantially higher rates of complications, even after accounting for confounding variables. Limitations include the retrospective design of the study and short follow-up period.

A single center RCT with a follow-up time of 10 years was completed by Eggen et al. (2021) to evaluate the long-term results of saphenofemoral ligation and stripping (SFL/S) compared with 980-nm bare fiber EVLA for the treatment of GSV incompetence. Participants with GSV incompetence were randomized to undergo SFL/S or EVLA under tumescent anesthesia. Inclusion criteria were, among others: GSV and saphenofemoral junction (SFJ) incompetence defined as reflux lasting more than 0.5 seconds on ultrasound imaging after calf compression and release or after the Valsalva maneuver, over an intrafascial length of 15 centimeters (cm) or more measured from the SFJ downward, with a GSV diameter of three millimeters (mm) or more or 15 mm or less. The primary outcome was recurrence of groin-related varicose veins seen on duplex ultrasound imaging and clinical examination. The secondary outcomes were (changes or improvement in) clinical, etiology, anatomy, pathophysiology (CEAP) clinical class, venous symptoms, cosmetic results, QOL, reinterventions, and complications. Between June 2007 and December 2008, 122 participants (130 limbs) were included; of these, 68 limbs were treated with SFL/S and 62 limbs with EVLA. The 10-year estimated freedom from groin recurrence as seen on duplex ultrasound imaging was higher in the SFL/S group (73% versus 44% in the EVLA group; p = .002), and the same trend was seen for clinically evident recurrence (77% versus 58%, respectively; p = .034). Nine reinterventions (17%) were deemed necessary in the SFL/S group versus 18 (36%) in the EVLA group (p = .059). All re-interventions in the SFL/S group consisted of foam sclerotherapy. Re-interventions in the EVLA group included foam sclerotherapy (n = five), crossectomy (n = two), and endovenous procedures (n = 11). There were no significant

differences in QOL and relief of venous symptoms. Cosmetic appearance improved, with a better cosmetic rating in the SFL/S group compared with the EVLA group (p = .026). One participant in the SFL/S group had a persisting neurosensory deficit remaining at 10 years. The authors concluded that the study showed no clear long-term advantage of EVLA with a 980-nm wavelength and bare-tip fiber over high ligation and stripping (L&S) of the GSV under local tumescent anesthesia.

Gibson et al. (2020) conducted a multicenter, prospective, nonrandomized study (SeCure trial) to evaluate the safety and efficacy of perforator ablation and QOL using a 400-µm optical fiber with a 1470-nm laser in individuals with advanced skin changes or ulceration (CEAP class C4b, C5, and C6). Ten-day primary closure and procedural technical success were evaluated. The primary pathologic perforator vein closure (at 10-day visit) rate was 76.9%. Successful primary closure rates of 75.7%, 70.3%, 62.1%, 68.8%, and 71.3% of pathologic perforator veins were achieved at one month, three months, six months, nine months, and 12 months, respectively. Statistically significant improvements ($p < .05$) were seen in participants' QOL at one month, three months, six months, nine months, and 12 months compared with screening. The percentage of participants with ulcers (22.9% at screening, 14.1% at one month, 13.7% at three months, 10.1% at six months, 12.3% at nine months, and 11.1% at 12 months) displayed improvement during the course of the study. Tibial DVT and procedural pain were the only device-related adverse events observed. According to the authors, the 400-µm optical fiber with the 1470-nm laser safe and effective for treatment pathologic perforator veins with high technical success rates and closure rates that were comparable to previous studies of pathologic perforator vein treatments. Limitations included lack of comparator group and conflicts of interest which may limit the study's conclusions.

In a meta-analysis, Hamann et al. (2017) compared the long-term efficacy of different treatment modalities for varicose veins: high ligation with stripping (HL + S), EVTA, mainly consisting of EVLA or RFA, and UGFS. Three RCTs and 10 follow-up studies of RCTs with follow-up ≥ five years were included. In total, 611 legs were treated with EVLA, 549 with HL + S, 121 with UGFS, and 114 with HL + EVLA. UGFS had significantly lower pooled anatomical success rates than HL + S, EVLA, and EVLA with high ligation: 34% (95% CI 26-44) versus 83% (95% CI 72-90), 88% (95% CI 82-92), and 88% (95% CI 17-100) respectively; $p \leq .001$. The pooled recurrent reflux rate at the SFJ was significantly lower for HL + S than UGFS (12%, 95% CI 7-20, versus 29%, 95% CI 21-38; $p \leq .001$) and EVLA (12%, 95% CI 7-20, versus 22%, 95% CI 14-32; p = .038). Venous Clinical Severity Score were pooled for EVLA and HL + S, which showed similar improvements. Based on the results of the meta-analysis, EVLA and HL + S show higher success rates than UGFS five years after GSV treatment. Recurrent reflux rates at the SFJ were significantly lower in HL + S than UGFS and EVLA. VCSS scores were similar between EVLA and HL + S. Rass et al. (2015), Gauw et al. (2016), and Flessenkämper et al. (2016), which were previously cited in this policy, are included in this meta-analysis.

In a systematic review and meta-analysis of RCTs of endovenous ablation of the GSV, O'Donnell et al. (2016) evaluated recurrence and cause of varicose veins after surgery (REVAS). Seven RCTs provided eight comparisons (one study compared both types of endovenous ablation to a comparator arm): three used RFA, and five employed EVLA. Overall recurrent varicose veins developed in 125 limbs after endovenous ablation (22%), with no difference in the incidence versus the L&S group (22%) based on the number of limbs available at the time of the development of recurrence for both groups, but this incidence is dependent on the length of follow-up after the initial treatment. Neovascularization occurred in only two limbs (2%) after endovenous ablation versus 18 (18%) in the L&S group. Recanalization was the most common cause of REVAS for endovenous ablation (32%; 40 of 125 limbs), followed by the development of anterior accessory saphenous vein incompetence (19%; 23 of 125 limbs). The authors concluded that there is no difference in the incidence of REVAS for endovenous ablation versus L&S, but the causes of REVAS are different with L&S.

In a systematic review and meta-analysis to compare traditional surgery and EVLA for the treatment of venous insufficiency of the GSVs, Quarto et al. (2016) evaluated 756 legs treated with a conventional surgical procedure and 755 legs treated with EVLA. Only RCTs based at least on six months follow-up were considered eligible in the study. The authors did not find a statistically significant difference in the presence or absence of reflux between the two techniques and noted that although EVLA did not prove to be superior in terms of recurrence to the surgical technique, EVLA remains a viable treatment option in individuals with impaired GSV, reducing postoperative pain and hospital stay.

Theivacumar et al. (2011) conducted a cohort study to assess the effectiveness and safety of EVLA in the management of recurrent varicose veins. One-hundred four limbs (95 individuals) undergoing EVLA for recurrent varicose veins were grouped according to pattern of reflux. For individuals with recurrent SFJ/GSV (Group GR) and saphenopopliteal junction (SPJ)/ SSV (Group SR) varicosities ablation rates and QOL using the Aberdeen Varicose Vein Severity Scores (AVVSS) were compared with those for age/sex matched individuals undergoing EVLA for primary GSV/SSV dependent varicose veins (Groups GP and SP). In individuals with recurrent varicose veins the axial vein was ablated in 102/104 (98%) limbs while two GSVs (group GR) partially recanalized by three months (GSV ablated in 49/51 (96%) limbs versus 50/51 (98%) limbs in GP [p = 0.2]). Improvements in AVVSS at three months (median GR: 14.2 IQR 10.2-18.9) to 3.2(1.2-6.4), $p < 0.001$; GP: median 15.9(IQR 11.4-22.7) to 3.8(1.1-5.6), $p < 0.001$, Mann-Whitney u-test) were similar (78% versus 76%, p = 0.23). The SSV was ablated in 24/24 limbs in groups SR and SP and the percent improvement in AVVSS was 83%

(median 14.4 (IQR 8.2-19.4) to 2.4 (1.9-4.6), p < 0.001, Mann-Whitney u-test) and 84% (median 13.8 (IQR 6.3-17.5) to 2.2 (1.2-5.1), p < 0.001) respectively (p = 0.33). These improvements persisted at one year follow-up. A further 29 limbs with isolated anterior accessory great saphenous vein (AAGSV) or segmental GSV/SSV reflux were successfully ablated. Complication rates for primary and recurrent varicose veins were similar. The authors concluded that EVLA is a safe and effective option for the treatment of recurrent varicose veins and could be a preferred option for suitable individuals.

In a systematic review, Darwood and Gough (2009) found that adjunctive saphenofemoral ligation is not necessary to achieve success with endovenous laser therapy of the GSV. Similarly, a RCT conducted by Disselhoff et al. (2008) found that the addition of saphenofemoral ligation to endovenous ablation made no difference to the short-term outcome of varicose vein treatment. Long-term follow-up at five years found similar results (Disselhoff et al. 2011). Further larger studies are needed to establish the superiority of adjunctive saphenofemoral ligation in improving long-term outcomes.

Theivacumar et al. (2009) compared 33 individuals (21 women and 12 men) undergoing AAGSV EVLA alone (group A) and 33 age/sex-matched controls undergoing GSV EVLA (Group B) to assess assesses the short-term efficacy (abolition of reflux on duplex ultrasound) of EVLA of the AAGSV with preservation of a competent GSV in the treatment of varicose veins occurring due to isolated AAGSV incompetence. Comparisons included ultrasound assessment of SFJ competence, successful axial vein ablation, AVVSS and a visual analogue patient-satisfaction scale. At the one-year follow-up, EVLA had successfully abolished the target vein reflux AAGSV: median length 19 cm (IQR: 14-24 cm) versus GSV: 32 cm (IQR 24-42 cm) and had restored SFJ competence in all individuals. Twenty of the 33 individuals (61%) in group A and 14 of the 33 (42%) in group B (p = 0.218) required post-ablation sclerotherapy at six weeks post-procedure for residual varicosities. The AVVSS at 12 months follow-up had improved from the pre-treatment scores in both the groups (group A: median score 4.1 (IQR 2.1-5.2) versus 11.6 (IQR: 6.9-15.1) p < 0.001; group B: median score 3.3 (IQR 1.1-4.5) versus 14.5 (IQR 7.6-20.2), p < 0.001), with no significant difference between the groups. The authors concluded that AAGSV EVLA abolishes SFJ reflux, improves symptom scores and is, therefore, suitable for treating varicose veins associated with AAGSV reflux.

