Selected treatments for varicose veins

Draft evidence report

February 24, 2017
Selected Treatments for Varicose Veins

A Health Technology Assessment

Prepared for Washington State Health Care Authority

DRAFT REPORT

February 24, 2017

Acknowledgement

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List of Abbreviations

AGREE – Appraisal of Guidelines Research and Evaluation tool

CEAP – Clinical, Etiologic, Anatomic, Pathophysiologic

CHIVA – Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire

CVD – chronic venous disease

CVI – chronic venous insufficiency

DVT – deep vein thrombosis

EVLAs – endovenous laser ablation

FDA – Food and Drug Administration

FS – foam sclerotherapy

GSV – great saphenous vein

HL&S or HL/S – high ligation and stripping

HTA – health technology assessment

L&S or L/S – ligation and stripping

PICOS – population, intervention, comparator, outcomes, setting

RCT(s) – randomized controlled trial(s)

RF – radiofrequency

RFA – radiofrequency ablation

SFJ – saphenofemoral junction

SPJ – saphenopopliteal junction

SR – systematic review

SSV – small saphenous vein

STS – sodium tetradecyl sulfate

UGFS – ultrasound-guided foam sclerotherapy

VCSS – Venous Clinical Severity Score
EVIDENCE SUMMARY

The EVIDENCE SUMMARY provides background information, the methods and search results for this report, findings with respect to the Key Questions, and payer policies and practice guidelines. The EVIDENCE SUMMARY also includes conclusions and an assessment of the quality of the evidence for each Key Question. In general, references are not cited in the EVIDENCE SUMMARY. The EVIDENCE SUMMARY ends with an Overall Summary and Discussion. The TECHNICAL REPORT provides additional detail, with full citation, regarding background information, study results, and payer policies and guidelines, but does not include conclusions or quality assessment.

Summary of Clinical Background

Varicose Veins

Varicose veins, also known as varicosities, are a common manifestation of chronic venous insufficiency (CVI), a category of chronic venous disease (CVD). CVD of the lower extremities is typically classified based on symptoms and using the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) categories C₀–C₆. Varicose veins are in the C₂ category, and can be further described by characteristics from the other categories within the classification scheme. The prevalence of varicose veins is estimated to be from 5% to 30% in the adult population. Varicose veins are enlarged and tortuous vessels (≥ 3 millimeters [mm] in diameter) that develop when the thin flaps of the venous valves no longer meet in the midline, allowing blood to reflux, or flow backwards. Approximately 25 million adults in the United States are affected by varicose veins. Great saphenous vein (GSV) reflux, a frequent form of CVI, is most commonly responsible for the development of varicose veins and is often the result of reflux through the valve at the junction between the GSV and the common femoral vein. Although reflux is more prevalent in the GSV, reflux in the small saphenous vein (SSV) also occurs in approximately 6% to 15% of patients with CVI.

Risk factors include older age, a family history of the condition, obesity, pregnancy, inactivity, and prolonged standing or sitting. Often, varicose veins initially present only a cosmetic concern, but they can become clinically important when symptoms such as cramping, throbbing, burning, swelling, feeling of heaviness or fatigue, and alterations in skin pigmentation in the afflicted area become pronounced. Severe varicosities may be associated with dermatitis, ulceration, and thrombophlebitis, which result when metabolic waste products are no longer removed due to pooling of venous blood and increased hydrostatic pressure.

Conservative treatments for symptomatic varicose veins of the legs include compression hosiery, elevating the legs, walking, and weight management. Surgical ligation and excision (vein stripping) or
minimally invasive procedures (e.g., sclerotherapy, endovenous laser ablation [EVLA], and endovenous radiofrequency ablation [RFA]) may be employed to destroy or remove affected vessels. Traditional open techniques have been associated with postoperative morbidity, including complications from groin incisions, pain, scarring, and long recovery periods. Techniques such as sclerotherapy and endoluminal occlusion using radiofrequency or laser light energy are also used for the treatment of varicose veins due to GSV, SSV, or saphenofemoral junction (SFJ) reflux. These may reduce postoperative morbidity and improve recovery time compared with conventional surgical options, but are also associated with some complications. For example, complications associated with endovenous thermal ablation techniques (laser and radiofrequency [RF]) include hematoma, thrombophlebitis, venous thrombosis, vessel perforation, thermal injury to adjacent nerves, skin burns, and discoloration. Regardless of treatment, patients often experience a recurrence and repeated treatment may be necessary.

EVLA, RFA, sclerotherapy, and ambulatory phlebectomy compared with ligation with or without vein stripping are the focus of this technology assessment.

**Endovascular Laser Ablation**

EVLA is the removal or destruction of a vein or vein segment by means of laser. It involves the delivery of laser light through a glass fiber placed into the lumen of a refluxing vein. The goal of EVLA is to use laser energy to seal off the damaged portions of varicose veins to prevent further varicose vein formation, eliminate associated discomfort, and improve cosmetic appearance. This therapy is intended primarily for the treatment of varicose veins that result from GSV, SSV, or accessory vein reflux. Compression stockings are worn for 1 to 2 weeks after the procedure and normal activity is encouraged. The procedure can be repeated if the treated vessel is not occluded after 7 days. EVLA may not be suitable or contraindicated in select patients who are pregnant, have extremely tortuous great or small saphenous veins that would prevent catheterization and passage of laser fiber, have peripheral inflammatory artery disease, have a history of deep vein thrombosis (DVT) or deep venous insufficiency, exhibit nonpalpable pedal pulses, or in patients who have difficulty walking.

**Radiofrequency Ablation**

RFA is the removal or destruction of a vein or vein segment by means of RF energy. Endoluminal RFA is a treatment for symptomatic varicose veins that involves delivery of controlled RF energy through a catheter inserted into the affected vein. The heat generated by the RF energy causes the vein to contract and become occluded. The treatment is intended as a minimally invasive alternative to standard surgery for symptomatic varicosities. Contraindications for endovenous RFA include presence of a pacemaker or internal defibrillator, aneurysmal section in the vein segment for which the treatment is intended, and peripheral arterial disease as determined by an ankle-brachial index < 0.9.

**Sclerotherapy**

Sclerotherapy is obliteration of a vein or vein segment by chemical introduction (liquid or foam). The solution or sclerosant causes the vein to scar closed, prohibiting the flow of blood through the occluded vein. The affected vein is converted into a thread of fibrous connective tissue and absorbed into the body over time. This therapy is intended for primary and secondary treatment in adults with varicose
veins that result from GSV, SSV, or accessory vein reflux. The goals of sclerotherapy for varicose veins are improved function, symptoms, and appearance, and reducing complications associated with varicose veins. Food and Drug Administration (FDA)-approved sclerosing agents include polidocanol and sodium tetradecyl sulfate (STS). Liquid sclerotherapy is more commonly used for telangiectasia and reticular veins or small to medium varicose veins; foam sclerotherapy (FS) may be used for larger refluxing veins. According to a local coverage determination document issued by Noridian Healthcare Solutions LLC, FS is FDA indicated for the treatment of incompetent GSVs, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee. FS products are administered under ultrasound (US) guidance via cannulation of the affected veins with the use of local anesthesia. After injection, spasm of the vein segment is confirmed by US before an additional injection. Multiple treatments sessions may be needed depending on the extent and severity of the condition. After treatment, compression bandages or stockings are worn for several days. Contraindications include allergies to sclerosants, severe systemic disease, acute superficial or DVT, local infection in the area to be treated or severe generalized infections, immobility, confinement to bed, advanced arterial occlusive disease, and known symptomatic patent foramen ovale. Sclerotherapy should not be used during pregnancy. Other factors to consider include leg edema, uncontrolled diabetes, delayed complications after diabetes, mild arterial occlusive disease, poor general health, bronchial asthma, marked allergic diathesis, history of anaphylaxis, hypercoagulability syndromes, bleeding disorders, and a history of DVT.

Ambulatory Phlebectomy
Ambulatory phlebectomy is the removal of a vein segment through small incisions (1 to 3 mm) with the aid of instruments such as a vein retractor or phlebectomy hook. The procedure is usually done as an outpatient procedure using local anesthesia. Indications for this technique are side branch varicose veins, and varicose veins of the foot, around the ankle, and the knee pit. Generally, incisions are small enough to not require closure with sutures. Post-procedure care includes dressings and anti-inflammatory pain medication if needed. Patients are allowed to walk immediately following the procedure. Return to work and normal activities is usually within a day or so and depends on the extent of the phlebectomy. Ambulatory phlebectomy may be performed in conjunction with other techniques such as RFA, EVLA, or surgical stripping. Adverse events such as phlebitis, inflammation, numbness, or hypersensitivity can occur. Warm compresses and anti-inflammatories may be used to address phlebitis or inflammation, and any numbness or sensitivity usually goes away.

Vein Ligation and Stripping
Vein ligation and stripping, or closing off a vein and removing it, is the traditional method of surgical management of GSV and SSV varices. Variations of the procedure exist, including ligation without stripping. In general, the technique involves making an incision at either the SFJ or the popliteal fossa, depending on whether the GSV or SSV is the target of the treatment and another incision lower in the leg. In the case of GSV varices, the procedure involves saphenofemoral ligation and stripping of the GSV to the knee; this is known as high ligation and stripping. Surgical management of SSV varices involves disconnecting the saphenopopliteal junction (SPJ) and either cutting away or stripping a segment of the SSV. Different methods of stripping have been employed; a common method is the use of a metal probe or wire inserted at the lower incision and threaded to the upper end of the target vein. The wire is tied
to the vein and retracted through the lower incision, bringing the vein with it. Open surgical procedures are associated with adverse effects such as hematomas, pain, nerve injury, scarring, long recovery periods, and complications such as infection at the groin incision site. Also, the risk of recurrence of varicose veins within 5 years is considered high.

Policy Context

This topic was selected for review through the Washington State Health Technology Assessment program. State agencies in Washington that purchase healthcare identify topics and evaluate potential topics based on concerns related to safety, efficacy, and cost-effectiveness. A variety of treatments for varicose veins are available. Treatment goals include reducing pain or discomfort and for cosmetic reasons. Participating agencies identified this topic based on uncertainties related to the safety, efficacy, and value of the certain procedures, including chemical ablation, stab phlebectomy, and laser ablation. Participating agencies ranked concerns for treatments for varicose veins as medium for safety, high for efficacy, and medium for cost-effectiveness. An evidence-based assessment of the comparative effectiveness, safety, and cost is warranted to guide coverage policy.

Summary of Review Objectives and Methods

Review Objectives

Population: Adult patients being treated for varicose veins

Interventions: EVLA, endovascular RFA, sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy)

Comparisons: Vein ligation with or without stripping

Outcomes:

Clinical outcomes: Failure of the procedure, second or additional procedures after failure of initial procedure, technical recurrence, symptomatic recurrence, second or additional procedures to treat recurrence, changes in symptom scores measured by validated scales (e.g., Venous Clinical Severity Score [VCSS])

Patient-centered outcomes: Patient satisfaction/quality of life (QOL); time to return to work or normal activity; pain

Adverse events: Nerve damage, skin burns, deep venous thermal injury, DVT, pulmonary embolism, transient ischemic attacks, stroke, bleeding, infection, thrombophlebitis, headache, visual disturbance, skin staining, pain at injection site, back pain, anaphylaxis, lymph leak, cellulitis
Cost/cost-effectiveness outcomes

Settings: Inpatient or outpatient

Study Designs: For clinical effectiveness (Key Questions #1 and #3), good-quality systematic reviews and randomized controlled trials (RCTs); for harms (Key Questions #2 and #3) in addition to good-quality systematic reviews and RCTs, large observational studies, including registry data (n ≥ 500), may be employed; similarly, for Key Question #4, observational and modelling studies may be also be employed.