Theivacumar et al. (2008) conducted a RCT to assess whether more extensive GSV ablation enhances resolution and influences symptom improvement in individuals with previous above-knee (AK) GSV EVLA. Sixty-eight limbs (65 individuals) with varicosities and above and below-knee GSV reflux were randomized to Group A: AK-EVLA (n = 23); Group B: EVLA mid-calf to groin (n = 23); and Group C: AK-EVLA, concomitant below-knee GSV foam sclerotherapy (n = 22). Primary outcomes were residual varicosities requiring sclerotherapy (six weeks), improvement in AVVSS, (12 weeks), patient satisfaction, and complication rates. EVLA ablated the treated GSV in all limbs. Sclerotherapy requirements were Group A: 14/23 (61%); Group B: 4/23 (17%); and Group C: 8/22 (36%); chi2 = 9.3 (2 df) p = .01 with p(A-B) = 0.006; P(B-C) = 0.19; P(A-C) = 0.14. AVVSS scores improved in all groups as follows: A: 14.8 (9.3-22.6) to 6.4 (3.2-9.1), (p < .001); B: 15.8 (10.2-24.5) to 2.5 (1.1-3.7), (p < .001); and C: 15.1 (9.0-23.1) to 4.1 (2.3-6.8), (p < .001) and P(A-B) = 0.011, P(A-C) = 0.042. Patient satisfaction was highest in Group B. BK-EVLA was not associated with saphenous nerve injury. The authors concluded that extended EVLA is safe, increases spontaneous resolution of varicosities, and has a greater impact on symptom reduction.

Wichers et al. (2005) performed a systematic review of randomized trials evaluating the safety and efficacy of medical (anticoagulants) or surgical (ligation or stripping of the affected veins) treatments of superficial vein thrombosis (SVT) for the prevention of DVT and pulmonary embolism (PE). Five studies were included. Pooling of the data was not possible due to the heterogeneity among the studies. Three studies had major methodological drawbacks limiting the clinical applicability of the results. One of the remaining (pilot) studies showed a non-significant trend in favor of high-compared to low-dose unfractionated heparin for the prevention of VTE. The last remaining study showed a non-significant trend in favor of short-term treatment with low-molecular-weight heparin, or a non-steroidal anti-inflammatory drug (NSAID) as compared to placebo shortly after treatment with respect to VTE, but the apparent benefit disappeared after three months of follow-up. More RCTs are needed before any evidence-based recommendations on the treatment of SVT for the prevention of VTE can be given. With the lack of solid evidence, the authors suggest treating individuals with at least intermediate doses of low-molecular-weight heparin. Surgical treatment of SVT may be considered when varicose veins are involved.

In a literature review of long-term results following high ligation supplemented by sclerotherapy, Recek (2004) found that ligation of the SFJ alone provokes a higher recurrence rate in comparison with high L&S. The hemodynamic improvement achieved immediately after high ligation deteriorates progressively during the follow-up owing to recurrent reflux.

In 2004, Winterborn conducted an 11-year follow-up study to a randomized clinical trial (Jones, et al. 1996). The objective of the Jones et al. (1996) trial was to determine whether routine stripping of the long saphenous vein reduced recurrence after varicose vein surgery. Two years after the procedure, 81 individuals (113 legs: 53 strip, 60 ligated) with a mean follow-up of 31-months (range 28-33 months) were reassessed with a satisfaction questionnaire, clinical exam, and

duplex scanning. Eighty-nine percent were satisfied with their results, although 35% had recurrent veins on clinical examination. Recurrence was reduced from 43% to 25% in individuals who had their long saphenous vein stripped (p = 0.04). Neovascularization (serpentine tributaries arising from the ligated SFJ) was detected in 52% of limbs and was the commonest cause of recurrence. Most tributaries were less than three mm in diameter and only caused recurrence if the long saphenous vein or a major thigh vein was intact. Twelve individuals had tributaries greater than three mm diameter, and all had recurrent varicose veins. Winterborn et al. (2004) reported that a cumulative total of 83 legs had developed clinically recurrent varicose veins by 11 years (62%). There was no statistically significant difference between the ligation-only and the stripping groups. Reoperation was required for 20 of 69 legs that underwent ligation alone compared with seven of 64 legs that had additional long saphenous vein stripping. Freedom from reoperation at 11 years was 70% after ligation, compared with 86% after stripping. The presence of neovascularization, an incompetent superficial vessel in the thigh or an incompetent SFJ on duplex imaging at two years postoperatively increased the risk of an individual developing clinically recurrent veins. Results from the study indicate that stripping the long saphenous vein is recommended as part of routine varicose vein surgery as it reduces the risk of reoperation after 11 years, although it did not reduce the rate of visible recurrent veins.

Sullivan et al. (2001) performed a systematic review of the literature evaluating surgical and medical management of above-knee superficial thrombophlebitis (AK-STP) not involving the deep venous system. Six studies were included for a total of 246 individuals in the surgical arm and 88 individuals in the medical arm. Surgical treatment modalities halt the progression of thrombus into the deep venous system through the SFJ and reduce the incidence of PE. The two types of surgical treatment were ligation of the GSV at the SFJ or ligation in combination with stripping of the phlebitic vein. Medical therapy consisted of initial IV heparin followed by warfarin therapy for a duration varying between six weeks and six months. The authors offered no definitive conclusions due to reporting of varied outcomes, different follow-up criteria and the retrospective nature of the studies. The differences between the surgical and medical groups were small. The review concludes that medical management with anticoagulants is superior for minimizing complications and preventing subsequent DVT and PE development as compared to surgical treatment with ligation of the GSV at the SFJ or L&S.

Chandler et al. (2000) conducted a prospective, comparative study to evaluate the effect of extended SFJ ligation when the GSV has been eliminated from participating in thigh reflux by means of endovenous obliteration. Sixty limbs treated with SFJ ligation, and 120 limbs treated without high ligation were selected from an ongoing, multicenter, endovenous obliteration trial on the basis of their having primary varicose veins, GSV reflux, and early treatment dates. Five (8%) high ligation limbs and seven (6%) limbs without high ligation with patent veins at six weeks or less were excluded as unsuccessful obliterations. Treatment significantly reduced symptoms and CEAP clinical class in both groups (p = .0001). Recurrent reflux developed in one (2%) of 49 high ligation limbs and eight (8%) of 97 limbs without high ligation by six months (p = .273). New instances of reflux did not appear thereafter in 57 limbs followed to 12 months. Recurrent varicose veins occurred in three high ligation limbs and four limbs without high ligation by six months and in one additional high ligation limb and two additional limbs without high ligation by 12 months. Actuarial recurrence curves were not statistically different with or without SFJ ligation (p > .156), predicting greater than 90% freedom from recurrent reflux and varicosities at one year for both groups. According to the authors, these early results suggest that extended SFJ ligation may add little to effective GSV obliteration, but their findings are not sufficiently robust to warrant abandonment of SFJ ligation as currently practiced in the management of primary varicose veins associated with GSV vein reflux.

Dwerryhouse et al. (1999) reported the five-year results of a RCT conducted on participants who were randomized to stripping of the long saphenous vein versus saphenofemoral ligation alone during routine varicose vein surgery. Originally, 100 participants, 133 legs were included in the study. After five years, 78 participants (110 legs) participated in a clinical review and duplex scan. Sixty-five participants remained pleased with the results of their surgery (35 of 39 stripped versus 30 of 39 ligated; p = .13). Reoperation, either done or awaited, for recurrent long saphenous veins was necessary for three of 52 of the legs that underwent stripping versus 12 of 58 ligated legs. Neovascularization at the SFJ was responsible for 10 of 12 recurrent veins that underwent reoperation and also was the cause of recurrent saphenofemoral incompetence in 12 of 52 stripped veins versus 30 of 58 ligated legs. The authors concluded that after five years follow-up, stripping reduced the risk of reoperation by two thirds and should be routine for primary long saphenous varicose vein treatment.

Endovascular Embolization With Cyanoacrylate-Based Adhesive

A multicenter, randomized control study by Alhewy et al. (2024) aimed to compare the efficacy, safety, and clinical outcomes of treatments with cyanoacrylate closure (CAC) or RFA in those with incompetent GSVs. Two hundred and forty-eight adults (286 limbs) with symptomatic, CEAP classifications of C2 - C5, and GSV reflux of 0.5 seconds measured by duplex ultrasound were included in the study. Participants were randomized to either receive CAC (n = 128) or RFA (n = 120) procedures. Exclusion criteria included reflux of the SSV or AAGSV, prior treatment of GSV, symptomatic peripheral arterial disease, history of DVT or PE, aneurysm of the target GSV greater than 12 mm, BMI over 35, active treatment for hypercoagulable disorder, current use of anticoagulant, sensitivity to cyanoacrylate adhesives, and CEAP

class six. Complete closure of the GSV at the three-month visit was the primary end point. Postprocedural follow-up exams were performed on day three, one month, three months, then every six months for two years. At the one-month duration, the closure rates were 128/128 at the CAC and 154/158 at the RFA. At month 24, closure rates were 122/128 at CAC and 146/158 at RFA. Apart from phlebitis and pigmentation, the incidences of bruising, skin burn, and paresthesia were lower in the CAC group compared to the RFA group. The mean procedural times were shorter for CAC. The satisfaction level with the treatment was moderately higher among CAC participants than RFA participants. The authors concluded that both CAC of the GSV and RFA are effective techniques for managing primary varicose veins. However, CAC of the GSV tends to have fewer complications, higher patient satisfaction, quicker return to normal activities, and shorter procedure times. Additionally, it does not require tumescent anesthesia or post-procedure compression stockings, unlike RFA. The authors recommended future research with longer follow-up periods and larger sample sizes.

Chen et al. (2023) performed a systematic review and meta-analysis of RCTs to evaluate the efficacy and safety of chemical agent injections in individuals with varicose veins. Inclusion criteria included RCTs where foam and liquid sclerotherapy or cyanoacrylate glue were used as interventions without other invasive treatments. The control treatments consisted of surgery, EVLA, RFA, placebo, and conservative treatments. A total of 50 studies, published between 1972 and 2022, were included in the review. Results showed that at all postprocedural time intervals, cyanoacrylate glue therapy exhibited a significantly higher success rate compared with foam and liquid sclerotherapy. According to the plot of P-score lines, cyanoacrylate glue had an overall tendency of higher success rate and lower complication rate compared with foam and liquid sclerotherapy. The authors noted that when comparing with the other invasive treatments, cyanoacrylate glue may be non-inferior and could be considered as an option for treating varicose veins. However, the clinical benefits and safety of endovascular agents for varicose vein treatment need to be confirmed through RCTs.

Amshar et al. (2022) conducted a systematic review and meta-analysis to evaluate the efficacy, intervention time, and safety of cyanoacrylate embolization (CAE) in comparison to EVLA in treatment of saphenous vein insufficiency. Efficacy was determined by venous closure rate one-year post-intervention and VCSS one-year post-intervention. Safety was determined by rates of periprocedural pain, skin pigmentation, nerve damage, phlebitis, DVT and ecchymosis. Two RCTs and three cohort studies were included in this review. The total number of individuals was 1,432 (710 CAE and 722 EVLA). Venous closure rates and VCSS did not differ significantly between CAE group and EVLA group. Pooled data showed that CAE group was associated with less periprocedural pain score ($p < 0.001$), lower skin pigmentation rates (0.60% versus 4.46%; $p = 0.008$), and lower nerve damage rates (0% versus 3.94%; $p = 0.007$). Rates of phlebitis, DVT, and ecchymosis did not differ significantly between the two groups. In addition, intervention time was significantly faster in CAE group compared to EVLA group ($p < 0.001$). The authors concluded CAE was not inferior to EVLA in terms of efficacy and CAE showed less adverse effects occurrence rates of periprocedural pain, skin pigmentation, and nerve damage complications. Additionally, intervention time is stated to be faster with CAE compared to EVLA. The authors note that future RCTs with larger sample sizes and longer post-procedural follow-up time are needed. Additionally, efficacy outcomes were limited to one year and longer-term outcome data may provide additional evidence of efficacy. Bozkurt and Yilmaz (2016), and Eroglu and Yasim (2018) which were previously cited in this policy, are included in this review. Currently, the VariClose Vein Sealing System (Biolas, FG Grup, Turkey) is under research in countries other than the United States and has neither been approved nor cleared for marketing by the FDA.

A 2022 Hayes Health Technology Assessment evaluated nine clinical studies on the efficacy and safety of CAE with the VenaSeal Closure System. The evidence included three RCTs and six retrospective comparative studies. The conclusion states that a low-quality body of evidence suggests VenaSeal has a high level of successful venous closure for at least one year that may result in reduced symptom severity and improved QOL. Efficacy and safety may be comparable to RFA, EVLA, and MOCA; however, substantial uncertainly remains regarding its effectiveness due to the lack of well-designed comparative studies and limited follow-up beyond one year. The authors overall conclusion is that CAE with the VenaSeal Closure System has potential but unproven benefits. The updated Hayes, 2024 summary included two newly published studies that met the inclusion criteria but made no change to the current rating.

Joh et al. (2021) conducted an open-label multicenter, prospective, RCT that compare the clinical outcomes of (CAC and surgical stripping (SS) for the treatment of incompetent GSVs. One hundred and twenty-six participants were randomized into two groups (63 with CAC and 63 with SS). Target vein occlusion was assessed on the third day and one, three, six, and 12 months postoperatively using duplex ultrasound. The primary endpoint of the study was to evaluate complete closure of the target vein at three months. Ecchymosis grades, VCSS, Aberdeen Varicose Vein Questionnaire (AVVQ) scores and pain were also assessed as secondary outcomes. Postoperative pain scores were significantly better in the CAC group than in the SS group. In addition, the mean ecchymosis grade was 0.3 ±0.5 in the CAC group and 1.1 ±1.1 in the SS group ($p < .001$). The VCSS and QOL had improved equally in both groups. Most complications were minor (nine events in CAC group and 20 events in SS group) with one major complication occurring in a participant who had undergone the SS procedure. Complete occlusion of the target vein at three months was achieved by both procedures. Postoperative pain and ecchymosis grades were significantly lower in the CAC group. The authors concluded that CAC

has a high success rate with few complications. Limitations noted by the authors include lack of information on participant return to work and daily activities, pain scores during the procedure and immediately after the procedure were not obtained, the two by two factorial design with one to one randomization, could contribute to differences in gender distribution and VCSSs in the two groups, and concomitant phlebectomy could have also influenced the occurrence of complications. Additionally, lack of masking could have introduced a bias in the findings.

A systematic review by Dimech and Cassar (2020) was performed to assess the efficacy of *n*-butyl-2-cyanoacrylate (NBCA) glue in ablating primary truncal varicose veins and eliminating reflux compared with existing endovascular techniques. Secondary outcomes include complications and QOL. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was used as a guide, and studies were screened for risk of bias and methodological quality. Subjects had to be ≥ 18 years of age and followed-up post-treatment with color duplex ultrasound. Eligibility criteria included SFJ or SPJ incompetence with reflux down truncal veins lasting > 0.5 seconds on duplex ultrasound interrogation and a CEAP classification of venous disorders ranging between C1 and C6. Out of 2,910 individuals (3,220 veins) in 17 studies, 1,981 were administered NBCA, 445 RFA, and 484 EVLA with mean procedure times of 25.7, 23.2, and 28.7 minutes, respectively. Mean recruitment period was nine months (1-36 months) and followed up for an average of 12.3 months (one to 36 months). The majority were C2 to C3. Two-year occlusion rates were 93.7, 90.9, and 91.5% for NBCA, RFA, and EVLA, respectively. NBCA-treated individuals experienced the least complications, with bruising, phlebitis, and pain being the most prevalent. Quality of life improved equally in all three modalities. The authors concluded that NBCA is simple to administer, safe, and effective even without compression stockings. The review was limited by lack of randomization for most included studies, and inclusion of products not currently FDA-approved. Further studies are required to assess longer-term benefit and the effect of anticoagulation on vein obliteration.

Kolluri et al. (2020) conducted a meta-analysis designed to compare VenaSeal closure system with EVLA, RFA, MOCA, sclerotherapy, and surgical management of chronic venous insufficiency achieve complete closure of the treated vein within six months after intervention. Secondary outcomes were QOL, VCSS, pain scores, and adverse effects. Twenty RCTs comprising 4570 individuals were analyzed. For the primary outcome measure of anatomic success, VenaSeal system had the highest probability of being ranked first (p = .980); RFA was ranked second (p = .365), EVLA third (p = .397), surgery fourth (p = .290), MOCA fifth (p = .695), and sclerotherapy sixth (p = .982). For secondary outcome measures, VenaSeal system ranked third for VCSS (p = .332), fifth for EuroQol-5 Dimension (EQ-5D) (p = .420), and third for AVVQ) (p = .300). Although, VenaSeal system was slightly inferior to some of the other interventions for health-related QOL, the 95% credible interval of log OR indicated insufficient evidence for any concrete conclusion to be drawn. VenaSeal system ranked first in reduction of postoperative pain score from baseline (p = .690) and was lowest in occurrence of adverse events (p = .650). Odds of occurrence of adverse events was 3.3 times in the sclerotherapy arm, 2.7 times in the EVLA arm, 1.6 times with surgery, and 1.1 times with RFA versus VenaSeal system arm. The authors concluded VenaSeal was a promising option for treatment for individuals with chronic venous insufficiency due to superior outcomes as assessed by anatomic success, reduction of pain score, and smaller chance of occurrence of adverse events when compared with other interventions. Limitations include short-term follow-up and restricted data availability in terms of time points and pooling of data.

The VenaSeal Sapheon Closure System Pivotal Study (VeClose) is a multi-center RCT that compared CAC to RFA for the treatment of incompetent GSVs. In this trial, 222 subjects with symptomatic GSV incompetence were randomly assigned to receive either CAC (n = 108) with the VenaSeal Sapheon Closure System or RFA (n = 114). The primary endpoint was closure of the target vein at month three, as assessed by duplex ultrasound. To determine non-inferiority of CAE to RFA, the investigators used a predetermined margin of 10%. Secondary endpoints included subject-rated pain experienced during the procedure (i.e., pain experienced after vein access but before all treatment/access catheters were removed), investigator-rated ecchymosis at day three, adverse events, and details of adjunctive procedures. Participant follow-up visits were on day three and at months one, three, six, 12, 24, and 36. For the extension study, participants who were successfully contacted and were interested in participation provided written informed consent for the 60-month follow-up visit. Assessments tools included the VCSS, AVVQ and EQ-5D QOL survey. This trial has generated multiple publications that reported outcomes with various follow-up periods e.g., three months (Morrison, 2015), 12 months (Morrison, 2017) 24 months (Gibson, 2018a) 36 months (Morrison, 2019), and 60 months (Morrison, 2020), as well as a publication with results of a roll-in phase analysis, which included 20 additional participants treated with CAC (Kolluri, 2016). Design limitations of this study and the resulting publications included lack of blinding of the subjects or assessors to the intervention. Furthermore, the primary endpoint of the study was complete closure of the target vein at three months after index treatment, thus the study may not have been powered to detect clinically significant differences between treatments groups for important outcomes and at different times of follow-up. These studies were also included in the Hayes report (2022). The individual studies are listed below:

- Morrison et al. (2015) reported three-month outcomes from the VeClose trial. No adjunctive procedures such as phlebectomy and UGFS were allowed until after the month three visit. The closure rates were 99% for VenaSeal and 96% for RFA. Pain experienced during the procedure was reported as mild and was similar between treatment

groups. Good safety profiles were reported with both treatments. The authors concluded that CAC did not require tumescent anesthesia, was associated with less post procedure ecchymosis, and was noninferior to RFA for the treatment of incompetent GSVs at month three after the procedure.

- Morrison et al. (2017) reported 12-month outcomes from the VeClose trial. Of 222 randomized participants, a 12-month follow-up was obtained for 192 (95 CAC and 97 RFA; total follow-up rate, 86.5%). The complete occlusion rate was nearly identical in both groups (97.2% in the CAC group and 97.0% in the RFA group). Twelve-month freedom from recanalization was similar in the CAC and RFA groups, although there was a trend toward greater freedom from recanalization in the CAC group (p = .08). The authors reported that participant symptoms and QOL improved equally in both groups.
- Twenty-four-month outcomes from the VeClose trial were reported by Gibson et al (2018a). One hundred and seventy-one participants completed the 24-month follow-up, which included 87 from the CAC group and 84 from the RFA group. The 24-month GSV closure rate was 95.3% in the CAC group and 94.0% in the RFA group. Symptoms and QOL improved similarly in both groups. No clinically significant device- or procedure-related late adverse events were reported. The authors concluded that both CAC and RFA were effective in closure of the target GSV, resulting in similar and significant improvements in the participant's QOL through 24 months.
- One hundred and forty-six participants completed the 36-month follow-up to the VeClose trial, which included 72 participants from the CAC group and 74 participants from the RFA group, with outcomes reported by Morrison et al. (2019). The 36-month GSV closure rate was 94.4% for the CAC group and 91.9% for the RFA group. Stable improvement in symptoms and QOL was observed in both groups. Adverse event rates between the 24- and 36-month visits were similar between the groups as were serious adverse events which were infrequent and judged unrelated to either the device or the procedure in both groups. The authors surmised the results of this trial continue to demonstrate the safety and efficacy of CAC for the treatment of GSV incompetence with vein closure rate at 36 months similar to that of RFA. The findings are limited by the loss to follow-up (34%), which could have introduced biases in the findings.
- Morrison et. al. (2020) reported 60-month outcomes from the VeClose trial with a total of 89 participants in the original study completing the 60-month visit. Of those, 47 participants were from the CAC group, 33 participants were from the RFA group, and nine participants were from the roll-in CAC group. No new recanalization events were observed between 36 and 60 months of follow-up. Kaplan-Meier estimates for freedom from recanalization in the randomized CAC and RFA groups were 91.4% and 85.2%, respectively. Both groups demonstrated sustained improvements in EQ-5D and QOL. Whereas participants assigned to C0 or C1 clinical class were excluded from the original study, more than half of all returning participants (64% [57/89]) were now assigned to C0 or C1, suggesting an improved clinical class from baseline. Furthermore, 41.1% of returning CAC participants and 39.4% of returning RFA participants at least two CEAP clinical classes lower than at baseline. The authors concluded that CAC and RFA were effective in achieving complete target vein closure of the GSV at long-term follow-up. CAC was also associated with sustained improvements in symptoms and QOL, lower CEAP class, and high level of participant satisfaction without serious adverse effects between 36 and 60 months. The limitations of this publication included the small rate of successful follow-up i.e., 36% of the original study randomized population, which could have introduced biases in the findings. (This study is included in the systematic review by Bontinis et al., 2023)