Key Questions

1. Among patients being treated for varicose veins, what is the clinical effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

2. Among patients being treated for varicose veins, what are the harms associated with endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

3. Among patients being treated for varicose veins, does the effectiveness or risk of adverse events of laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping vary by clinical history (e.g., comorbidities, previous treatment of varicose veins), patient characteristics (e.g., age, sex, body mass index [BMI], smoking history)?

4. What are the cost implications and cost-effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping for patients being treated for varicose veins?

Methods

See the Methods section of the TECHNICAL REPORT, Appendix I, Appendix II, and Appendix III for additional detail.

Search Strategy and Selection Criteria

A review of reviews methodology was employed for this health technology assessment (HTA) and a comprehensive search for systematic reviews and HTAs to answer the Key Questions was conducted first. PubMed and the Centre for Reviews and Dissemination (CRD) electronic databases were searched for relevant systematic reviews on September 6, 2016, and the following electronic databases were searched for additional systematic reviews on December 22, 2016: PubMed, Canadian Agency for Technology and Health (CADTH), Cochrane Library, National Health Service – National Institute for Health Research (NIH-NIHR), National Institute for Health and Care Excellence (NICE), and CRD. Following identification and selection of systematic reviews and HTAs, a targeted search of PubMed and relevant primary data studies published subsequent to the review(s) selected for each indication was conducted on September 6, 2016. The initial search was limited to RCTs published in the English
language from March 1, 2011, to the search date. A separate search was conducted for additional economic evaluations on February 1, 2017. In addition to guidelines found through the database and manual searches outlined above, we also searched the National Guidelines Clearinghouse and websites of professional organizations.

**Inclusion Criteria**

Population: Adult patients being treated for varicose veins

Intervention: EVLA, RFA, sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy)

Comparator: Vein ligation with or without stripping

Outcomes:

- **Clinical outcomes** – Failure of the procedure, second or additional procedures after failure of initial procedure, technical recurrence, symptomatic recurrence, second or additional procedures to treat recurrence, changes in symptom scores measured by validated scales (e.g., VCSS)
- **Patient-centered outcomes** – Patient satisfaction/QOL; time to return to work or normal activity; pain
- **Safety** – Nerve damage, skin burns, deep venous thermal injury, DVT, pulmonary embolism, transient ischemic attacks, stroke, bleeding, infection, thrombophlebitis, headache, visual disturbance, skin staining, pain at injection site, back pain, anaphylaxis, lymph leak, cellulitis
- **Cost/cost-effectiveness outcomes**

Study design: For clinical effectiveness (Key Questions #1 and #3), good-quality systematic reviews and RCTs; for harms (Key Questions #2 and #3) in addition to good-quality systematic reviews and RCTs, large observational studies, including registry data \( n \geq 500 \), may be employed; similarly, for Key Question #4, observational and modelling studies may be also be employed.

Setting: Inpatient or outpatient

More details of these criteria, the rationale for these criteria, and the rationale for using existing systematic reviews are presented in the **METHODS** section of the **TECHNICAL REPORT**.

**Exclusion Criteria**

Population: Patients < 18 years of age; patients being treated for complications from varicose veins or other forms of venous insufficiency (e.g., ulcer).

Thermal ablation other than laser and RF (e.g., steam ablation); Cure Conservatrice et Hemodynamique de l'Insufficience Veineuse en Ambulatoire (CHIVA); cryostripping.
Placebo/sham, other active comparators, or no comparison group.

Non-English-language publication, no original data (narrative reviews, editorials, letters), abstracts, and conference posters; for systematic reviews: older reviews that have been updated or superseded by more recent reviews, no meta-analyses.

More details of these criteria and the rationale for these criteria are presented in the METHODS section of the TECHNICAL REPORT.

**Quality Assessment**

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was employed to determine the quality of systematic reviews. The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase *strength of evidence*. A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. See the Methods section of the TECHNICAL REPORT and Appendix II and Appendix III for details on quality assessment methods.

**Summary of Search Results**

A total of 18 publications were identified through searches for SRs and additional publications of primary data to answer the Key Questions. This includes 8 SRs and 10 publications of primary data not already included in 1 or more of the SRs. Five of the 10 primary publications represent newer data from studies that were included in the SRs based on earlier publications.

See Appendix IV for a list of the 88 studies that were excluded from analysis after full-text review.

Eight practice guidelines published in the last 10 years were identified.

**Findings**

Summary of Findings tables are provided in each Key Question #1. See EVIDENCE SUMMARY, Methods, Quality Assessment, and the corresponding section in the TECHNICAL REPORT, as well as Appendix II and Appendix III, for details regarding the assessment of bodies of evidence. See Appendix V for full evidence tables.
Key Question #1: Among patients being treated for varicose veins, what is the clinical effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

Study Characteristics

Systematic Reviews

Seven systematic reviews covering interventions of interest for this HTA were identified for Key Question #1. The number of included relevant primary studies ranged from 3 to 25. See Table 6 in the Technical Report for a list of individual study references in each of the reviews. Three reviews assessed EVLA, RFA, and FS compared with traditional surgery. One of the reviews evaluated evidence for EVLA compared with surgery, 1 evaluated EVLA and RFA compared with surgery, and 2 evaluated sclerotherapy compared with surgery. Most of the reviews included only RCTs; however, 2 reviews also included observational studies. One of the reviews included 104 studies; however, most of them did not include comparison groups and therefore did not contribute data to meta-analyses comparing treatments. There was considerable overlap of the individual studies included across the 7 reviews; however, none of the reviews includes exactly the same set of studies as another because of variations in search dates and inclusion and exclusion criteria. Overlap of studies between reviews was considered when assessing bodies of evidence to minimize “double counting” of study populations.

Interventions described in the reviews included EVLA with 810 nanometers (nm), 980 nm, or 1470 nm lasers; RFA with the Closure PLUS or ClosureFast catheters; and US-guided FS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation or high ligation with or without stripping. Several of the reviews described differences across individual studies with respect to reporting or analyzing data, for example, randomization was by patient in some studies and by limb in others. As noted by several of the review authors, the use of data randomized by limbs can introduce some bias into pooled analyses.

Primary Studies

Seven recent publications evaluating interventions of interest for this HTA, and not included in the SRs described above, were identified for Key Question #1. Five of these are follow-up publications related to previously published studies, and 2 are publications unrelated to previously published studies. Five publications compare EVLA with surgery, 1 study compares sclerotherapy with surgery, and 1 study compares EVLA and sclerotherapy with surgery. Details about study characteristics can be found in Appendix V.
**Study Quality**

Applying AMSTAR criteria for rating the quality of systematic reviews, all of the included systematic reviews were deemed to be of good quality. Limitations of some of the reviews included not providing a list of excluded studies (presumably because of limited publication space for journal publications), and missing details about the quality of individual studies and/or the body of evidence. Generally, the reviews were well conducted; however, the strength of the conclusions may be limited by the quality of the individual studies and the availability of appropriate data to pool for analyses. Most reviews stated that the individual studies were predominantly of fair to low quality or exhibited high risk of bias in 1 or more domains (e.g., selection or attrition bias).

The quality of the primary studies identified through the update search ranged from fair (n=6) to poor (n=2). Limitations include lack of blinding, which is a common limitation in this area of research because of the nature of the interventions being studied. Other limitations include potential lack of statistical power or statistical testing, reporting bias, attrition bias, and unclear method of randomization. Attrition for longer-term follow-up results is also a consideration.

**Clinical and Patient-Centered Outcomes**

**Tables 1, 2, and 3** follow this narrative summary and provide an overview of key data and quality of evidence ratings for each outcome and comparison.

**Failure of Procedure**

**EVLA Versus Surgery:** There is moderate quality evidence that technical failure is similar or reduced with EVLA compared with conventional surgical techniques. Two of the 4 SRs analyzing data for this outcome either did not report statistical significance or found no difference between EVLA and surgery. The other 2 reviews reported statistically significant differences that suggest better results with EVLA than surgery.

**RFA Versus Surgery:** There is moderate quality evidence that there is no difference between RFA and conventional surgical techniques with respect to technical failure. The investigators who conducted the 2013 National Health Service National Institute for Health Research (NHS NIHR) review pooled results from 12 studies to determine the percentage of failure events among patients who received RFA compared with those who received surgery. The pooled percentage for the RFA patients was 4% (16/431), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20/681). The statistical significance of this difference was not reported. In another review, a meta-analysis of technical failure data from 5 studies of patients with GSV varices found no difference between RFA and surgery (odds ratio [OR]=0.82 [95% CI, 0.07-10.10]; P=0.88; I²=70%).

**Sclerotherapy Versus Surgery:** The evidence presented in 4 SRs represents low quality evidence suggesting that there may be no difference between sclerotherapy and surgery in terms of technical failure; however there is considerable uncertainty because of the heterogenous body of evidence. Two of the included SRs found no significant difference between FS and surgery. This was based on 2 studies in 1 review and 1 study in the other review. A third review reported a higher rate of failure in pooled
results from the FS study arms than in the surgery study arms, but did not report statistical test results. A fourth review conducted a meta-analysis with 6 studies of FS compared with surgery and found better results associated with surgery for this outcome. A fifth review did not conduct quantitative analyses, but noted a general trend showing sclerotherapy was better than surgery at 1 year as reported in 3 studies; however, results at 2-, 3-, and 5-year follow-up points either reported that surgery was significantly better than sclerotherapy or there were no differences between groups at these time points.

**Technical Recurrence**

**EVLA Versus Surgery:** There is moderate quality evidence that EVLA is similar to conventional surgical techniques with respect to technical recurrence. One of the reviews conducted a network meta-analysis using data from 23 studies to compare the hazard of having technical recurrence when treated with EVLA, RFA, and FS compared with stripping for 6 months, 1 year, and 2 years. The analysis indicated that EVLA exhibited the greatest effect on technical recurrence relative to stripping, with some decrease in efficacy over time. The 2-year hazard ratio (HR) for EVLA compared with stripping was 0.84 (95% critical interval [CrI], 0.44-1.81), with a probability HR > 1 of 0.257. At 6 months and 1 year the HRs were 0.70 (95% CrI, 0.27-1.45 [0.150]) and 0.77 (0.37-1.54 [0.182]), respectively. A meta-analysis of 2 studies examining EVLA compared with surgery for treating SSV varices found better results with EVLA with respect to technical recurrence. Two other reviews reported no difference between EVLA and surgery based on their analyses. One review found no difference between endothermal ablation procedures and surgery when the authors pooled results from studies of EVLA and RFA and compared them with surgery.

**RFA Versus Surgery:** There is low quality evidence that RFA and conventional surgery are similar with respect to technical recurrence. One review of patients with GSV varices presented results from a meta-analysis of 4 studies comparing RFA with surgery that reported “clinician noted” recurrence. The meta-analysis of these studies suggested no statistically significant difference between treatment groups (OR=0.82 [95% CI 0.49-1.39]; P=0.47; I²=39%). In a network meta-analysis using data from 23 studies, presented in another review, the relative likelihood of experiencing a technical recurrence of varicose veins over time was lower with RFA than surgery: at 6 months, HR=0.92 (95% CrI, 0.39-2.11 [probability HR > 1, 0.409]); at 1 year, HR=0.93 (95% CrI, 0.42-2.22); and at 2-years, HR=0.94 (95% CrI, 0.42-2.51 [0.421]). While the relative effect of RFA on recurrence was small, it remained consistent over time.

**Sclerotherapy Versus Surgery:** There is low quality evidence suggesting no difference between sclerotherapy and surgery with respect to technical recurrence in the short term; however longer term evidence suggests that rates of recurrence may be similar between the two treatments or better with surgery. Two reviews concluded that differences between FS and surgery were not statistically significant based on a network meta-analysis of 23 studies and a meta-analysis of 3 studies. A third review included only 1 study, which reported not significant differences between the FS and surgery groups for recurrence of reflux at 6 months. A fourth review noted a trend favoring sclerotherapy at 1 year, but at 2, 3, and 5 year follow-up there was either not difference, or outcomes were better among the surgical patients. In a 5-year follow-up publication, rates of recurrence were statistically significantly
higher in the US-guided FS (UGFS) group compared with the surgery group (77% versus 14.5%, respectively; P<0.001). An RCT comparing LS with surgery found no difference at 1, 2, or 3 years between the treatment groups.