Gibson et al. (2018b) reported three-month outcomes from a post-market case series study of endovenous CAC by the VenaSeal system (the WAVES study). Fifty subjects with symptomatic GSV, SSV, and/or accessory saphenous vein incompetence were treated with the VenaSeal system with no post procedure compression stockings. Concomitant procedures were not allowed as part of the original study protocol. Treating physicians predicted the type and nature of any concomitant procedures that they would usually perform at the time of ablation, if not limited by the constraints of the study. Evaluations were performed at one week, one and three months and included duplex ultrasound, numeric pain rating scale, revised VCSS, the AVVQ, and time to return to work and normal activities. At the three-month visit, the need for and type of adjunctive procedures were recorded. Complete closure at three months was achieved in 70 (99%) of the treated veins (48 GSVs, 14 accessory saphenous veins, eight SSVs). Revised VCSS improved from 6.4 ±2.2 to 1.8 ±1.5 (p < .001) and AVVQ from 17.3 ±7.9 to 6.5 ±7.2 (p < .0001). Sixty-six percent of individuals underwent tributary treatment at three months. The percentage of individuals who required adjunctive treatments at three months was lower than had been predicted by the treating physicians (65% versus 96%, p = .0002). The authors reported that closure rates were high in the absence of the use of compression stockings or side branch treatment. Improvement in QOL was significant, and the need for and extent of concomitant procedures was significantly less than had been predicted by the treating physicians. Additional studies with larger sample sizes are needed to further evaluate the need for concomitant procedures with the VenaSeal system. These findings are limited by lack of comparison group undergoing a different treatment. This study was also included in the Hayes report (2022).

Gibson and Ferris (2017b) reported results of a prospective case series study (the WAVES study) of cyanoacrylate closure for the treatment of GSVs, SSVs, and/or accessory saphenous veins up to 20 mm in diameter (n = 50). Compression stockings post-procedure were not utilized. Individuals returned at one week and one month for follow-up.

All treated veins (48 GSV, 14 accessory saphenous veins, and eight SSVs) had complete closure by duplex ultrasound at seven days and one month. Mean time to return to work and normal activities was 0.2 ±1.1 and 2.4 ±4.1 days, respectively. The revised VCSS was improved to 1.8 ±1.4 ($p < .001$) and AVVQ score to 8.9 ±6.6 ($p < .001$) at one month. Phlebitis in the treatment area or side branches occurred in 10 subjects (20%) and completely resolved in all but one subject (two percent) by one month. The authors concluded that cyanoacrylate closure is safe and effective for the treatment of one or more incompetent saphenous or accessory saphenous veins, closure rates were high even in the absence of the use of compression stockings or side branch treatment. Time back to work or normal activities was short and improvements in venous severity scores and QOL were in the authors' opinion significant, comparing favorably with alternative treatment methods. RCTs with a larger sample size and longer follow-up periods are needed to validate findings. The findings of this study are limited by lack of comparison group undergoing a different treatment approach. This study was also included in the Hayes report (2022).

An ECRI clinical evidence assessment (2015) suggests that VenaSeal is safe and as effective as RFA for treating varicose veins in individuals with venous reflux disease. However, how well VenaSeal works compared with other treatment modalities cannot be determined because the systematic review assessed too few individuals for each comparison and no studies in the systematic review performed head-to-head comparisons. The report determined the evidence was somewhat favorable but RCTs are needed to compare VenaSeal with other treatment modalities. Limitations of the reviewed studies include risk for lack of blinding, single-center focus, and lack of randomization (ECRI, updated 2021).

A prospective multicenter study was conducted in seven centers in four European countries, on 70 individuals with GSV reflux using CAE (Proebstle et al., 2015). Clinical examination, QOL assessment and duplex ultrasound were performed at two days, one, three, six, and 12 months. Sixty-eight individuals (97.1%) were available for 12-month follow-up, with 70 GSVs treated. Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalization's were observed at three-month (n = two) and six-month (n = one) follow-up. Cumulative 12-month survival free from recanalization was 92.9% (95% CI, 87.0%-99.1%). Mean (standard deviation) VCSS improved from 4.3 ±2.3 at baseline to 1.1 ±1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months ($p < .0001$). Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days (range, two to 12 days). Pain without a phlebitic reaction was observed in five individuals (8.6%) for a median duration of one day (range, zero to12 days). No serious adverse event occurred. Paresthesia was not observed. The authors determined that endovenous CAE of refluxing GSVs is both safe and effective, even without the use of tumescent anesthesia or compression stockings. However, further research is needed to validate the efficacy of CAE. The study by Proebstle et al. (2021) presented the three-year follow-up results of the prospective, multicenter, cohort study above. Out of the 70 individuals who received treatment, 64 (91%) were available for the three-year follow-up. The closure rates by Kaplan-Meier life table methods at six-, 12-, 24-, and 36-month time points were 91.4%, 90.0%, 88.5%, and 88.5%, respectively. Additionally, there were significant improvements in the VCSS, which decreased from 4.3 at baseline to 0.9 at the three-year follow-up ($p < .001$). According to the authors, CAE is both safe and effective for long-term treatment of refluxing GSVs. Limitations included lack of randomization, small sample size, and the study lacked a control group.

Endovascular Embolization With Cyanoacrylate-Based Adhesive for Incompetent Perforator Veins

Quality evidence in peer review literature evaluating endovascular embolization with cyanoacrylate-based adhesive for the treatment of incompetent perforator veins is limited. Future robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this procedure.

Prasad et al. (2018) evaluated the efficacy and safety of CAE and sclerotherapy in the treatment of primary veins due to GSV reflux with or without incompetent perforators. The total number of perforators treated was 269, 189 of which were direct perforators. The study found that the combination of cyanoacrylate adhesion and sodium tetradecyl sulphate sclerotherapy was technically straightforward, highly effective, and well-suited for outpatient settings. Despite these advantages, the safety profile was considered guarded. The study's primary limitations included a relatively small sample size of 69 participants and a short follow-up period of six months. Additionally, the results were potentially confounded by the simultaneous use of both treatment methods. Further research with larger sample sizes and longer follow-up periods is needed to validate these findings. The 2022 systematic review supporting the Society for Vascular Surgery, the American Venous Forum, and the American Vein and Lymphatic Society guidelines on the management of varicose veins by Farah et al. (2022) did not address the role of perforator incompetence in individuals with venous ulcers. Several retrospective reviews including Mordhorst et al. (2021), Türkmen (2024), have reported promising results but are limited by the retrospective nature of the studies, small sample sizes, lack of randomization, and lack of a comparator group.

Endovenous Foam Sclerotherapy

In a 2024 systematic review and meta-analysis, Kabnick et al. evaluated and compared the safety and efficacy of two primary treatment modalities, polidocanol 1% endovenous microfoam (PEM) ablation and either RFA or laser ablation, for venous insufficiency caused by incompetence of the lower extremity truncal veins, Eligible studies (n = 13) had chronic venous insufficiency treatments with a randomized or nonrandomized comparison of at least one of the two treatments (PEM or EVTA) between January 2000 and January 2023. Studies that were single arm, did not target the truncal veins, involved combination treatments, or lacked a common comparator (i.e., an alternate treatment used in at least one PEM study and one EVTA study) were excluded. Occlusion rate at three months or more after the procedure and the mean or median change in VCSS (or rVCSS) were the primary outcomes measured. The primary outcome for the subgroup of individuals with a venous ulcer was the ulcer healing rate. Safety and patient-reported outcomes were secondary endpoints. The results found that PEM was not statistically different from EVTA for venous closure (OR, 0.65; 95% CI, 0.36-1.18; p = .16). The network meta-analysis also provided evidence to confirm that PEM was significantly differentiated statistically from physician-compounded foam (PCF), with higher odds for vein closure (OR, 2.91; 95% CI, 1.58-5.37; p < .01). A sensitivity analysis using the longest available time point for closure in each study, with a minimum of 12 months of follow-up (median, 48 months; range, 12-72 months), showed results similar to those of the main analysis. No association was found between the risk of DVT and the treatment received. The available data were insufficient for a network meta-analysis of VCSS improvement and ulcer healing rates. The authors concluded PEM did not exhibit a statistically significant difference from EVTA regarding vein closure and DVT risk in the treatment of chronic venous insufficiency. The authors highlighted that the network meta-analysis confirmed the hypothesis, showing that PEM was statistically distinct from PCF, with higher likelihood of achieving vein closure. Furthermore, the sensitivity analysis revealed that venous closure outcomes remained robust at follow-up intervals of 12 months or more, extending up to six years. Limitations included insufficient data were available for some outcomes and treatment techniques, some studies were non-randomized, and neither randomized nor randomized studies blinded participants to the treatment received.

In an updated Cochrane review, Whing et al. (2021) compared interventions for treating varicosities of the GSV. The review included 24 RCTs with 5135 participants who underwent EVLA, RFA, EVSA, UGFS, cyanoacrylate glue, MOCA, or high L&S. The review compared EVLA and UGFS and found technical success may be better with EVLA up to five years and over five years. Recurrence rates had no clear difference up to three years and at five years. The authors state there were a relatively small number of studies for comparison and differences in outcome definitions and time points reported limited their conclusions. Future studies which provide more evidence on the breadth of treatments are recommended by the authors. Lawaetz et al. (2017) and Vähäaho et al. (2018), which were previously cited in this policy, are included in this review.

A Hayes Health Technology Assessment (2019) researched six clinical studies (n = 77-399) that evaluated the efficacy or safety of PEM 1% in treating varicose veins. Eligible studies included five RCTs and one case series. The individuals included in the studies had SFJ, GSV or SSV incompetence. The assessment concluded there was a low-quality body of evidence that suggested PEM 1% may provide relief of symptoms and result in occlusion and elimination of reflux. The authors concluded that this approach has potential but unproven benefit. Additionally, substantial uncertainty remains regarding the effectiveness of PEM 1% in relation to other sclerosants and other surgical approaches. The authors overall conclusion is that PEM has potential but unproven benefits. The report recommended more well-designed, independent RCTs to further establish the comparative safety and effectiveness of PEM 1%, identify optimal patient selection, and determine the durability of its beneficial effects. (Hayes, 2019; updated 2022).

Gibson et al. (2017a) conducted a randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of PEM 1%, Varithena® [polidocanol injectable foam]). Participants (n = 77) with symptomatic, visible varicose veins were randomized to treatment with either Varithena 1% or placebo. Participants were assessed at baseline and weeks one, four, eight, and 12 post-treatment. The data showed that Varithena provided greater mean changes from baseline in patient-reported assessments of symptoms (e.g., heaviness, achiness, swelling, throbbing, itching [HASTI®] score 30.7 points versus 16.7 points, p = 0.0009, primary endpoint; and modified Venous Insufficiency Epidemiological and Economic Study-Quality-of-Life/Symptoms [m-VEINES-QOL/Sym; p < 0.001]), physician-assessed VCSS, and physician- and patient-assessed appearance compared with placebo. The HASTI score correlated highly with the modified-VEINES-QOL/Sym and Chronic Venous Insufficiency Questionnaire-2 scores (r = 0.7 to > 0.9, p ≤ 0.001). Adverse events included contusion, incision-site hematoma, and limb discomfort. Venous thrombus adverse events were reported as mild and generally resolved without sequelae. Large RCTs with longer-term outcomes and comparisons to established treatments for varicose veins are needed to evaluate the clinical utility of this procedure. The findings of this study are limited by the short follow-up and lack of comparison with an established therapy.