Symptomatic Recurrence

EVLA Versus Surgery: There is moderate quality evidence of no difference in symptomatic recurrence between EVLA and conventional surgery. None of 5 reviews found statistically significant results between EVLA and surgery with respect to symptomatic recurrence. One publication of primary data contributed 5-year follow-up to 1 of the studies included in 1 of the SRs. The 5-year results from this study suggest a higher rate of recurrence in the EVLA group than the surgery group; however, statistical significance was not reported. In a separate 5-year follow-up publication, overall recurrence of varicose veins after surgery at 5 years was similar between groups and occurred in 45% of the EVLA group and 54% of the high ligation and stripping (HL/S) group (P=0.152). In a 6-year follow-up publication, there was no significant difference between EVLA and HL/S with respect to time to clinical recurrence. Two other 5-year follow-up publications found statistically significant differences between EVLA and surgery with respect to recurrence. In both studies, results were better in the surgery group. Results from 1 study reporting recurrence at 12 months found a higher rate of recurrence in the surgery group compared with the EVLA group, but statistical significance was not reported.

RFA Versus Surgery: There is low quality evidence of no difference in rates of symptomatic recurrence between patients receiving treatment for varicose veins with RFA compared with those receiving conventional surgery. Two studies included in 1 review provided data for symptomatic recurrence for RFA compared with vein stripping. One study reported no symptomatic recurrence in either group at 4 months, and the other study reported that 4 of 15 patients (26%) in the RFA group had symptomatic recurrence at 3 years compared with 2 of 13 (15.4%) in the vein stripping group, the difference was not statistically significant. Another review reported symptomatic recurrence results for RFA compared with surgery from 1 study. Results were not statistically significant (OR=2.00 [95% CI, 0.30-13.26]; P=NR).

Sclerotherapy Versus Surgery: There is very low quality evidence that includes few studies and inconsistent results for symptomatic recurrence. Only 1 of the reviews noted a single study of FS that specifically reported symptomatic recurrence. This study found no statistically significant difference for between FS and surgery (OR=1.28 [95% CI, 0.66-2.49]; P=NR). Another study, not included in the SR reported no visible varicosities in 76% of surgery grp vs. 39% of LS grp (P<0.05) at 1 year.

Change in VCSS (or other measures of disease severity)

EVLA Versus Surgery: The overall quality of evidence for this outcome is low and suggests no difference in disease severity measures between EVLA and conventional surgery; relatively few studies used the same measures to assess this outcome. A network meta-analysis was conducted in 1 review. Six studies contributed data for this analysis, which found slightly lower post-intervention VCSS for EVLA than for stripping (mean difference [MD]=−0.10 [95% CrI, −0.94 to 0.73] with a probability that the MD > 0 of 0.324). In a single 5-year follow-up study, clinical improvement was measured using the C category of the CEAP classification; there was no difference in the distribution of class C between legs in the surgery
group and those treated with EVLA (OR=1.3 [95% CI, 1.1-1.5]). In 2 other 5-year follow-up publications, investigators reported no difference between EVLA and surgery with respect to disease severity as measured by the Homburg Varicose Vein Severity Score (HVSS) in 1 study and the CEAP classification in the other. In 1 study reporting outcomes at 1 year and 18 months, the Aberdeen Varicose Vein Symptom Severity (AVVSS) score was lower in the EVLA group at 12 months than in the high ligation group (P=0.019), this difference was sustained at 18 months (P=0.008).

**RFA Versus Surgery:** There is low quality evidence of no difference between RFA and conventional surgery with respect to disease severity measures. A network meta-analysis found slightly higher post-intervention VCSS scores for RFA than surgery (MD=0.15 [95% CrI, −0.50 to 0.95]; probability MD > 0, 0.739) based on data available at 1 year (or 6 months if 1-year data was not available) from 6 studies. Based on a qualitative summary in another SR of results from 3 studies comparing RFA with surgery for treating patients with GSV varices, investigators concluded that disease severity scores generally improved over the length of the follow-up for both treatment groups, with most studies reporting no overall differences between the groups.

**Sclerotherapy Versus Surgery:** There is very low quality evidence suggesting either no difference between FS and surgery or better results with FS. A network meta-analysis of VCSS scores found that FS exhibited the greatest effect among the 3 interventions analyzed (EVLA, RFA, and FS) relative to stripping (MD=−1.63 [95% CrI, −2.90 to −0.42]; probability MD > 0, 0.015) based on data available at 1 year (or 6 months if 1-year data was not available) from 6 studies. Two studies summarized in another review found no difference between FS and surgery for VCSS; in both studies, both groups showed improvement from baseline to the final follow up time point. In a publication of 5-year follow-up results, there was no difference in the distribution of class C (of the CEAP classification) between legs in the surgery group (OR=1.4 [95% CI, 1.2-1.6]) and those treated with UGFS (OR=1.3 [95% CI 1.1-1.5]).

**Pain**

**EVLA Versus Surgery:** The quality of evidence for postoperative pain was determined to be very low due to inconstancies across the body of evidence for this outcome. In 1 of the reviews, data from 9 studies contributed to a network meta-analysis of pain within 7 to 14 days of treatment as assessed using a visual analog scale (VAS). For EVLA compared with stripping, the MD was 0.10 (95% CrI, −0.49 to 0.64) with a probability of MD > 0 of 0.653. Three other reviews qualitatively summarized data on pain outcomes, noting that measures of pain varied between studies. Results were summarized in 1 review as being inconclusive, and summarized in another as follows: 3 of 8 studies found higher levels of postoperative pain in the HL/S group; 4 found no difference between EVLA and surgery; and 1 reported significantly more pain in the EVLA group that the surgery group.

**RFA Versus Surgery:** There is moderate quality evidence that RFA is associated with less post-procedural pain than conventional surgery. A qualitative assessment of findings gleaned from data on pain outcomes from studies of patients with GSV varices suggested that there may be less pain associated with RFA than with surgery. A network meta-analysis presented in another review used data from 9
Studies. Results suggest that relative to vein stripping, RFA is associated with decreased pain in the first 2 weeks after the procedure (MD = -1.26 [95% CrI, -1.95 to -0.61] [0.001]).

Sclerotherapy Versus Surgery: Low quality body of evidence suggests that FS or LS may be associated with less postoperative pain than surgery. With respect to pain, a network meta-analysis found no difference between treatment groups. Another review found conflicting results in 2 studies. One of the studies found that scoring for “more,” “stable,” or “less” pain were similar between the groups at 3, 12, and 24 months. Results from the other study suggest that the FS group experienced significantly less postoperative pain than the surgery group (P<0.001), and the number of phlebectomies did not influence pain scores (P=0.136). One RCT not included in a SR reported less pain in the LS group than the surgery group at 1 year (P<0.05).

Return to Work or Normal Activity

EVLA Versus Surgery: There is low quality evidence that time to return to work or normal activities is shorter following treatment of varicose veins with EVLA compared with conventional surgery. As with the pain outcomes, metrics to measure return to work or normal activity varied, and none of the included reviews conducted analyses of these data. In general, the narrative summaries concluded that study results ranged from not statistically significant between the groups to indicating statistically significantly less time needed to return to work or normal activities after EVLA compared with surgery. One study described in the SRs found a statistically significantly longer return time to work for the group that received EVLA; this study compared HL+EVLA with HL/S.

RFA Versus Surgery: Low quality evidence suggests that patients who receive RFA for treatment of varicose veins may take less time to return to work or normal activities. Authors of 1 review narratively summarized findings from 4 studies comparing RFA with surgery as follows: 1 study found no statistically significant difference, while 3 other studies reported significantly quicker return to work or normal activities for RFA compared with surgery. Nesbitt et al. (2014) presented results from the same 4 studies included in the Carroll et al. (2013) review, plus an additional study. Nesbitt et al. (2014) noted that while the 5 studies reported either time to return to work or time to return to normal activities, the results were reported differently between the studies, precluding meta-analysis for this outcome. All 5 studies reported less time for RFA than for surgery.

Sclerotherapy Versus Surgery: Very low quality evidence consisting of few studies suggests that patients who receive FS may return to work or normal activities faster than those who receive surgery for the treatment of varicose veins. Few sclerotherapy studies reported time to return to work; only 3 studies across 2 SRs reported this outcome. One did not report statistical test results, and the other 2 suggest that FS patients returned to work or normal activities significantly faster than the surgery patients.

Quality of Life

EVLA Versus Surgery: Evidence of moderate quality suggests no difference between EVLA and conventional surgical techniques for treating varicose veins with respect to QOL scores. The reviews documented different QOL measurement tools used across studies, and generally found no statistically
significant differences between EVLA and surgery. In a 5-year follow-up publication, no significant differences between EVLA and surgery with respect to changes in CIVIQ Venous Quality of Life Questionnaire scores or EQ-5D scores were found. In 2 other 5-year follow-up publications, there was also no difference between groups for QOL based on the CIVIQ-2 scores. Also in these 2 studies, patient satisfaction was similar between groups at 5 years. Twelve-month follow-up results from another study were similar.

**RFA Versus Surgery**: Based on mixed results from 3 studies using different measurement tools, the quality of the overall body of evidence for this outcome is very low. In 1 review, different QOL measurement tools were used across 3 studies, 2 of which reported no significant difference between RFA and surgery. The third study reported an initial decrease in QOL in the surgery group compared with an initial increase in the RFA group; at 3 weeks, differences were not statistically significant, but at 1 year there was a significant difference suggesting better QOL among patients who received RFA.

**Sclerotherapy Versus Surgery**: A low quality body of evidence consisting of heterogeneous outcome measures in a few studies, suggests no difference in QOL measures between FS or LS and surgery. One of the reviews narratively summarized results from 3 studies because differences in QOL measurement tools precluded meta-analysis. Both groups showed similar QOL scores by the final follow-up assessment in all 3 of the studies and no significant differences between the FS and surgery groups were evident. In a 5-year follow-up publication, QOL results from 1 study were generally similar between the treatment groups as measured with 2 different assessment tools. Another publication of primary data reported a statistically significant difference at 1 year based on EQ-5D scores, but there were no significant differences in SF-36 scores at 1 or 2 years or EQ-5D at 2 yrs.

**Reintervention**

**EVLA Versus Surgery**: There is low quality evidence of no difference between EVLA and conventional surgery with respect to proportion of patients requiring reintervention either in the short-term (because of technical failure) or in the longer term (presumably because of recurrence after successful initial treatment). Only 1 of the reviews conducted an analysis of pooled data for this outcome. This analysis found no statistically significant difference in the pooled percentages of endovenous ablation (EVLA, RFA) and surgery patients who underwent reintervention after recurrence. EVLA (5 studies): 27.2% (95% CI, 23.3-31.3); RFA (1 study): 16.2% (95% CI, 10.4-35.9); surgery (4 studies): 17.3% (95% CI, 13.6-21.4); P=0.74. In a 5-year follow-up publication, reintervention and additional treatments were given 1 or more times to 10% of the limbs in the surgery and EVLA groups. Another 5-year follow-up publication reported no statistically significant differences between groups with respect to reintervention.

**RFA Versus Surgery**: There is low quality evidence of mixed results for reintervention after varicose vein treatment with RFA compared with conventional surgery. According to one SR, 2 studies reported on this outcome. One study found that 6 of 81 (7.4%) patients who received surgery had reintervention due to technical failure, compared with 0 of 81 (0%) who received RFA. The second study reported 2 of 13 (15.4%) in the surgery group compared with 2 of 15 (13.3%) in the RFA group received reintervention. Statistical differences were not provided. Another SR conducted an analysis of pooled data for this
outcome. This analysis found no statistically significant difference in the pooled percentages of endovenous ablation (EVLA, RFA) and surgery patients who underwent reintervention after recurrence. EVLA (5 studies): 27.2% (95% CI, 23.3-31.3); RFA (1 study): 16.2% (95% CI, 10.4-35.9); surgery (4 studies): 17.3% (95% CI, 13.6-21.4); \( P=0.74 \).

**Sclerotherapy Versus Surgery:** The quality of the overall body of evidence for this outcome is very low and no conclusions can be drawn based on available data. One review reported data for reintervention due to technical failure from 2 studies comparing FS with surgery. Only 1 of these studies provided data for both groups; in the FS group 40 of 123 (18.8%) patients needed reintervention compared with 10 of 177 (5.6%) in the surgery group. The second study reported 5 of 144 (3.5%) patients in the FS group had a reintervention (no data were provided for the surgery group). In a 5-year follow-up publication, it was reported that reintervention and additional treatments were given 1 or more times to 10% of the limbs in the surgery group compared with 32% of legs in the UGFS group (log rank test, \( P<0.001 \)).

**Table 1. Summary of Findings, Key Question 1: EVLA vs. Surgery**

<table>
<thead>
<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ #1. Clinical outcome: failure of procedure, EVLA vs. surgery</strong></td>
<td><strong>OVERALL:</strong> Moderate</td>
<td>Reduced with EVLA or similar</td>
<td><strong>Carroll, 2013 (n=12 studies)</strong></td>
</tr>
<tr>
<td>4 GQ SRs</td>
<td><strong>Consistency:</strong> Consistent</td>
<td></td>
<td>Pooled percentage: EVLA, 1% (5/467); S/L, 3% (20/681); ( P=NR )</td>
</tr>
<tr>
<td>Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014</td>
<td><strong>Applicability to PICOS:</strong> ( \checkmark )</td>
<td></td>
<td><strong>Nesbitt, 2014 (n=6 studies)</strong></td>
</tr>
<tr>
<td>No additional primary studies</td>
<td><strong>Publication bias:</strong> Unknown</td>
<td></td>
<td>OR=0.29 (95% CI 0.14-0.60), ( P=0.0009 )</td>
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<td></td>
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<td></td>
<td><strong>Paravastu, 2016 (n=3 studies)</strong></td>
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<td></td>
<td></td>
<td></td>
<td>OR=0.07 (95% CI 0.02-0.22), ( P&lt;0.00001 )</td>
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<td></td>
<td><strong>Pan, 2014 (n=9 studies)</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled percentage (1-12 wks): EVLA 97.3%; HL/S 97.6%, ( P=NS )</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>( RR=1.1 (95% CI 0.62-1397), P=0.72 )</td>
</tr>
<tr>
<td>Number, Type, and Quality of Studies</td>
<td>Quality of Evidence</td>
<td>Direction of Findings</td>
<td>Key Study Results</td>
</tr>
<tr>
<td>-------------------------------------</td>
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</tr>
</tbody>
</table>
| KQ #1. Clinical outcome: technical recurrence, EVLA vs. surgery | OVERALL: Moderate Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=23 studies, network MA)**  
2 yr HR=0.84 (95% CI 0.44-1.81)  
1 yr HR=0.77 (95% CI 0.37-1.54)  
6 mo HR=0.70 (95% CI 0.27-1.45)  
**Nesbitt, 2014 (n=7 studies)**  
OR=0.72 (95% CI 0.43-1.22), P=0.22  
**Paravastu, 2016 (n=1 & 2 studies)**  
1 yr OR=0.24 (95% CI 0.07-0.77), P=0.016  
2 yr OR=0.43 (95% CI 0.16-1.15), P=0.09  
**Pan, 2014 (n=5 & 6 studies)**  
1 yr RR=0.65 (95% CI 0.41-1.02), P=0.06  
2 yr RR=0.65 (95% CI 0.37-1.12), P=0.12  
**O’Donnell, 2016**  
Pooled percentage: EVLA (4 studies), 12.5% (95% CI 8.9-16.5); RFA (3 studies), 12.4% (95% CI 7.3-18.6); L/S (5 studies), 7.2% (95% CI 4.4-10.6);  
P=0.32 for EVLA and RFA combined compared with L/S  
**van der Velden, 2015 (n=135 pts; 147 legs)**  
EVLA, 23%; surgery, 14.5%; P=NR  
**Flessenkamper, 2016 (n=81 pts at 72 mos)**  
No difference in time to clinical recurrence within 6 yr f/u (log rank test P=0.5479)  
**Ross, 2015 (RELACS) (n=281 legs at 5 yrs)**  
45% EVLA; 54% HL/S (P=0.152)  
**Gauw, 2016 (n=112 pts at 5 yrs)**  
EVLA 49%; SFL/S, 23%; log-rank test P=0.02  
**Kalteis, 2015 (n=72 at 5 yrs)**  
No recurrence in 43% of the HL+EVLA; 67% of HL/S, P=0.049  
**Mozafar, 2014 (n=65)**  
12 mos: 6.7% EVLA; 11.7% HL, P=NR |
| 5 GQ SRs  
Carroll, 2013;  
Nesbitt, 2014;  
Paravastu, 2016;  
Pan, 2014;  
O’Donnell, 2016  
5 FQ RCTs  
van der Velden, 2015 (5-yr f/u from MAGNA trial)  
Flessenkamper, 2016 (6-yr f/u)  
Rass, 2015 (5-yr f/u from RELACS trial)  
Gauw, 2016 (5-yr f/u)  
Kalteis, 2015 (5-yr f/u)  
1 PQ RCT  
Mozafar, 2014 | | | |
| KQ1. Clinical outcome: symptomatic recurrence, EVLA vs. surgery | OVERALL: Moderate Consistency: Consistent | No difference | **Carroll, 2013 (n=3 studies)**  
Differences b/t grps NS |
**Selected treatments for varicose veins:** Draft evidence report

### Table: Number, Type, and Quality of Studies

<table>
<thead>
<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014; O’Donnell, 2016</td>
<td>Applicability to PICOS: ✓ Publication bias: Unknown</td>
<td></td>
<td>Nesbitt, 2014 (n=3 studies) OR 0.87 (95% CI, 0.47-1.62), P=0.67</td>
</tr>
<tr>
<td>1 FQ RCT Kalteis, 2015 (5-yr f/u)</td>
<td></td>
<td></td>
<td>Paravastu, 2016 (n=1 study) OR=0.54 (95% CI 0.17 to 1.75), P=NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pan, 2014 (n=5 &amp; 6 studies) 1 yr RR=0.83 (95% CI 0.39-1.77), P=0.63 2 yr RR=0.85 (95% CI 0.64-1.11), P=0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>O’Donnell, 2016 EVLA (5 studies): 20.6% (95% CI 17.0-24.3); RFA (3 studies): 21.4% (95% CI 14.8-28.8); surgery (6 studies): 19.2% (95% CI 15.5-23.2); P=0.98 for EVLA and RFA combined compared with surgery</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Kalteis, 2015 (n=72 at 5 yrs) Visible recurrence: HL+EVLA, 40%; HL/S 40%, P=NR</td>
</tr>
</tbody>
</table>

**KQ1. Clinical outcome: change in VCSS or other measure of disease severity, EVLA vs. surgery**

| 1 GQ SR Carroll, 2013 | OVERALL: Low Consistency: CND Applicability to PICOS: ✓ Publication bias: Unknown | No difference | Carroll, 2013 (n=6 studies, network MA) MD = -0.10 (95% CrI -0.94-0.73) |
| 2 FQ RCT van der Velden, 2015 (5-yr f/u for the MAGNA trial) Rass, 2015 (5-yr f/u from RELACS trial) |  |  | van der Velden, 2015 (n=135 pts; 147 legs) Distribution of class C: EVLA, OR=1.3 (95% CI 1.1-1.5); surgery, OR=1.4 (95% CI 1.2-1.6), P=NS |
| 1 PQ RCT Mozafar, 2014 |  |  | Rass, 2015 (n=281 legs at 5 yrs) HVVSS: EVLA, 3.00 ± 2.87; HL/S, 3.16 ± 3.48; P=0.789 |
|  |  |  | Mozafar, 2014 (n=65) AVVSS: lower in EVLA than HL at 12 mos (P=0.019) and 18 mos (P=0.008) |

**KQ1. Patient-centered outcome: pain, EVLA vs. surgery**

<p>| 4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014 | OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown | Mixed | Carroll, 2013 (n=9 studies, network MA) Pain within 7-14 days: MD=0.10 (95% CrI -0.49-0.64) |
|  |  |  | Nesbitt, 2014 Described results from studies measuring pain as inconclusive |</p>
<table>
<thead>
<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravastu, 2016 (n=2 studies)</td>
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<tr>
<td>Pan, 2014 (n=8 studies)</td>
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</tbody>
</table>

**KQ1. Patient-centered outcome: return to work or normal activity, EVLA vs. surgery**

<table>
<thead>
<tr>
<th>4 GQ SRs</th>
<th>OVERALL: Low</th>
<th>Reduced with EVLA</th>
<th>Carroll, 2013 (n=6 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014</td>
<td>Consistency: Inconsistent</td>
<td></td>
<td>1 study, &lt; time in surgery grp; 1 study, &lt; time in EVLA grp; 2 studies, no difference; 2 studies, <em>P</em>=NR</td>
</tr>
<tr>
<td>Applicability to PICOS: ✓</td>
<td>Publication bias: Unknown</td>
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<tr>
<td>6 studies summarized as generally &lt; time for the EVLA group</td>
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<tr>
<td>Paravastu (2016) (n=2 studies)</td>
<td>&lt; time for EVLA grp</td>
<td></td>
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</tr>
<tr>
<td>Pan (2014) (n=7 studies)</td>
<td>Time to return to normal activities (5 studies): no difference</td>
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<tr>
<td></td>
<td>Time to return to work: 2 studies, &lt; time in EVLA grp; 3 studies no difference; 1 study, &lt; time in surgery grp</td>
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</tbody>
</table>

**KQ1. Patient-centered outcome: quality of life/patient satisfaction, EVLA vs. surgery**

<table>
<thead>
<tr>
<th>2 GQ SRs</th>
<th>OVERALL: Moderate</th>
<th>No difference</th>
<th>Nesbitt, 2014 (n=5 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesbitt, 2014; Paravastu, 2016</td>
<td>Consistency: Consistent</td>
<td></td>
<td>No difference</td>
</tr>
<tr>
<td>3 FQ RCTs</td>
<td>Applicability to PICOS: ✓</td>
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<tr>
<td>van der Velden, 2015 (5-yr f/u for the MAGNA trial)</td>
<td>Publication bias: Unknown</td>
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<tr>
<td>Rass, 2015 (5-yr f/u from RELACS trial)</td>
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<tr>
<td>Kalteis, 2015 (5-yr f/u)</td>
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<tr>
<td>Paravastu, 2016</td>
<td>AVVQ at 6 wks (2 studies): MD=0.15 (95% CI, −1.65 to 1.95); <em>P</em>=0.87</td>
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<td></td>
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<tr>
<td></td>
<td>AVVQ at 1 yr (1 study): MD=−1.08 (95% CI, −3.39 to 1.23); <em>P</em>=NR</td>
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<td></td>
<td>EQ-5D (2 studies): No difference</td>
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<tr>
<td>van der Velden, 2015 (n=135 pts; 147 legs)</td>
<td>CIVIQ and EQ-5D scores: no difference at 5 yrs</td>
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<tr>
<td>Rass, 2015 (n=281 legs at 5 yrs)</td>
<td>CIVIQ-2 scores: no difference</td>
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<td></td>
<td>Pt satisfaction: EVLA, 1.28 ± 0.51; HL/S, 1.39 ± 0.58; <em>P</em>=0.078</td>
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<tr>
<td>Kalteis, 2015 (n=72 at 5 yrs)</td>
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<td>Number, Type, and Quality of Studies</td>
<td>Quality of Evidence</td>
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<td>Key Study Results</td>
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<tr>
<td>CIVIQ-2: EVLA, 94; HL/S, 93; P=NR</td>
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<tr>
<td>Pt satisfaction: 87%, EVLA; 88% HL/S rated good or very good; P=NR</td>
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</table>