Lal et al. (2017) evaluated the relationship between patient-reported symptoms and functional and psychological impact of varicose veins following treatment with PEM 1%. Data were pooled from two randomized trials on varicose vein treatment. In 221 participants (109 PEM 1%; 112 placebo), PEM 1% was associated with median improvements of 2.5 points and

4.0 points on the m-VEINES-QOL/Sym functional limitations and m-VEINES-QOL/Sym psychological limitations scores, compared to 0 and 1.0 point. Cumulative distribution function curves revealed that 20-30% more participants in the PEM 1% group achieved clinically meaningful functional and psychological improvement versus placebo group. Participants with above-average symptom improvement had better functional and psychological improvement. PEM 1% treatment had higher odds of clinically meaningful functional and psychological improvement. Length of post-procedure follow-up was not provided. Furthermore, this study did not compare endovenous microfoam to established treatment for varicose veins.

In a multicenter, randomized, placebo-controlled, blinded study in participants with GSV incompetence and symptomatic and visible superficial venous disease, Vasquez et al. (2017) evaluated the efficacy and safety of PEM 0.5%, 1.0%, or placebo each administered with EVTA. Co-primary endpoints were physician-assessed, and patient-assessed appearance change from baseline to week eight. A total of 117 participants received treatment (38 placebo, 39 PEM 0.5%, 40 PEM 1%). Physician-rated vein appearance at week eight was significantly better with PEM ($p = 0.001$ versus placebo); patient-assessed appearance trended similarly. In the authors' opinion, PEM provided improvements in clinically meaningful change in patient-assessed and physician-assessed appearance ($p < 0.05$), need for additional treatment ($p < 0.05$), SFJ reflux elimination, symptoms, and QOL. In PEM recipients, the most frequent adverse event was superficial thrombophlebitis (35.4%). While these results appear promising, PEM outcomes were compared with placebo and with a short follow-up period. Additional RCTs comparing PEM outcomes with other established varicose vein treatment outcomes, and with a longer follow-up period are needed.

In an ECRI Clinical Evidence Assessment (2015), Varithena injectable foam was found to improve symptoms and appearance of varicose veins when compared to placebo or other unspecified sclerotherapy agents. Evidence was based on three double-blind and one open-label, multicenter, RCTs. A small open-label extension of one of the RCTs found the beneficial effects with Varithena were sustained at one-year follow-up. A separate cohort study found individuals had better vein occlusion rates with high ligation surgery than with Varithena at one-year follow-up. Adverse effects included pain, thrombophlebitis, bruising and thrombus in nontarget vessels and were considered minor. The report notes that longer-term, independent RCTs would be useful to confirm results and to compare Varithena with other varicose vein treatments because no data were available on RFA or laser therapy. The updated 2024 analysis notes evidence from multiple studies including a meta-analysis and four RCTS found Varithena to be safe and improve vein symptoms and appearance. The report notes Varithena appears to be similar to thermal ablation techniques; however, studies comparing Varithena with thermal ablation modalities are needed with longer-term follow-ups. The Evidence Bar is noted as favorable. (ECRI, 2015; updated 2024).

King et al. (2015) reported a multicenter, parallel group study (VANISH-1), to determine if a single administration of ≤ 15 mL of pharmaceutical-grade PEM (Varithena [polidocanol injectable foam]) could alleviate symptoms and improve appearance of varicose veins in a typical population of individuals with moderate to very severe symptoms of superficial venous incompetence and visible varicosities of the GSV system. The primary endpoint was patient-reported venous symptom improvement measured by change from baseline to week eight in seven-day average VVSymQ score. Individuals (n = 279) were randomized to five groups: PEM 0.125% (control), 0.5%, 1%, 2%, or placebo. At week eight, VVSymQ scores for the pooled PEM group (0.5% + 1% + 2%; $p < .0001$) and individual dose concentrations ($p < .001$) were greater as compared to placebo. Most adverse events were mild and resolved without sequelae. No PE were reported. The authors concluded that this study demonstrated that a single administration of up to 15 mL of PEM is a safe, effective, and convenient treatment for the symptoms of superficial venous incompetence and the appearance of visible varicosities of the GSV system. Doses of 0.5%, 1%, and 2% PEM appear to have an acceptable risk-benefit ratio. Additional studies with comparisons to other varicose vein treatments and over a longer period of time are needed before determining the safety and efficacy of this procedure.

In the VANISH-2 trial, Todd et al. (2014) evaluated the efficacy and safety of PEM in treatment of symptoms and appearance in participants with SFJ incompetence due to reflux of the GSV or major accessory veins. Participants were randomized equally to receive PEM 0.5%, PEM 1.0%, or placebo. In 232 treated participants, PEM 0.5% and PEM 1.0% were superior to placebo, with a larger improvement in symptoms (VVSymQ (-6.01 and-5.06, respectively, versus -2.00; $p < 0.0001$) and greater improvements in physician and participant assessments of appearance ($p < 0.0001$). These findings were supported by the results of duplex ultrasound and other clinical measures. Of the 230 PEM-treated participants (including open-label participants), 60% had an adverse event compared with 39% of placebo; 95% were mild or moderate. The authors concluded that PEM provided clinically meaningful benefit in treating symptoms and appearance in participants with varicose veins. However, longer-term outcomes with comparisons between PEM and other established treatments for varicose veins are needed to evaluate the clinical utility of this procedure. In 2015, Todd et al. assessed the durability of response to treatment and the long-term safety of participants treated with PEM 1% foam. The primary outcome was the efficacy and safety data from the day after visit five/week eight through the one-year study visit. Of the 230 participants who completed visit five/week eight, 56 received PEM 1% at visit two/week zero and were subsequently assessed for efficacy at visit five/ week eight and visit ten/one year (one participant of the 57 who completed

visit five/week eight received a non-PEM intervention and was not included in the assessment). At one year after the first study treatment, participants treated with PEM demonstrated consistent, durable, and clinically meaningful improvements in symptoms, as measured by reductions in mean VVSymQ score; appearance, as measured by IPR-V3 (clinician assessment) and PA-V3 (participant self-assessment) scores; disease severity, as measured by the VCSS; and QOL, as measured by the VEINESQOL score. At one year, there were no new venous thrombus adverse events (VTAEs) and no clinically important sequelae in participants who had a VTAE in the study. In addition, there were no serious adverse events that were determined by the investigator to be related to the study drug. No new safety signals were identified. In participants who previously had a VTAE, none had a recurrence of thrombus or evidence of post-thrombotic syndrome at one year. The authors concluded the one-year data for individuals in VANISH-2 showed venous thrombus after treatment with PEM 1% does not result in important clinical sequelae and is clinically manageable.

Endovenous Foam Sclerotherapy for Incompetent Perforator Veins

Evidence in peer review literature evaluating endovenous foam sclerotherapy for the treatment of perforator veins is limited and does not support a benefit compared to established therapies. Future robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this procedure.

Hager et al. (2016) performed 296 perforator ablations on 112 individuals with advanced chronic venous insufficiency comparing ELVA, RFA and UGFS. The study concluded RFA was the most reliable means of perforator closure and was significantly better than UGFS. The 2022 systematic review supporting the Society for Vascular Surgery, the American Venous Forum, and the American Vein and Lymphatic Society guidelines on the management of varicose veins by Farah et al. (2022) did not address the role of perforator incompetence in individuals with venous ulcers. Lloret et al. (2015) conducted an observational cohort study to evaluate wound healing rates and recurrence rates in 180 of individuals with venous leg ulcers treated with UGFS. Forty-eight of the individuals had mixed GSV and perforator reflux, and 38 had isolated perforator reflux. The authors found UGFS of superficial and perforator incompetent veins was well-tolerated and an effective outpatient procedure with a high healing rate and low mid-term recurrence rate. The study was limited by small perforator vein sample size, short-term follow-up, and lack of a comparison group.

Endovenous Mechanochemical Ablation (MOCA)

Evidence in peer review literature evaluating MOCA for the treatment of venous insufficiency and varicose veins is limited. Future robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this procedure.

Bontinis et al. (2023) conducted a systematic review and meta-analysis encompassing 14 studies and 4,177 individuals to evaluate the effectiveness and safety of thermal and nonthermal endovenous ablation techniques for treating superficial venous insufficiency in the lower limbs. The primary endpoints were GSV closure and VCSS improvement; the mean follow-up period was 25.7 months. Radiofrequency ablation (OR, 3.99; 95% CI, 1.82-10.53), cyanoacrylate ablation (CAC) (OR, 3.09; 95% CI, 1.35-8.37), and EVLA (OR, 2.72; 95% CI, 1.23-7.38) displayed increased odds for GSV closure compared with MOCA. Mechanochemical ablation inferiority compared with RFA (MD, 0.96; 95% CI, 0.71-1.20), EVLA (MD, 0.94; 95% CI, 0.61-1.24), and CAC (MD, 0.89; 95% CI, 0.65-1.15) was also depicted regarding VCSS improvement. EVLA resulted in an increased risk of postoperative paresthesia compared with MOCA (RR, 9.61; 95% CI, 2.32-62.29), CAC (RR, 7.90; 95% CI, 2.44-38.16), and RFA (RR, 6.96; 95% CI, 2.31-28.04). Although the overall analysis identified nonstatistical significant differences for AVVQ score improvement, thrombophlebitis, ecchymosis, and pain, further investigation revealed an increase pain profile for EVLA at 1470 nm compared with RFA (MD, 3.22; 95% CI, 0.93-5.47) and CAC (MD, 3.04; 95% CI, 1.05-4.97). A sensitivity analysis displayed a persistent underperformance of MOCA compared with RFA (OR, 4.33; 95% CI, 1.1555.54) for GSV closure and both RFA (MD, 0.99; 95% CI, 0.22-1.77) and CAC (MD, 0.84; 95% CI, 0.08-1.65) regarding VCCS improvement. Although no regression model reached statistical significance, the GSV closure regression model revealed a trend for considerably decreased efficacy for both CAC and MOCA with larger GSV diameters compared with RFA and EVLA. The authors concluded that the results of the study raised doubts on the mid-term effectiveness of MOCA for improving VCSS and achieving GSV closure rates. However, CAC demonstrated comparable results to both RFA and EVLA. Moreover, CAC was associated with a lower risk of postprocedural paresthesia, pigmentation, and induration compared to EVLA and both RFA and CAC had a better pain profile than EVLA. The authors noted that nonthermal, non-tumescent ablation methods for the treatment of large GSVs warrants further investigation. Limitations included the heterogeneity of the studies and limited long-term data.