**KQ1. Clinical outcome: reintervention, EVLA vs. surgery**

| 3 GQ SRs Nesbitt, 2014; Paravastu, 2016; Pan, 2014; O’Donnell, 2016 |
| 3 FQ RCTs van der Velden, 2015 (5-yr f/u for the MAGNA trial) Rass, 2015 (5-yr f/u from RELACS trial) Gauw, 2016 (5-yr f/u) |
| OVERALL: Low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown |
| No difference |
| **Nesbitt, 2014 (n=2 studies)** Reintervention b/c of technical failure: EVLA, 13%; surgery, 8.8%; P=NR EVLA, 3.5%; 1.4% surgery; P=NR |
| **Paravastu, 2016 (n=1 study)** Reintervention b/c of technical failure: EVLA 4 pts; surgery, 3 pts; P=NR |
| **O’Donnell, 2016** No difference for EVLA and RFA combined compared with surgery Pooled percentages: EVLA (5 studies): 27.2% (95% CI, 23.3-31.3); RFA (1 study): 16.2% (95% CI, 10.4-35.9); surgery (4 studies): 17.3% (95% CI, 13.6-21.4); P=0.74. |
| **van der Velden, 2015 (n=135 pts; 147 legs)** Reintervention at 5yrs: 10% in EVLA and surgery grps |
| **Ross, 2015 (n=281 legs at 5 yrs)** Types of reintervention for recurrence (n=69 EVLA; n=70 HL/S): “Wait and see” – EVLA, 49%; HL/S 67%; P=0.040 Sclerotherapy – EVLA, 33%; HL/S, 11%; P=0.004 Phlebectomy – EVLA, 14%; HL/S, 26%; P=0.138 Redo tx (SFJ, GSV, AASV) – EVLA, 9%; HL/S, 0%; P=0.0028 SSV surgery – EVLA, 1%; HL/S 4%; P=0.620 |
| **Gauw, 2016 (n=121 legs at 5 yrs)** Did not receive reintervention: EVLA 70%; 80% SF/L; log-rank P=0.20 |
Table 2. Summary of Findings, Key Question 1 – RFA vs. Surgery

Key: CI, confidence interval; CIVIQ-2, Chronic Venous Insufficiency Quality-of-Life Questionnaire-2; CND, cannot determine; Crl, critical interval; GQ, good quality; grp, group; HR, hazard ratio; MA, meta-analysis; MD, mean difference; NR, not reported; NS, not significant; PICS, population, intervention, comparator, outcomes, setting; OR, odds ratio; RFA, radiofrequency ablation; S/L stripping and ligation; SR, systematic review; tx, treatment, VCSS, Venous Clinical Severity Score

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<thead>
<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
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<tr>
<td><strong>KQ #1. Clinical outcome: failure of procedure, RFA vs. surgery</strong></td>
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</table>
| 2 GQ SRs Carroll, 2013; Nesbitt, 2014 | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=12 studies)**  
Pooled percentage: RFA, 4% (16/431); S/L, 3% (20/681); P=NR  
**Nesbitt, 2014 (n=5 studies)**  
OR=0.82 (95% CI, 0.07-10.10); P=0.88 |
| **KQ #1. Clinical outcome: technical recurrence, RFA vs. surgery** | | | |
| 2 GQ SRs Carroll, 2013; Nesbitt, 2014 | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=23 studies, network MA)**  
2 yr HR=0.94 (95% Crl, 0.42-2.51)  
1 yr HR=0.93 (95% Crl, 0.42-2.22)  
6 mo HR=0.92 (95% Crl, 0.39-2.11)  
**Nesbitt, 2014 (n=4 studies)**  
OR=0.82 (95% CI, 0.49-1.39) |
| **KQ1. Clinical outcome: symptomatic recurrence, RFA vs. surgery** | | | |
| 2 GQ SRs Carroll, 2013; Nesbitt, 2014 | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=2 studies)**  
Differences b/t grps NS  
**Nesbitt, 2014 (n=1 study)**  
OR=2.00 (95% CI, 0.30-13.26), P=NR |
| **KQ1. Clinical outcome: change in VCSS or other measure of disease severity, RFA vs. surgery** | | | |
| 2 GQ SRs Carroll, 2013; Nesbitt, 2014 | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=6 studies, network MA)**  
MD=0.15 (95% Crl, −0.50 to 0.95)  
**Nesbitt, 2014 (3 studies)**  
No overall differences b/t grps |
| **KQ1. Patient-centered outcome: pain, RFA vs. surgery** | | | |
| 2 GQ SRs Carroll, 2013; Nesbitt, 2014 | OVERALL: Moderate Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | Benefit with RFA | **Carroll, 2013 (n=9 studies, network MA)**  
MD=−1.26 (95% Crl, −1.95 to −0.61)  
**Nesbitt, 2014 (4 studies)**  
3 studies less pain in RFA grp (P<0.001); 1 study no difference |
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<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
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<tr>
<td><strong>KQ1. Patient-centered outcome: return to work or normal activity, RFA vs. surgery</strong></td>
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</table>
| 2 GQ SRs
Carroll, 2013; Nesbitt, 2014 | OVERALL: Low
Consistency: Consistent
Applicability to PICOS: ✓
Publication bias: Unknown | Reduced with RFA | *Carroll, 2013* (n=4 studies)
1 study, P=NR; 3 studies, < time in RFA grp
*Nesbitt (2014)* (n=5 studies)
< time in RFA grp, P=NR |
| **KQ1. Patient-centered outcome: quality of life/patient satisfaction, RFA vs. surgery** |
| 1 GQ SR
Nesbitt, 2014 | OVERALL: Very low
Consistency: CND
Applicability to PICOS: ✓
Publication bias: Unknown | Mixed | *Nesbitt, 2014* (n=3 studies)
2 studies, no difference; 1 study reported no difference at 3 wks, then better CIVIQ-2 scores for RFA at 1 and 2 yrs |
| **KQ1. Clinical outcome: reintervention, RFA vs. surgery** |
| 2 GQ SR
Nesbitt, 2014; O’Donnell, 2016 | OVERALL: Low
Consistency: CND
Applicability to PICOS: ✓
Publication bias: Unknown | Mixed | *Nesbitt, 2014* (n=2 studies)
Reintervention b/c of technical failure:
RFA, 0%; surgery, 7.4%; P=NR
RFA, 13.3%; 15.4% surgery; P=NR
*O’Donnell, 2016*
No difference for EVLA and RFA combined compared with surgery for reoperation
Pooled percentages: EVLA (5 studies): 27.2% (95% CI, 23.3-31.3); RFA (1 study): 16.2% (95% CI, 10.4-35.9); surgery (4 studies): 17.3% (95% CI, 13.6-21.4); P=0.74. |
Table 3. Summary of Findings, Key Question 1 – Sclerotherapy vs. Surgery

Key: CI, confidence interval; CIVIQ, Chronic Venous Insufficiency Quality-of-Life Questionnaire; CND, cannot determine; CrI, critical interval; EQ-5D, EuroQol Group 5-dimension Questionnaire; FQ, fair quality; FS, foam sclerotherapy; GQ, good quality; grp, group; HR, hazard ratio; KQ, key question; LS, liquid sclerotherapy; MA, meta-analysis; MD, mean difference; NR, not reported; NS, not significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, risk ratio; SD, standard deviation; SF, saphenofemoral; SF-36 Health Survey (QualityMetric Inc.); S/L stripping and ligation; SR, systematic review; tx, treatment; VAS, visual analog scale; VCSS, Venous Clinical Severity Score

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<tr>
<th>Number, Type, and Quality of Studies</th>
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<tr>
<td><strong>KQ #1. Clinical outcome: failure of procedure, sclerotherapy vs. surgery</strong></td>
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</table>
| 4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Rathbun, 2012; | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=12 studies)**  
Pooled percentage: FS, 7% (7/295); S/L, 3% (20/681); P=NR  
**Nesbitt, 2014 (n=2 studies)**  
OR=0.44 (95% CI, 0.12-1.57); P=0.20  
**Paravastu, 2016 (1 study)**  
OR=0.34 [95% CI, 0.06-2.10]; P=0.25  
**Rathbun, 2012 (6 studies)**  
Anatomical closure (6 studies): RR=0.92 (95% CI, 0.86-0.97); P=0.0036  
Residual SF incompetence (4 studies): RR=0.92 (95% CI 0.56-1.51); P=0.73 |
| 2 FQ RCT van der Velden, 2015 (5-yr f/u for MAGNA trial) Michaels, 2006 | OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference | **Carroll, 2013 (n=23 studies, network MA)**  
2 yr HR=0.92 (95% CrI, 0.43-1.60)  
1 yr HR=1.02 (95% CrI, 0.49-1.84)  
6 mo HR=1.12 (95% CrI, 0.53-2.27)  
**Nesbitt, 2014 (n=3 studies)**  
OR=1.74 (95% CI, 0.97-3.12); P=0.06  
**Paravastu, 2016 (1 study)**  
OR=1.19 (95% CI, 0.29-4.92); P=NR  
**Rigby, 2009 (5 studies)**  
Benefit with sclerotherapy at 1 yr, then favoring surgery or no difference at 2, 3, and 5 yrs  
**van der Velden, 2015**  
Recurrence at 5 yrs: FS, 77%; surgery, 14.5%; P<0.001 |
<table>
<thead>
<tr>
<th>Number, Type, and Quality of Studies</th>
<th>Quality of Evidence</th>
<th>Direction of Findings</th>
<th>Key Study Results</th>
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</thead>
<tbody>
<tr>
<td><strong>KQ1. Clinical outcome: symptomatic recurrence, sclerotherapy vs. surgery</strong></td>
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<tr>
<td>1 GQ SRs Nesbitt, 2014</td>
<td>OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown</td>
<td>Mixed</td>
<td>Nesbitt, 2014 (n=1 study) OR=1.28 (95% CI, 0.66-2.49); P=NR</td>
</tr>
<tr>
<td>1 FQ RCT Michaels, 2006</td>
<td>Michaels, 2006 No difference at 1, 2, or 3 yrs</td>
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<tr>
<td><strong>KQ1. Clinical outcome: change in VCSS or other measure of disease severity, sclerotherapy vs. surgery</strong></td>
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<tr>
<td>2 GQ SRs Carroll, 2013; Nesbitt, 2014</td>
<td>OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown</td>
<td>Mixed</td>
<td>Carroll, 2013 (n=6 studies, network MA) MD=−1.63 (95% CrI, −2.90 to −0.42)</td>
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<tr>
<td>1 FQ RCT van der Velden, 2015</td>
<td>Nesbitt, 2014 (2 studies) No difference</td>
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<td></td>
<td>van der Velden, 2015 No difference at 5 yrs in C class distribution between the tx grps</td>
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<tr>
<td><strong>KQ1. Patient-centered outcome: pain, sclerotherapy vs. surgery</strong></td>
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<tr>
<td>2 GQ SRs Carroll, 2013; Nesbitt, 2014</td>
<td>OVERALL: Low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown</td>
<td>Benefit with sclerotherapy</td>
<td>Carroll, 2013 (n=9 studies, network MA) MD=−0.80 (95% CrI, −1.93 to 0.30)</td>
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<tr>
<td>1 FQ RCT Michaels, 2006</td>
<td>Nesbitt, 2014 (2 studies) 1 study, no difference; 1 study significantly less pain in FS grp (P&lt;0.001)</td>
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<td>Michaels, 2006 VAS at 1 yr, mean (SD): LS, 0.77 (0.18); surgery 0.83 (0.14); P&lt;0.05</td>
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<td><strong>KQ1. Patient-centered outcome: time return to work or normal activity, sclerotherapy vs. surgery</strong></td>
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<tr>
<td>2 GQ SRs Carroll, 2013; Nesbitt, 2014</td>
<td>OVERALL: Very low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown</td>
<td>Reduced with sclerotherapy</td>
<td>Carroll, 2013 (n=3 studies) 1 study, &lt; time in RFA grp, P=NR 2 studies, &lt; time in FS grp, P&lt;(0.001)</td>
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<tr>
<td>Michaels, 2006</td>
<td>Nesbitt (2014) (n=1 study) Return to work &lt; time in RFA grp, median 2.9 vs 4.3 days; P=NR Return to normal activities &lt; time in RFA grp, median 1 vs 4 days; P=NR</td>
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### Key Question #2: Among patients being treated for varicose veins, what are the harms associated with endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

### Study Characteristics

Seven systematic reviews were identified for this Key Question. Three reviews assessed EVLA, RFA, and FS compared with traditional surgery. One the reviews evaluated evidence for EVLA compared with surgery, 2 evaluated EVLA and RFA compared with surgery, and 2 evaluated sclerotherapy compared with surgery. Most of the reviews included only RCTs for primary data; however, 2 reviews also included observational studies. One review included 104 studies; however, most of them did not include comparison groups and therefore did not contribute data to meta-analyses comparing treatments.
Interventions described in the reviews included EVLA with 810 nanometer (nm), 980 nm, or 1470 nm lasers; RFA with the Closure PLUS or ClosureFast catheters; and UGFS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation or high ligation with or without stripping.

Four additional publications not already included in the SRs described above were also identified for this Key Question. Two of these are follow-up publications related to studies already included in 1 or more SR, and 2 are not related to previously published studies. One of these recent publications represents an observational study that met inclusion criteria for this key question.

**Complications**

Complication rates were generally low and few statistically significant differences were reported for any of the interventions compared with surgery. Serious complications such as DVT, PE, and sural nerve damage were rare, with no significant differences between treatment groups noted in the SRs or RCTs; 1 large observational study reported a 50% decrease in the odds of DVT for patients undergoing open surgery compared with endovenous ablation; the percent of patients in each group with DVT was 0.8% in the surgery group and 1.6% in the endovenous ablation group (*P*=0.027). Adverse events such as bruising, paresthesia, hematoma, phlebitis, and infection were more common, but generally self-limiting or resolved with conservative management. The overall quality of evidence for this key question is considered to be moderate. Limitations of the evidence include methodological limitations of the individual studies contributing to pooled analyses, few available studies for some comparisons, and obvious or potential heterogeneity within the body of evidence with respect to aspects such as treatment delivery, comparators, and methods.

**DVT and PE**

**EVLA Versus Surgery:** As reported in all of the included SRs, serious adverse events such as DVT and PE were rare and there were no statistically significant differences between EVLA and surgery for these events based on data mostly from RCTs. Data from a recent publication of an RCT are consistent with these findings; there were no DVTs reported in the study. However, a statistically significant difference was reported in a publication of an analysis of data from the American College of Surgeons National Surgical Quality Improvement Program in which data were collect from 2005 to 2011 and represented 4366 patients (2580 received open surgery for varicose veins, and 1786 received endovenous ablation [EVLA or RFA]). The investigators found a 50% decrease in the odds of DVT for patients undergoing open surgery compared with endovenous ablation (adjusted OR=0.52 [95% CI, 0.28-0.97]; *P*=0.040). Analyses suggested that age, gender, race, BMI, specialty of the treating surgeon, and venous ulcer did not significantly affect the odds of postoperative DVT. There were 21 DVT events in the open surgery group compared with 28 events in the endovenous ablation group (0.8% and 1.6% respectively; *P*=0.027). There were baseline differences between the groups in this study. Patients in the endovenous ablation group were older, had a higher BMI, and were more likely to present with a venous ulcer.
RFA Versus Surgery: Similar to findings for EVLA compared with surgery, rates of DVT and PE were rare and there were no differences between groups in studies of RFA compared with surgery according 2 SRs.

Sclerotherapy Versus Surgery: One meta-analysis found no difference between FS and surgery with respect to the incidence of DVT. Another review reported rates of unspecified “major events requiring intervention” of 1 of 363 (0.3%) among surgery patients and 3 of 418 (0.7%) among FS patients (P=NR). A third review found 3 studies that reported a total of 13 DVT events in the FS group and 1 in the surgery group. Eleven of these DVTs occurred in the FS group of 1 study; they all occurred prior to a dose reduction in the FS group.

Nerve Damage (including paresthesia)

EVLA Versus Surgery: Across the included systematic reviews, analyses generally showed statistically significantly lower rates of paresthesia and nerve damage among EVLA patients than surgery patients.

RFA Versus Surgery: Two systematic reviews suggest no statistically significant differences between RFA and surgery with respect to paresthesia. In 1 of the reviews, 2 of 4 studies reported a statically significant difference suggesting worse outcomes after surgery than EVLA; the other 2 studies did not find a difference between the groups. Analyses conducted in the other review concluded there is no difference between the treatment groups.

Sclerotherapy Versus Surgery: In 1 review, 2 studies reported on this outcome, but only 1 reported a difference between FS and surgery. This study found better results for FS than surgery. Pooled incidences reported in another review suggest a higher rate of nerve damage among those who received surgery (15/363 [4.1%]) than among those who received FS (3/418 [0.7%]), but statistical significance is not reported.

Infection

EVLA Versus Surgery: The authors of 1 review noted that infection was 1 of the complications most frequently reported in all of the studies evaluated in their review (this includes all interventions and comparisons assessed in the review). However, overall the number of adverse events was very small and statistically significant differences were not often reported for most types of events. Only 1 study identified in this review reported significantly fewer infections in the EVLA group than the surgery group (P<0.05). In another review, investigators found a statistically significant difference between the pooled incidence of infection from 12 studies with a ligation and stripping (L/S) arm (2.1% [95% CI 1.3-3.1]) and the pooled incidence of infection from 12 studies with an EVLA arm (0.7% [95% CI 0.3-1.3]); P=0.006. A meta-analysis of 7 comparisons (2 studies with zero events were excluded) comparing EVLA with L/S also found a statistically significant difference in favor of EVLA (OR=0.24 [95% CI0.10-0.58]; I²=0%). A similar result was found in another meta-analysis that included 6 of the same studies in the other meta-analysis. The RR=0.28 (95% CI, 0.11-0.70); I²=0% is in favor of EVLA. In a fourth review, the authors reported that 2% of surgery patients in 1 study and 11% in another study experienced wound infection; no infection events were reported for the EVLA arms in these studies. In a publication of primary data,
the odds of experiencing a superficial surgical site infection were increased for patients undergoing open surgery compared with patients undergoing endovenous ablation (adjusted OR=2.56 [95% CI, 1.19-5.50]; P=0.016).

**RFA Versus Surgery:** Two systematic reviews reported finding no statistically significant differences in rates of infection between RFA and surgery.

**Sclerotherapy Versus Surgery:** One study identified by the authors of 1 of the reviews found higher infection rates in the FS group than in the surgery group.

**Other Complications**

**EVLA Versus Surgery:** With respect to rates of other postprocedural complications, only the following were reported as statistically significantly different in more than 1 study. Analyses suggest better outcomes associated with EVLA than with surgery for hematoma. With respect to superficial venous thrombosis or thrombophlebitis, results favor surgery.

**RFA Versus Surgery:** Analyses in 1 review found statistically significant differences between surgery and RFA for superficial venous thrombosis or thrombophlebitis, bruising, and hematoma. Results for the pooled incidences of superficial venous thrombosis favored surgery (P=0.003). For hematoma and bruising, RFA was associated with better results (P<0.001).

**Sclerotherapy Versus Surgery:** In 1 review, 2 studies are described as having found that FS had significantly better outcomes with respect to bruising than surgery. In the same review, 2 studies were described as finding better results for surgery than for FS with respect to rates of phlebitis. Hematoma was reported in 2 studies included in another review, total incidence across these 2 studies was 4 of 295 (1.4%) for the surgery group, and 1 of 341 (0.3%) for the FS groups. With respect to the incidence of phlebitis, 1 review reported 5 of 295 (1.7%) and 34 of 341 (10%) in the surgery and FS groups, respectively, based on data from 2 studies. In a third review, a meta-analysis suggested that the rate of superficial thrombophlebitis was higher in the FS group than in the surgery group (RR=16.85 [95% CI, 2.27-124.74]; P=0.0057). The authors of this review note that rates of skin pigmentation did not differ between surgery and FS; however, ecchymosis was significantly lower with FS compared with surgery (RR=0.40 [95% CI, 0.25-0.64]; P=0.0001).

**Key Question #3:** Among patients being treated for varicose veins, does the effectiveness or risk of adverse events of laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping vary by clinical history (e.g., comorbidities, previous treatment of varicose veins), patient characteristics (e.g., age, sex, body mass index [BMI], smoking history)?

Four of the SRs described in Key Questions #1 and #2 focused specifically on varicosities of either the GSV or SSV (Dermody et al., 2013; Nesbitt et al., 2014; O'Donnell et al., 2016; Paravastu et al., 2016). One publication of primary data from an observational study described in Key Question #2 offered
limited subgroup analyses, but no comparisons between treatment types with respect to subgroups. These studies and their results are described in Key Questions #1 and #2. No other studies were identified that reported on subgroup analyses by previous treatment, race, comorbidities, or other clinical history or patient characteristics.

**Key Question #4:** What are the cost implications and cost-effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping for patients being treated for varicose veins?

Three of the SRs identified for Key Questions #1 and #2 also included assessments of cost information (Rigby et al., 2009; Carroll et al., 2013; Nesbitt et al., 2014). No recent publications of primary cost-effectiveness data from a U.S. perspective comparing the interventions of interest with surgery were identified. Two primary studies assessing the cost of varicose vein treatments in U.S. facilities were identified.

Conclusions from the 3 SRs, suggest that available economic data and analyses are limited by variations in reporting, lack of applicability to settings outside of the UK or Europe, poor methodological quality, and in adequate reporting or out-of-date information. The two U.S.-based cost analyses identified through the recent literature search found that the minimally invasive varicose vein treatments were associated with lower costs than surgery. These studies are limited by small sample size and retrospective study design, and they may not be generalizable.

**Practice Guidelines**

The search of the core sources and relevant specialty groups identified 8 guidelines regarding selected treatments for varicose veins and published within the past 10 years. The general recommendations provided by the guidelines are summarized in Table 4. Additional details, by guideline, are presented in Appendix VI. See also Practice Guidelines in the TECHNICAL REPORT for additional background information on guidelines.