Lim et al. (2023) conducted a meta-analysis to compare outcomes from RCTs regarding MOCA versus EVTA in the treatment of adult individuals with symptomatic or complicated superficial venous incompetence of CEAP classes two to six. Occlusion rate, QOL, procedural and postprocedural pain, and rates of VTE were the outcomes assessed. Four RCTs were included in the meta-analysis comprised of 654 individuals. The anatomical occlusion rate at one year was lower after MOCA than EVTA (RR 0.85, 95 % CI 0.78 to 0.91; $p < 0.001$). No significant differences were detected in procedural pain (MD -3.25, -14.25 to 7.74; $p = 0.560$) or postprocedural pain (MD -0.63, -2.15 to 0.89; $p = 0.420$). There were no

significant differences in AVVQ score at one year (MD 0.06, -0.50 to 0.62; p = 0.830) or in incidence of VTE (RR 0.72, 95% CI. 0.14 to 3.61; p = 0.690). The authors concluded there was no difference in procedural and postprocedural pain between the interventions but the success rate of occlusion after MOCA was significantly lower than after EVTA. Additionally, the authors noted this study supported existing international guidelines which advocated EVTA as the preferred first-line treatment for superficial venous incompetence in the majority of individuals. The authors stated additional long-term studies are needed to evaluate the impact of reduced vein occlusion rate on QOL and reinterventions. Mohamed et al. (2021) which was previously cited in this policy, is included in this review.

A systematic review and meta-analysis consisting of eight RCTs was conducted by Shahzad et al. (2023) who compared the technical success, complications, and QOL after thermal versus non-thermal EVLA for the treatment of superficial venous incompetence. Vein occlusion rate up to four weeks and one to two years from procedure was the primary outcome. Peri-procedural pain, nerve injury, endothermal heat induced thrombosis, and QOL were the secondary outcomes measured. The study comprised a total of 1956 individuals, EVTA was received by 1042 individuals and 915 underwent endovenous non-thermal ablation. There was no statistically significant difference in occlusion rate at all time points. Relative risk at four weeks and one to two years was 0.99 and 0.95, respectively. Non-thermal ablation was tolerated better and had less risk of nerve injury. There was no statistically significant difference in risk of endothermal heat induced thrombosis. There was improvement in QOL scores post-procedure but there was no statistically significant difference in thermal versus non-thermal ablation. The quality of evidence assessed using GRADE methodology showed high quality for occlusion rate at four weeks and one to two years, moderate quality for nerve injury and peri-procedural pain, and low quality for endothermal heat induced thrombosis. The authors concluded there is no statistically significant difference in vein occlusion rates between thermal and glue ablation of truncal varicose veins, QOL after both thermal and non-thermal endovenous ablation are similar and non-thermal endovenous ablation resulted in less pain and less risk of nerve injury. However, the occlusion rate using MOCA, considered in isolation, is statistically significantly worse than for thermal ablation. Limitations include the impact of stab phlebectomies and compression therapy to endovenous ablation was not explored, the lack of information on differences in heat energy and laser wavelengths used in trials, and individual modalities within each group were not separately evaluated. Bootun et al. (2016), Holewijn et al. (2019), Mohamed et al. (2021), and Vähäaho et al. (2019), which were previously cited in this policy, are included in this review.

A Hayes Health Technology Assessment states MOCA with the ClariVein infusion catheter appears safe and effective over the short-term but the low-quality body of evidence does not allow conclusions to be drawn regarding the long-term durability of the procedure. The report states that MOCA resulted in slightly poorer technical outcomes and higher rates of recanalization than thermal ablation and surgical procedures. The report recommends future well-designed trials with larger sample sizes that compare MOCA using the ClariVein infusion catheter with clinical alternatives with a long-term follow-up. The updated annual review included two newly published studies but recommends no change in the current rating (Hayes, 2022; updated 2024).

In an updated Cochrane review, Whing et al. (2021) compared interventions for treating varicosities of the GSV. The review included 24 RCTs with 5135 participants who underwent EVLA, RFA, EVSA, UGFS, cyanoacrylate glue, MOCA, or high L&S. The authors found there was no clear difference in technical success or recurrence between RFA compared to MOCA, however, long-term data were not available, and the CIs of the combined data were broad, making these findings largely inconclusive. Additionally, the authors noted all the trials had some risk of bias concerns. The authors determined there were a relatively small number of studies for comparison and differences in outcome definitions and time points reported limited their conclusions. Future studies which provide more evidence on the breadth of treatments are recommended by the authors. Bootun et al. (2016), Lane et al. (2017), Holewijn et al. (2019), Vähäaho et al. (2019), which were previously cited in this policy, are included in this review.

Kim et al. (2017) evaluated in a case series whether early efficacy in endovenous MOCA is maintained at 24 months. Individuals with reflux in the GSV involving the SFJ and no previous venous interventions were included. The occlusion rate of treated veins was assessed with duplex ultrasound. Individual clinical improvement was assessed by CEAP class and VCSS. Of the initial 126 individuals, there were 65 individuals with 24-month follow-up. Of these 65 individuals, 70% were female, with a mean age of 70 ±14 years and an average BMI of 30.5 ±6. The mean GSV diameter in the upper thigh was 7.6 mm and the mean treatment length was 39 cm. Adjunctive treatment of the varicosities was performed in 14% of individuals during the procedure. Closure rates were 100% at one week, 98% at three months, 95% at 12 months, and 92% at 24 months. There was one individual with complete and four with partial recanalization ranging from seven to 12 cm (mean length 9 cm). There was significant improvement in CEAP and VCSS ($p < .001$) for all time intervals. Early high occlusion rate with MOCA is associated with significant clinical improvement, which was maintained at 24 months. According to the authors, this finding is suggestive of a good option for the treatment of GSV incompetence. Longer-term outcomes are needed to evaluate MOCA's efficacy. The study is limited by lack of comparison group and large loss to follow-up.

Vos et al. (2017) conducted a systematic review and meta-analysis to evaluate the efficacy of MOCA and cyanoacrylate vein ablation (CAVA) for GSV incompetence. Eligible articles were prospective studies that included individuals treated for GSV incompetence and described the primary outcome. Exclusion criteria were full text not available, case reports, retrospective studies, small series (n < 10), reviews, abstracts, animal studies, studies of SSV incompetence, and recurrent GSV incompetence. Primary outcome was anatomic success. Secondary outcomes were initial technical success, VCSS, AVVQ score, and complications. Fifteen articles met the inclusion criteria. Pooled anatomic success for MOCA and CAVA was 94.7% and 94.8% at six months and 94.1% and 89.0% at one year, respectively. VCSS and AVVQ score significantly improved after treatment with MOCA and CAVA. The authors conclude that both of these non-thermal techniques are promising that could serve as alternatives for thermal ablation techniques. However, to determine their exact role in clinical practice, high-quality RCTs comparing these novel modalities with well-established techniques are required. This study is limited by inclusion or mostly uncontrolled studies to assess the efficacy and safety of MOCA. Elias and Raines (2012) and Bishawi et al. (2014), which were previously cited in this policy, are included in this meta-analysis.

Witte et al. (2017a) conducted a systematic review and meta-analysis of MOCA of saphenous veins using the ClariVein to report on the anatomical, technical, and clinical success. The literature search identified 759 records, of which 13 were included, describing 10 unique cohorts. A total of 1521 veins (1267 GSV and 254 SSV) were included, with cohort sizes ranging from 30 to 570 veins. The pooled anatomical success rate after short-term follow-up was 92% (95% CI 90-94%) (n = 1314 veins). After six and 12 months these numbers were 92% (95% CI 88-95%) (n = 284) and 91% (95% CI 86-94%) (n = 228), respectively. The long-term anatomical success rates at two and three years were 91% (95% CI 85-95%) (n = 136) and 87% (95% CI 75-94%) (n = 48), respectively. Major complications and especially nerve injury were very rare (≤ 0.2%). All studies were of moderate or good quality using the methodological index for non-randomized studies (MINORS) scoring scale. The authors concluded that MOCA using the ClariVein in combination with liquid sclerosant is associated with an anatomical success rate ranging from 87% to 92% and good clinical success. However, they reported that no RCTs are available studying the anatomical success after MOCA compared to the endothermal ablation.

Witte et al. (2017b) reported midterm results of MOCA for treating GSV insufficiency. In a one-year period, 85 consecutive individuals undergoing MOCA with polidocanol in 104 limbs were enrolled in a prospective registry. The individuals were evaluated at baseline and during follow-up (four weeks and one, two, and three years) using duplex ultrasound, the CEAP classification, the VCSS, the RAND Short Form 36-Item Health Survey (RAND-SF36), and the AVVQ. Primary outcome measures were clinical and anatomic success. Secondary outcome measures included general and disease-specific QOL and re-interventions. After a median follow-up of 36 months (IQR12.5, 46.3), recanalization occurred in 15 (15%) of 102 successfully treated vein segments. Anatomic success was 92%, 90%, and 87% after one, two, and three years, respectively. The VCSS improved at all time intervals compared to the preprocedural median. The clinical success at three years was 83%. The AVVQ and RAND-SF36 scores showed an improvement at all time intervals compared to baseline values. Between 12 and 36 months, however, a significant deterioration was observed in VCSS, which was accompanied by worsening of disease-specific and general QOL. Although the authors concluded that MOCA demonstrated to be an effective treatment modality for GSV insufficiency at midterm follow-up, clinical results seemed to drop over time. Additionally, these findings are limited by lack of comparison group undergoing a different treatment.

In a pilot study, van Eekeren et al. (2011) evaluated the feasibility and safety of endovenous MOCA for the treatment of GSV incompetence. Thirty limbs in 25 individuals (18 women; mean age 52 years) with GSV incompetence were treated with the ClariVein® device. Initial technical success, complications, patient satisfaction, and classification by VCSS) were assessed 6 weeks after the treatment. Initial technical success of MOCA was 100%. There were no major adverse events. Duplex ultrasonography at six weeks showed 26 (87%) of 30 veins were completely occluded. Three veins showed partial recanalization in the proximal and distal GSV. One individual had full segment recanalization and was successfully retreated. The VCSS significantly improved at six weeks. Patient satisfaction was high, with a median satisfaction of 8.8 on a zero to 10 scale. The authors concluded that endovenous MOCA is feasible and safe in the treatment of GSV incompetence. Larger studies with a prolonged follow-up are indicated to prove the efficacy of this technique. This study is limited by lack of comparison group undergoing a different treatment approach.

VenoValve

Evidence in peer review literature evaluating VenoValve porcine bioprosthetic valve for the treatment of chronic venous insufficiency is limited. Future robust RCTs are warranted along with long-term outcomes to establish the safety and efficacy of this procedure.

A 2022 Hayes Emerging Technology Report states published evidence is limited to publications reporting six-month and one-year outcomes for 11 individuals. The VenoValve will be the first porcine bioprosthetic valve to reach the market in the U.S., and the first device approved to treat chronic venous insufficiency, if eventually FDA-approved. VenoValve is currently under investigation in the Surgical Anti-Reflux Venous Valve Endoprosthesis (SAVVE) trial (NCT04943172). The

updated 2024 Hayes report states the estimated time to commercial availability is less than one to two years. However, the device is not yet FDA approved.