The guidelines reviewed generally conclude that there is adequate evidence to support the use of EVLA, RFA, and sclerotherapy for treatment of varicose veins, although the quality of individual studies and grade of the overall evidence vary depending on the intervention being assessed. Levels and grades of evidence attributed by the guideline authors are provided in Appendix VI along with a more detailed description of the recommendations. The guidelines summarized here generally recommend EVLA or RFA over surgery unless endovenous thermal ablation is not appropriate for the patient. Sclerotherapy and phlebectomy are also recommended in some clinical situations, but not always as a first choice of treatment. Endovenous treatments are not recommended during pregnancy. Phlebectomy is often considered as a concomitant treatment along with other approaches.
Table 4. Summary of Practice Guideline Recommendations

Key: CEAP, Clinical, Etiologic, Anatomic, Pathophysiologic; CVD, chronic venous disease; EVLA, endovenous laser ablation; FS, foam sclerotherapy; GL(s), guideline(s); GSV, great saphenous vein; RCTs, randomized controlled trials; RFA, radiofrequency ablation; SSV, small saphenous vein; UGFS, ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Quality of Individual GLs, Title (Author, Year)</th>
<th>Recommendations</th>
</tr>
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<tr>
<td>Good <em>Society for Vascular Surgery (SVS) and the American Venous Forum (AVF): The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines</em> (Gloviczki et al., 2011)</td>
<td>The 2011 clinical practice guidelines of the SVS and AVF Venous Guideline Committee recommend EVLA, RFA, and FS as effective alternatives to stripping and other modalities.</td>
</tr>
<tr>
<td>Good <em>Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF): (O’Donnell et al., 2014)</em></td>
<td>The 2014 GLs on management of venous leg ulcers aim to address the twofold goal of venous leg ulcer treatment, which includes ulcer healing and prevention of ulcer recurrence. The GL authors note that in general, they found the quality of the available evidence for operative or endovascular management was largely limited to level “C” because of a lack of RCTs evaluating treatment techniques. The GLs generally, with a few exceptions, suggest or recommend the use of ablation followed by compression for specific types of venous incompetence and reflux occurring with venous leg ulcers.</td>
</tr>
<tr>
<td>Good <em>Diagnosis and management of varicose veins in the legs: NICE guideline</em> (National Clinical Guideline Centre, 2013)</td>
<td>National Institute for Health and Care Excellence recommended a treatment hierarchy for confirmed varicose veins and truncal reflux: RFA/EVLA &gt; UGFS &gt; surgery. During pregnancy, consideration should be given to compression hosiery instead of interventional treatment (except in exceptional circumstances).</td>
</tr>
</tbody>
</table>
| Good *Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)* (Wittens et al., 2015) | • Recommends against sclerotherapy for first-choice treatment except in elderly and frail patients with venous ulcers; sclerotherapy is recommended as a second-choice treatment for some CEAP classifications or for more advanced stages of CVD for patients not eligible for surgery or endovascular ablation.  
• Recommends endovenous thermal ablation techniques in preference to surgery and sclerotherapy for patients with GSV reflux, and endovenous thermal ablation should be considered for patients with SSV reflux.  
• Recommends surgical treatment for non-complicated varicose veins instead of conservative treatment; when surgical treatment is performed, high ligation and stripping is recommended instead of high ligation alone; surgical stripping of the saphenous vein without high ligation leaving a 2 cm stump may be considered. |
<table>
<thead>
<tr>
<th>Quality of Individual GLs, Title (Author, Year)</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| • Concomitant phlebectomies should be considered when performing endovenous thermal ablation for truncal reflux; ambulatory phlebectomy should be considered to treat tributary varicose veins.  
• EVLA, RFA, UGFS, or phlebectomies should be considered for treating recurrent varicose veins; extensive redo surgery is not recommended as first choice for patients with recurrent varicose veins. | |
| Fair  
American College of Phlebology Guidelines – Treatment of refluxing accessory saphenous veins (Gibson et al., 2016) | The group’s recommendation is that patients with symptomatic incompetence of the accessory GSV be treated with endovenous thermal ablation (EVLA or RFA) or with UGFS to reduce symptoms. |
| Fair  
Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines (Rathbun et al., 2014) | The GLs state that endovenous FS is effective for treating primary and recurrent GSV, SSV, and accessory varicose veins. However, no randomized controlled trials were available for assessment and the group could not draw conclusions about the comparative efficacy or safety of FS and endovenous thermal ablation. |
| Poor  
Treatment of Superficial Venous Disease of the Lower Leg (ACP, 2014) | • Generally recommend EVLA or RFA as preferred treatment instead of surgery, except when veins are not amendable to endovenous procedures; recommends against compression therapy as a prerequisite for symptomatic venous disease when treatments such as endovenous ablation are appropriate.  
• Recommends treating visible symptomatic tributary veins with stab phlebectomy, liquid sclerotherapy, or FS; non-visible symptomatic tributary veins should be treated with UGFS or FS. |
| Fair  
ACR Appropriateness Criteria: Radiologic Management of Lower-extremity Venous Insufficiency (Rochon et al., 2012) | Recommendations state that EVLA or RFA is “usually appropriate” in several specific clinical situations described, and “usually not appropriate” during pregnancy. Surgical vein stripping and injection sclerotherapy were classified as “may be appropriate” for the same clinical scenarios, except pregnancy for which these were also rated as “not usually appropriate.” |

**Selected Payer Policies**

At the direction of WA HCA, published coverage policies for the following organizations were sought: Aetna, Centers for Medicare & Medicaid Services (CMS), Oregon Health Evidence Review Commission (HERC), Group Health Cooperative, and Regence Blue Cross/Blue Shield. The lack of a published coverage policy does not necessarily mean the payer does not provide coverage.
See Selected Payer Policies in the TECHNICAL REPORT for additional details and links to policy documents.

Information about coverage policies were sought from these 5 payer organizations: Aetna, Centers for Medicare & Medicaid Services (CMS), Group Health Cooperative, Oregon Health Evidence Review Commission (HERC), and Regence Group. Only the Oregon HERC did not have a published coverage policy available for review. The remaining organizations have coverage policies for varicose vein treatment, including EVLA, RFA, sclerotherapy, and/or phlebectomy. Each policy describes specific diagnostic, symptom, and/or prior treatment criteria that must be met for coverage eligibility.

Overall Summary and Discussion

Evidence-Based Summary Statement

Overall, moderate-quality evidence for Key Question #1 suggests that EVLA is similar to or better than conventional surgery in the treatment of varicose veins for many clinical and patient-centered outcomes. However, the evidence for some outcomes such as pain and time to return to work or normal activities is mixed or inconclusive. Limitations of the evidence include lack of reporting of statistical test results and methodological limitations of individual studies. A low-quality body of evidence suggests that the effectiveness of RFA is similar to or better than surgery for many outcomes, most notably, RFA may be associated with less postoperative pain than conventional surgery. Limitations of the evidence include few studies reporting some outcomes, lack of reporting of statistical test results, and methodological limitations of individual studies. Similarly, a low-quality body of evidence suggests similarities in many clinical and patient-centered outcomes between sclerotherapy and conventional surgery; however, it is difficult to draw conclusions on comparative effectiveness due to a lack of sufficient or consistent data on several outcomes. No studies comparing ambulatory phlebectomy to surgery meeting inclusion criteria were identified, however phlebectomy may have been an adjunctive treatment in studies of the other interventions.

The overall quality of evidence for Key Question #2 is moderate and suggests that EVLA, RFA, and sclerotherapy are relatively safe compared with surgery--few significant differences were reported. Rates of serious complications are low and similar when compared with surgery. More common complications included bruising, phlebitis, hematoma, and infection. Limitations of the evidence include methodological limitations of the individual studies contributing to pooled analyses, few available studies for some comparisons, and obvious or potential heterogeneity within the body of evidence with respect to aspects such as treatment delivery, comparators, and methods.

Subgroup analyses were not available in any of the included SRs or primary data publications. Three SRs described in Key Questions #1 and #2 focused on either GSV or SSV varices. Results and conclusions considering results from those publications are discussed in Key Questions #1 and #2. Economic analyses were described in 3 SRs. Conclusions from these reviews suggest that available economic data and analyses are limited by variations in reporting, lack of applicability to settings outside of the UK or Europe, poor methodological quality, and inadequate reporting or out-of-date information. The two U.S.-based cost analyses identified through the recent literature search found that the minimally
invasive varicose vein treatments were associated with lower costs than surgery. These studies are limited by small sample size and retrospective study design, and they may not be generalizable.

**Gaps in the Evidence**

The following evidence is needed to better answer the Key Questions of this report:

- Future studies that address the methodological limitations of individual studies such as variation in outcome definitions and metrics, and better reporting or conduct of randomization procedures.
TECHNICAL REPORT

Clinical Background
The purpose of this health technology assessment (HTA) is to assess the evidence on selected interventions for varicose veins compared with surgery (vein ligation with or without stripping). The interventions of interest are endovascular laser ablation (EVLA), endovascular radiofrequency ablation (RFA), sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy).

Varicose Veins
Varicose veins, also known as varicosities, are a common manifestation of chronic venous insufficiency (CVI), a category of chronic venous disease (CVD). CVD of the lower extremities is typically classified based on symptoms and using the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) categories C0-C6. Varicose veins are in the C2 category, and can be further described by characteristics from the other categories within the classification scheme. The following lists the criteria for each category in the classification system (Eberhardt and Raffetto, 2014).

- Clinical classification (C): C0, no visible sign of venous disease; C1, telangiectases or reticular veins; C2, varicose veins; C3, edema; C4, changes in skin and subcutaneous tissue (A - pigmentation or eczema, B - lipodermatosclerosis or atrophie blanche); C5, healed ulcer; C6, active ulcer.
- Etiologic (E): Ec, congenital; Ep, primary; Es, secondary (e.g., postthrombotic syndrome, trauma); En, no venous cause identified.
- Anatomic (A): As, superficial; Ad, deep; Ap, perforator; An, no venous location identified.
- Pathophysiologic classification (P): Pr, reflux; Pd, obstruction; Pr, reflux and obstruction; Pn, no venous pathophysiology identified.

The prevalence of varicose veins is estimated to be 5% to 30% in the adult population. Approximately 25 million adults in the United States are affected by varicose veins. They are more common among women than men (Eberhardt and Raffetto, 2014). Varicose veins are enlarged and tortuous vessels that develop when the thin flaps of the venous valves no longer meet in the midline, allowing blood to reflux, or flow backward (see Figure 1). Superficial venous reflux introduces elevated intravascular pressure into veins that are intended to function as a low pressure system, which leads to progressive distension, dilation, and tortuosity of the vein. Since the superficial veins lack muscle support and lie close to the surface of the skin, they become visible with increased intravascular pressure. The condition is further aggravated
as the walls of the affected vein weaken. Varicose veins are found most often on the back of the calf or on the inside of the leg between the groin and ankle, but may appear anywhere on the body. Great saphenous vein (GSV) reflux, a frequent form of CVI, is most commonly responsible for the development of varicose veins (Dietzek, 2007; Gonzalez-Zeh et al., 2008), and is often the result of reflux through the valve at the junction between the GSV and the common femoral vein. Although reflux is more prevalent in the GSV, reflux in the small saphenous vein (SSV) also occurs in approximately 6% to 15% of patients with CVI. The SSV and its tributaries drain the subcutaneous tissues of the heel and posterior aspect of the leg (see Figure 2). The SSV has variable anatomy and connects with the GSV, the deep veins, and the muscular vein at various levels (Labropoulos and Abai, 2007). SSV reflux is generally caused by incompetence at the saphenopopliteal junction (SPJ) (Engelhorn et al., 2005; Kurt et al., 2007; O’Hare et al., 2008). Risk factors include older age, a family history of the condition, obesity, pregnancy, inactivity, and prolonged standing or sitting (Heller and Evans, 2015).

Figure 1. Varicose Veins  
Figure 2. Great and Small Saphenous Veins

Varicose veins measure ≥ 3 millimeters (mm) in diameter, whereas telangiectases are < 1 mm and reticular veins are from 1 to 3 mm (Eberhardt and Raffetto, 2014). Often, varicose veins initially present only a cosmetic concern, but they can become clinically important when symptoms such as cramping, throbbing, burning, swelling, feeling of heaviness or fatigue, and alterations in skin pigmentation in the afflicted area become pronounced. Severe varicosities may be associated with dermatitis, ulceration, and thrombophlebitis, which result when metabolic waste products are no longer removed due to pooling of venous blood and increased hydrostatic pressure (Carr, 2006). Conservative treatments for
symptomatic varicose veins of the legs include compression hosiery, elevating the legs, walking, and weight management. In cases with severe discomfort, ulceration, or thrombosis, surgical ligation and excision (vein stripping) or minimally invasive procedures (e.g., sclerotherapy, EVLA, and endovenous RFA) may be used to destroy or remove affected vessels. Traditional open techniques have been associated with postoperative morbidity, including complications from groin incisions, pain, scarring, and long recovery periods (Zhan and Bush, 2014). Techniques such as sclerotherapy and endoluminal occlusion using radiofrequency (RF) or laser light energy have been introduced for the treatment of varicose veins due to GSV, SSV, or saphenofemoral junction (SFJ) reflux (Proebstle et al., 2003; Eberhardt and Raffetto, 2014; Zhan and Bush, 2014; Douketis, 2017). These techniques may reduce postoperative morbidity and improve recovery time compared with conventional surgical options, but are also associated with some complications (Desmyttere et al., 2007; Eberhardt and Raffetto, 2014; Goodyear and Nyamekye, 2015). For example, complications associated with endovenous thermal ablation techniques (laser and RF) include hematoma, thrombophlebitis, venous thrombosis, vessel perforation, thermal injury to adjacent nerves, skin burns, and discoloration (Goodyear and Nyamekye, 2015). Regardless of treatment, patients often experience a recurrence and repeated treatment may be necessary (Douketis, 2017). EVLA, RFA, sclerotherapy, and ambulatory phlebectomy compared with ligation with or without vein stripping are the focus of this technology assessment.