Ulloa and Glickman (2021) conducted a single-center, prospective, non-randomized, first-in-human trial using a prosthetic venous valve, VenoValve, for participants with severe chronic venous insufficiency (C4b-C6 disease). Ten participants had the prosthetic valve surgically implanted into the femoral vein. Follow-up examinations were conducted postoperatively at two and 14 days and then every 30 days for six months to evaluate feasibility, initial safety, and performance outcomes of the VenoValve. Six participants had required bovine patch angioplasty of the vein. Four adverse events occurred, including one case of hematoma at the incision site that was aspirated, two cases of superficial wound infection in C6 participants treated with antibiotics, and one case of a bleeding complication due to warfarin anticoagulation. One participant's VenoValve had thrombosed at five months due to nontherapeutic anticoagulation. Improvements in all five participants who had reached the six-month follow-up mark with the VenoValve were demonstrated during the study period by decreases in the VCSS (61% decrease from baseline), visual analog scale for pain scores (57% decrease), and reflux time (40% decrease) and a statistically significant improvement in the VEINES-QOL/Sym questionnaire. The participant with the occluded VenoValve had experienced improvements in all areas except for the reflux time. The authors concluded that VenoValve showed promising results with improvements noted in QOL and clinical outcomes. The authors recommended further follow-up and larger studies in the future. In 2022, Ulloa and Glickman reported promising one-year post-implantation results. Adverse events included one hematoma, three superficial wound infections, and one bleeding complication due to over-anticoagulation. One VenoValve became occluded due to participant non-compliance with anticoagulation medication. One-year clinical outcomes included significant decreases in mean reflux times (54%), and significant improvements in mean disease severity rVCSS (56%), mean visual analog scale pain scores (76%), and VEINES-QOL/Sym scores. Ulloa et al. (2023) reported on two-year follow-up results aimed to evaluate the long-term clinical safety and performance of the eleven participants who were implanted with the VenoValve into the midthigh femoral vein. All eleven implant procedures were successful. Two-year follow-up data was obtained for eight subjects: one participant died of non-device related causes, one was lost to follow-up, and one refused to follow-up due to the COVID-19 pandemic. No device-related adverse events occurred between the first and second years of follow-up. Reported two-year clinical performance outcomes included significant decreases in mean reflux times of the mid-popliteal vein (61%), and significant improvements in mean scores for disease severity revised VCSS (56%) and VAS pain (87%). The authors surmised the long-term safety and performance of the VenoValve was sustained as the participants obtained wound healing without ulcer recurrence. Additionally, there were significant improvements in reflux time, disease severity, pain scores and diagnosis were reclassified from severe to mild disease. The authors endorse continued long-term follow-up, future larger, multi-center studies, and note the clinical trial NCT04943172 currently underway.

Clinical Practice Guidelines

American Vein and Lymphatic Society (AVLS)

Vasquez et al. (2024) developed a position statement with recommendations for the appropriate use of cyanoacrylate endovenous ablation for individuals with venous insufficiency. The position statement noted that CAC has been employed off-label as a non-thermal method to close pathologic perforator veins, showing a good efficacy and safety profile. While CAC was originally designed and approved exclusively for catheter-directed procedures, expert clinicians have expanded its use beyond these intended applications. Despite the promising outcomes observed, additional evidence is necessary to fully validate this broader approach.

European Society for Vascular Surgery (ESVS)

The ESVS released a guideline for management of CVD (De Maeseneer et al., 2022). The guidelines state that for patients with GSV and SSV incompetence requiring treatment, EVTA is recommended as the first-choice treatment, in preference to high L&S and UGFS. However, UGFS may be considered for treating saphenous trunks with a diameter less than six mm. The guidelines note that in long-term follow-up of comparative studies, treatment with UGFS has been substantially less effective than EVLA, RFA, and surgery in terms of occlusion or absence rates. Additionally, foam sclerotherapy is the technique of choice for anatomical configurations that make endovenous cannulation or advancing the ablation device challenging, and is suitable for treating tortuous, recurrent varicose veins. Cyanoacrylate adhesive closure may be considered when a non-thermal technique is preferred for patients with GSV incompetence. For patients with GSV incompetence, high L&S should be considered, if EVTA options are not available. For patients with CVD requiring treatment of incompetent perforating veins, endovenous ablation, division or ligation should be considered. Endovenous non-thermal non tumescent ablation methods may be considered for treatment of SSV incompetence. Additionally, EVTA and UGFS may be considered for anterior accessory saphenous vein requiring treatment.

National Institute for Health and Care Excellence (NICE)

In 2020, NICE released an update to their guidance on Cyanoacrylate Glue Occlusion for Varicose Veins. The updated guidance states that current evidence on the safety and efficacy of cyanoacrylate glue occlusion for varicose veins is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit. In addition, the guideline states physicians should: 1) only perform the procedure after appropriate training and experience in the use of venous ultrasound; 2) discuss the available options with the patient before making a decision; and 3) follow their hospital's policies regarding performing procedures and monitoring results.

In an updated guideline on endovenous MOCA for varicose veins, NICE (2016) states that current evidence on the safety and efficacy of endovenous MOCA for varicose veins appears adequate to support the use of this procedure provided that standard arrangements are in place for consent, audit, and clinical governance. Clinicians are encouraged to collect longer-term follow-up data.

The NICE 2013 interventional procedure guidance on UGFS specifies that if symptoms related to varicose veins are severe, the main treatment options include endovenous laser treatment, RFA, and surgery (L&S of the GSVs or ligation with or without stripping of the SSVs, and phlebectomy). The NICE 2013 clinical guideline on the diagnosis and treatment of varicose veins adds that if endovenous ablation is unsuitable, offer UGFS.

Society for Vascular Surgery (SVS)/American Venous Forum (AVF)/American Vein and Lymphatic Society (AVLS)/Society of Interventional Radiology (SIR)

Gloviczki et al. 2023 published Part II of the guidelines for the management of varicose veins of the lower extremities which focuses on patients with compression, treatment with drugs and nutritional supplements, evaluation and treatment of varicose tributaries, superficial venous aneurysms, and on the management of complicated varicose veins. Recommendations of the guideline are summarized as follows (not all-inclusive):

- In symptomatic patients with C2 disease suggestion is made against using truncal vein diameter to determine which patients need venous ablation. Grade of recommendation, two (weak), quality of evidence, B (moderate).
- For patients with symptomatic telangiectasias and reticular veins, sclerotherapy with liquid or foam is recommended. Grade of recommendation, one (strong), quality of evidence, B (moderate).
- For treatment of symptomatic varicose tributaries, miniphlebectomy or ultrasound-guided sclerotherapy using PCF or PEM is recommended. Grade of recommendation, one (strong), quality of evidence, B (moderate).
- For patients with symptomatic reflux in the GSV or SSV and associated varicosities, ablation of the refluxing venous trunk and concomitant phlebectomy or UGFS of the varicosities with PCF or PEM is recommended. Grade of recommendation, one (strong), quality of evidence, C (low to very low).
- For patients with symptomatic reflux in the AAGSV or PAGSV, suggestion is made for simultaneous ablation of the refluxing venous trunk and phlebectomy or UGFS of the varicosities with PCF or PEM. Grade of recommendation, two (strong), quality of evidence, C (low to very low).
- For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the GSV or SSV, recommendation is made against treatment of incompetent perforating veins concomitant with initial ablation of the saphenous veins. Grade of recommendation, one (strong), quality of evidence, C (low to very low).
- For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the AAGSV or PAGSV, suggestion is made against treatment of incompetent perforating veins concomitant with initial ablation of the superficial truncal veins. Grade of recommendation, two (weak), quality of evidence, C (low to very low).
- For patients with incompetent pathologic perforators associated with symptomatic residual, recurrent, and rarely primary varicosities, without associated saphenous incompetence, either open or endovascular techniques can be used to treat the perforator veins. Consensus statement.
- In symptomatic patients with varicose veins (CEAP Class C2), the deep venous system should be routinely evaluated for infrainguinal obstruction or valvular incompetence. Consensus statement.

The SVS, AVF, and AVLS collaborated to update the 2011 SFS/AVF guideline to provide evidence-based recommendations for treating patients with varicose veins of the lower limbs (Gloviczki. et al., 2022). Recommendations of the guideline are summarized as follows (not all-inclusive):

- For patients with CVD of the lower extremities, duplex ultrasound scanning is the diagnostic test of choice for evaluation of venous reflux. Level of recommendation: grade one (strong), quality of evidence: B (moderate).
- Reflux is defined as a minimum value > 500 ms of reversed flow in the superficial truncal veins (GSV, SSV, AAGSV, PAGSV) and the tibial, deep femoral, and perforating veins. Level of recommendation: ungraded good practice statement.
- Axial reflux is defined as uninterrupted retrograde venous flow from the groin to the calf, and junctional reflux is limited to the SFJ or SPJ. Level of recommendation: ungraded good practice statement.

- Use of the 2020 upgraded CEAP classification of chronic venous disorders is recommended. Level of recommendation: ungraded good practice statement.
- "Pathologic" perforating veins in patients with varicose veins (CEAP clinical class C2) includes those with an outward flow duration of ≥ 500 ms and a diameter of ≥ 3.5 mm on duplex ultrasound. Level of recommendation: ungraded good practice statement.
- For patients with symptomatic varicose veins and axial reflux in the GSV and SSV, treatment with endovenous ablation over high L&S is recommended due to less post procedure pain and morbidity, and an earlier return to regular activity; if the technology or expertise in endovenous ablation is not available or the venous anatomy precludes endovenous treatment, L&S is recommended. Level of recommendation: grade 1 (strong), quality of evidence: GSV = B (moderate), SSV = C (low to very low).
- For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, treatment with L&S of the accessory saphenous vein, with additional phlebectomy, if needed, if technology or expertise in endovenous ablations is not available or if the venous anatomy precludes endovenous treatment is suggested. Level of recommendation: grade 2 (weak), quality of evidence: C (low to very low).
- For patients with symptomatic varicose veins and axial reflux in the GSV, SSV, who place a high priority on the long-term outcomes of treatment (QOL and recurrence), treatment with EVLA, RFA, or high L&S (L&S for SSV) over physician-compounded UGFS is suggested. Level of recommendation: grade 2 (weak) quality of evidence: GSV = B (moderate), SSV = C (low to very low).
- For patients with symptomatic axial reflux, both thermal and nonthermal ablation of the GSV from the groin to below the knee, are recommended depending on the available expertise of the treating physician and the preference of the patient. Level of recommendation: grade 1 (strong), quality of evidence: B (moderate).
- For patients with symptomatic axial reflux, both thermal and nonthermal ablation of the SSV from the knee to the upper or mid-calf, are recommended depending on the available expertise of the treating physician and the preference of the patient. Level of recommendation: grade 1 (strong), quality of evidence: C (low to very low).
- For patients with symptomatic axial reflux of the AAGSV or PAGSV, suggested treatment is either thermal or nonthermal ablation, with additional phlebectomy, if needed, depending on the available expertise of the treating physician and the preference of the patient. Level of recommendation: grade 2 (weak), quality of evidence: C (low to very low).
- For patients with varicose veins (C2) and persistent or recurrent symptoms after previous complete ablation of incompetent superficial truncal veins, treatment of incompetent perforator veins if they are the origin of symptomatic varicose tributaries is suggested. Level of recommendation: grade 2 (weak), quality of evidence: C (low to very low).
- In patients with symptomatic reflux in the GSV, SSV, AAGSV, or PAGSV, ablation of the refluxing venous trunk, and staged or UGFS of the varicosities is recommended only if anatomic or medical reasons are present. Level of recommendation: grade 2 (weak); quality of evidence: C (low to very low).

The SVS, AVF, AVLS, and SIR developed the Appropriate Use Criteria (AUC) for chronic lower extremity venous disease using the RAND/UCLA Appropriateness Method incorporating best available evidence with expert opinion and engaging a panel of experts in the field through a modified Delphi exercise (Masuda et al., 2020). One hundred and nineteen scenarios were rated on a scale of one to nine by an expert panel, with one being never appropriate and nine being appropriate. The panelists rated ablation for axial reflux of the GSV, with or without SFJ reflux, in symptomatic patients, CEAP classes two to six as appropriate. Per the AUC, when accompanied by no SFJ reflux (the junction is either assumed or proven to be competent or previously interrupted and communicates with the GSV through incompetent thigh perforators or other sources of collateral flow) the remaining refluxing GSV may be the source of recurrent symptoms. Therefore, for axial GSV reflux, ablating the GSV will likely lead to decreased recurrence even if the SFJ shows no reflux. The mean number of saphenous vein ablations per person ranges from 1.3 to 1.9. However, occasionally, treatment requiring three or more ablations in a limb is needed. Additionally, treatment of perforator veins with high outward flow and large diameter directed toward affected area in a symptomatic patient with skin or subcutaneous changes, healed or active ulcers (CEAP classes 4-6) is considered appropriate. The authors note that the AUC statements were intended to serve as a guide to patient care, particularly in areas where high quality evidence is lacking and was not meant to be a guide that addresses all clinical situations.

The SVS and AVF released a joint guideline regarding the care of patients with venous leg ulcers (O'Donnell et al., 2014). Recommendations of the guideline are summarized as follows (not all-inclusive):

- For patients with a venous leg ulcer (C6), and incompetent superficial veins that have reflux to the ulcer bed in addition to pathological perforating veins (> 500 ms reflux duration and diameter of > 3.5 mm), that are located beneath or associated with the ulcer bed, the guideline suggests ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and prevent recurrence. (Grade - 2; level of evidence - C).

- For patients who have a healed venous ulcer (C5), and have axial reflux directed to the bed of the affected ulcer, the guidelines recommend ablation of the incompetent superficial veins in addition to standard compressive therapy. (Grade - 1; level of evidence - C).
- For patients who are at risk for a venous leg ulcer (C4b) and have axial reflux directed to the bed of the affected skin, the guidelines suggest ablation of the incompetent superficial veins in addition to standard compressive therapy. (Grade - 2; level of evidence - C).
  For those patients who would benefit from pathologic perforator vein ablation, the guideline recommends treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or EVTA (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin. (Grade - 1; level of evidence - C).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Vein Ligation surgery is a procedure and therefore not subject to FDA regulation.

The ClariVein® infusion catheter (Vascular Insights) received FDA approval (K071468) on March 20, 2008. The device is designed to introduce physician-specified medicaments into the peripheral vasculature. Refer to the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf7/K071468.pdf. (Accessed January 10, 2025)

The U.S. Food and Drug Administration (FDA) has approved various sclerosing agents to treat Varicose Veins of the lower extremities. Two most commonly used include sodium tetradecyl sulfate and polidocanol. Asclera® (polidocanol) is a sclerosing agent approved by the FDA in March 2010 and is indicated to treat small spider veins and uncomplicated reticular veins (Varicose Veins one to three mm in diameter) in the lower extremity. It has not been studied in Varicose Veins larger than three mm in diameter.
https://www.accessdata.fda.gov/dru5satfda_docs/nda/2010/021201s000_Medr.pdf. (Accessed January 10, 2025)

Varithena (polidocanol injectable foam) (Provensis Ltd.) received FDA approval on November 25, 2013, as a sclerosing agent indicated for the treatment of incompetent GSVs, accessory saphenous veins and visible varicosities of the GSV system above and below the knee. Refer to the following websites for more information:
- https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/205098Orig1s000ltr.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205098s000lbl.pdf

(Accessed January 10, 2025)

The VenaSeal™ Closure System received the FDA's pre-market approval (PMA) on February 20, 2015 (P140018). The device is indicated for the permanent closure of lower extremity superficial truncal veins, such as the GSV, through endovascular embolization with coaptation. VenaSeal is intended for use in adults with clinically symptomatic venous reflux as diagnosed by duplex ultrasound. Refer to the following website for more information:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140018. (Accessed January 10, 2025)

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Policy History/Revision Information

Date	Summary of Changes

07/01/2025	**Coverage Rationale**
	• Removed language indicating:
	  ○ Ligation, subfascial, endoscopic surgery for treatment of perforating veins associated with chronic Venous Insufficiency is proven and medically necessary in certain circumstances; for medical necessity clinical coverage criteria, refer to the InterQual® CP: Procedures, Ligation, Subfascial, Endoscopic, Perforating Vein
	  ○ Ambulatory phlebectomy for treating Varicose Veins is proven and medically necessary in certain circumstances; for medical necessity clinical coverage criteria, refer to the InterQual® CP: Procedures, Ambulatory Phlebectomy, Varicose Vein for hook phlebectomy, microphlebectomy, mini phlebectomy, stab avulsion, or stab phlebectomy
	  ○ Endovascular embolization of Varicose Veins using cyanoacrylate-based adhesive is unproven and not medically necessary for treating Venous Reflux
	Thermal and Non-Thermal Treatments for Venous Insufficiency and Varicose Veins
	• Added language to indicate ablation of incompetent perforator veins using endovenous foam Sclerotherapy and/or cyanoacrylate-based adhesive is unproven and not medically necessary due to insufficient evidence of efficacy
	• Replaced language indicating:
	  ○ "The initial and subsequent radiofrequency ablation, endovenous laser ablation, Stripping, Ligation, and excision of the Great Saphenous Vein (GSV) and Small Saphenous Veins (SSV) are considered reconstructive, *proven*, and medically necessary when all of the [listed] criteria are *present*" with "the initial and subsequent *treatment* of the GSV, SSV, and *Accessory Veins with* radiofrequency ablation, endovenous laser ablation, Stripping *with* Ligation and excision, *endovenous foam Sclerotherapy, and/or cyanoacrylate-based adhesive* are considered reconstructive and medically necessary when all of the [listed] criteria are *met*"
	  ○ "Duplex ultrasound *readings will* describe [greater than or equal to 500 milliseconds (ms) for the GSV, SSV, or *principal tributaries*] as moderate to severe reflux which will be acceptable" with "duplex ultrasound *interpretations may* describe [greater than or equal to 500 milliseconds (ms) for the GSV, SSV, or *Accessory Veins*] as moderate to severe reflux which will be acceptable"
	  ○ "Ablation of perforator veins is considered reconstructive, *proven*, and medically necessary when the [listed] criteria are *present*" with "ablation of *incompetent* perforator veins *using radiofrequency ablation or endovenous laser ablation* is considered reconstructive and medically necessary when *all of* the [listed] criteria are *met*"
	• Revised coverage criteria:
	GSV, SSV, and Accessory Veins
	  ○ Replaced criterion requiring "duplex ultrasound study performed in the standing or reverse Trendelenburg position that shows duration of reflux that is greater than or equal to 500 milliseconds (ms) for the GSV, SSV, or *principal tributaries*" with "duplex ultrasound study performed in the standing or reverse Trendelenburg position that shows duration of reflux that is greater than or equal to 500 milliseconds (ms) for the GSV, SSV, or *Accessory Veins*"
	Incompetent Perforator Veins
	  ○ Added criterion requiring "[the incompetent perforator veins are] not secondary to acute deep vein thrombosis"
	  ○ Replaced criterion requiring:

Date	Summary of Changes
	▪ "Evidence of perforator Venous Insufficiency measured by recent Duplex *Ultrasonography report*" with "evidence of perforator Venous Insufficiency measured by recent duplex *ultrasound study performed in the standing or reverse Trendelenburg position*" ▪ "Perforating veins **>** 500 ms" with "perforating vein *reflux of* 500 ms *or greater*" **Medical Records Documentation Used for Review** • Updated list of Medical Records Documentation Used for Reviews: ○ Added examples of validated functional disability scales: ▪ Venous Clinical Severity Score (VCSS) ▪ Venous Disability Score (VDS) ○ Removed: ▪ History of prior treatment complications (e.g., recurrent bleeding or significant hemorrhage), including the dates of occurrence ○ Replaced: ▪ "History of the medical condition(s) requiring treatment or surgical intervention, *or relevant medical history*, including DVT (deep vein thrombosis), aneurysm, and tortuosity *or history of* previous relevant vein procedure(s), *if applicable*" with "history of the medical condition(s) requiring treatment or surgical intervention, including DVT (deep vein thrombosis), aneurysm, tortuosity, and previous relevant vein procedure(s)" ▪ "Prior *non-invasive* treatments *of the veins* that have been tried/failed or contraindicated; include the dates, duration, and reason for discontinuation" with "prior therapies/treatments that have been tried, failed, or were contraindicated; include the dates, duration, reason for discontinuation, and *complications [e.g., recurrent bleeding or significant hemorrhage, DVT or superficial vein thrombosis (SVT) etc.]*" **Definitions** • Added definition of: ○ Superficial Vein ○ Telangiectasias/Spider Veins ○ Tributary Vein • Removed definition of: ○ Cosmetic Procedures ○ Reconstructive Procedures ○ Reticular Vein ○ Spider Vein ○ Superficial Thrombophlebitis • Updated definition of: ○ Accessory Vein ○ Great Saphenous Vein ○ Sclerotherapy ○ Small Saphenous Vein **Applicable Codes** • Removed CPT codes 37500, 37765, 37766, and 37799 • Updated coding notations: ○ Added instruction to refer to CPT code 36465 or 36466, per AMA coding guidance, if the targeted vein is an extremity truncal vein and injection of non-compounded foam sclerosant with ultrasound guided compression maneuvers to guide dispersion of the injectate is performed ○ Removed notation pertaining to CPT code 37241 ○ Replaced notation indicating: ▪ "CPT code 36468 for sclerosant treatment for spider veins is considered cosmetic" with "CPT code 36468 for sclerosant treatment for spider veins/*telangiectasias* is considered cosmetic" ▪ "CPT codes *36465, 36466,* 36470, and 36471 are covered for sclerotherapy up to three sessions per leg within a year" with "CPT codes 36470 and 36471 are covered for sclerotherapy *(non-truncal, non-telangiectasia)* up to three sessions per leg within a year" **Supporting Information**

Date	Summary of Changes
	• Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version 2025T0447PP

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare c overage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.