**Endovascular Laser Ablation**

EVLA is the removal or destruction of a vein or vein segment by means of laser. It involves the delivery of laser light through a glass fiber placed into the lumen of a refluxing vein. The goal of EVLA is to use laser energy to seal off the damaged portions of varicose veins to prevent further varicose vein formation, eliminate associated discomfort, and improve cosmetic appearance. This therapy is intended primarily for the treatment of varicose veins that result from GSV, SSV, or accessory vein reflux.

Before a patient undergoes EVLA, Doppler or duplex ultrasonography (US) is performed to ensure that the varicose veins are not due to a deep vein obstruction and to confirm and map all areas of reflux (London and Nash, 2000). The surgeon then selects an appropriate entry point through a needle puncture, threads a catheter through the GSV up to the SFJ or through the SSV up to the SPJ, and then inserts an optical fiber through the catheter. Proper positioning of the tip of the optical fiber can be verified by US or by passing low-energy, visible laser light through the fiber, causing the tip of the fiber to be visible through the skin. The optical fiber is then connected to a surgical laser, allowing high-intensity laser light to induce photocoagulation of blood and occlusion of the vein. Laser intensities range from 10 to 15 watts at a wavelength from 810 to 1500 nm. Before venous occlusion with high-intensity laser light, the perivenous region is infiltrated with tumescent local anesthesia under US guidance to not only reduce pain, but also to compress the venous wall against the optical fiber tip, and to serve as a “heat sink” that prevents damage to surrounding tissue from excess heat. EVLA can also be performed under general anesthesia or spinal block. During EVLA, some practitioners withdraw the catheter containing the optical fiber in short steps and apply laser light pulses at regular intervals to prevent any further blood flow through the vein. Other practitioners prefer to withdraw the optical fiber at a steady, continuous rate, while applying a constant, high-intensity laser light. The parameters that practitioners use, the velocity, and technique in which the laser is withdrawn is variable and dependent
on the type of laser. Depending on the length of the vein segment being treated, the total duration of exposure to high-intensity laser light may range from 1 to 3 minutes. The mechanism of EVLA remains unclear, but a thermal reaction following laser exposure is believed to be important. The direct and indirect thermal reactions cause scar formation, vein occlusion, and finally vein absorption. Histological studies have demonstrated that EVLA damages the endothelial and intimal layers, internal elastic lamina, and media. Compression stockings are worn for 1 to 2 weeks after the procedure and normal activity is encouraged. The procedure can be repeated if the treated vessel is not occluded after 7 days (Navarro et al., 2001; Chang and Chua, 2002; Proebstle et al., 2002; Min et al., 2003; Proebstle et al., 2003; Sadick and Wasser, 2004; Mundy et al., 2005; van den Bos et al., 2008; Carradice et al., 2015).

EVLA may not be suitable or contraindicated in select patients who are pregnant, have extremely tortuous GSVs or SSVs that would prevent catheterization and passage of laser fiber, have peripheral inflammatory artery disease, have a history of deep vein thrombosis (DVT) or deep venous insufficiency, exhibit nonpalpable pedal pulses, or in patients who have difficulty walking.

**Radiofrequency Ablation**

RFA is the removal or destruction of a vein or vein segment by means of RF energy. Endoluminal RFA is a treatment for symptomatic varicose veins that involves delivery of controlled RF energy through a catheter inserted into the affected vein. The heat generated by the RF energy causes the vein to contract and become occluded. The treatment is intended as a minimally invasive alternative to standard surgery for symptomatic varicosities.

RFA is generally a 3-part procedure beginning with Doppler US imaging of the target vein, followed by the administration of tumescent anesthesia to reduce operative discomfort and reduce the risk of skin burns during application of RF energy. Once adequate anesthesia is achieved, the catheter is advanced to within 1 to 2 centimeters (cm) of the SFJ. In most cases, proper positioning of the catheter can be determined by palpation or, preferably, by US-guided imaging. When proper placement is confirmed, RF treatment proceeds incrementally. RF energy is emitted until the venous wall temperature reaches the indicated temperature. The catheter is then slowly pulled back through the refluxing vein, causing the entire length of the vein to collapse in on itself. Techniques and technical details may vary depending on the specific RFA device used (Goodyear and Nyamekye, 2015).

After the catheter is removed and duplex imaging has confirmed the absence of reflux, a bandage is placed over the insertion site and the leg is wrapped. Most patients can resume normal activity immediately, although patients may be directed to walk regularly, wear compression stockings, and refrain from long periods of standing for a few weeks following the procedure. The remaining vessels in the venous system eventually compensate for the ablated vein (Chandler et al., 2000).

Contraindications for endovenous RFA include presence of a pacemaker or internal defibrillator, aneurysmal section in the vein segment for which the treatment is intended, and peripheral arterial disease as determined by an ankle-branchial index < 0.9 (Chandler et al., 2000).
**Sclerotherapy**

Sclerotherapy is obliteration of a vein or vein segment by chemical introduction (liquid or foam). The solution or sclerosant causes the vein to scar closed, prohibiting the flow of blood through the occluded vein. The affected vein is converted into a thread of fibrous connective tissue and absorbed into the body over time (Weiss et al., 2014). This therapy is intended for primary and secondary treatment in adults with varicose veins that result from GSV, SSV, or accessory vein reflux. The goals of sclerotherapy for varicose veins are improved function, symptoms, and appearance, and reducing complications associated with varicose veins (Weiss et al., 2014). Food and Drug Administration (FDA)-approved sclerosing agents include polidocanol and sodium tetradecyl sulfate (STS). Other sclerosing agents may have been used historically or may be currently used “off-label” (Weiss et al., 2014). Liquid sclerotherapy is more commonly used for telangiectasia and reticular veins or small to medium varicose veins; foam sclerosant (FS) may be used for larger refluxing veins (Weiss et al., 2014; MFMER, 2017).

According to a local coverage determination document issued by Noridian Healthcare Solutions LLC, FS is FDA-indicated for the treatment of incompetent GSVs, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee (LCD L34010). FS is administered under US guidance via cannulation of the affected veins with the use of local anesthesia. After injection, spasm of the vein segment is confirmed by US before an additional injection. Multiple treatments sessions may be needed depending on the extent and severity of the condition (Lorenz et al., 2014). After treatment, compression bandages or stockings are worn for several days.

Contraindications include allergies to sclerosants, severe systemic disease, acute superficial or DVT, local infection in the area to be treated or severe generalized infections, immobility, confinement to bed, advanced arterial occlusive disease, and known symptomatic patent foramen ovale. Sclerotherapy should not be used during pregnancy. Other factors to consider include leg edema, uncontrolled diabetes, delayed complications after diabetes, mild arterial occlusive disease, poor general health, bronchial asthma, marked allergic diathesis, history of anaphylaxis, hypercoagulability syndromes, bleeding disorders, and a history of DVT (Weiss et al., 2014).

**Ambulatory Phlebectomy**

Ambulatory phlebectomy is the removal of a vein segment through small incisions (1 to 3 mm) with the aid of instruments such as a vein retractor or phlebectomy hook. The procedure is usually done as an outpatient procedure using local anesthesia (Wittens et al., 2015). Indications for this technique are side branch varicose veins, and varicose veins of the foot, around the ankle, and the knee pit (Heller and Evans, 2015; Lin et al., 2015). Generally, incisions are small enough to not require closure with sutures (Heller and Evans, 2015). Post-procedure care includes dressings and anti-inflammatory pain medication if needed. Patients are allowed to walk immediately following the procedure. Return to work and normal activities is usually within a day or so and depends on the extent of the phlebectomy (Heller and Evans, 2015). Ambulatory phlebectomy may be performed in conjunction with other techniques such as RFA, EVLA, or surgical stripping (Wittens et al., 2015; MFMER, 2017). Adverse events such as phlebitis, inflammation, numbness, or hypersensitivity can occur. Warm compresses and anti-inflammatoryatories may be used to address phlebitis or inflammation, and any numbness or sensitivity usually goes away (Heller and Evans, 2015).
**Vein Ligation and Stripping**

Vein ligation and stripping, or closing off a vein and removing it, is the traditional method of surgical management of GSV and SSV varices. Variations of the procedure exist, including ligation without stripping. In general, the technique involves making an incision at either the SFJ or the popliteal fossa, depending on whether the GSV or SSV is the target of the treatment and another incision lower in the leg. In the case of GSV varices, the procedure involves saphenofemoral ligation and stripping of the GSV to the knee; this is known as high ligation and stripping (Nesbitt et al., 2014). Surgical management of SSV varices involves disconnecting the SPJ and either cutting away or stripping a segment of the SSV (Paravastu et al., 2016). Different methods of stripping have been employed; a common method is the use of a metal probe or wire inserted at the lower incision and threaded to the upper end of the target vein. The wire is tied to the vein and retracted through the lower incision, bringing the vein with it (Chwala et al., 2015). Open surgical procedures are associated with adverse effects such as hematomas, pain, nerve injury, scarring, long recovery periods, and complications such as infection at the groin incision site. Also, the risk of recurrence of varicose veins within 5 years is considered high (Nesbitt et al., 2014; Chwala et al., 2015; Paravastu et al., 2016).
Washington State Agency Utilization and Costs

Selected Endovascular and Surgical Interventions for Treating Varicose Veins

Populations

The Selected Endovascular and Surgical Interventions for Treating Varicose Veins (varicose veins) analysis includes member utilization and cost data from the following agencies: PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan); PEBB Medicare, the Department of Labor and Industries (L&I) workers’ compensation plan; and the HCA Medicaid (formerly Fee-for-Service) and the Medicaid Managed Care program.

The analysis period was five (5) calendar years, 2012 - 2016. Primary population inclusion criteria included age greater than 17 years old at time of service AND incurring at least one of the CPT/HCPCS codes from Table I. Denied claims were excluded from the analysis.

Methods

Varicose vein procedures were identified when an agency member experienced one or more of the CPT codes from Table I, a provider claim was generated, and the claims was adjudicated and paid. Data evaluation included examining utilization by member; analysis of individual and aggregate CPT codes (Table I, TYPE), and by total claims’ costs incurred by a member on the date of their varicose vein procedure (Total Claims).

Analyzing Total Claims for the date of service provided an enhanced view of the cost of a varicose vein procedure (e.g., inpatient stay, anesthesia, nurse, instruments, etc.). “Dollars” refers to paid dollars.

The tables, charts, and graphs that follow refer to the Table I listed CPT codes as the “Procedures” or simply, “CPTs”
Table I. CPT Descriptions

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36470</td>
<td>Injection of sclerosing solution; single vein: TYPE: Sclerosing injection</td>
</tr>
<tr>
<td>36471</td>
<td>Injection of sclerosing solution; multiple veins, same leg TYPE: Sclerosing injection</td>
</tr>
<tr>
<td>36475</td>
<td>Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated.  TYPE: Radiofrequency Endovenous</td>
</tr>
<tr>
<td>36476</td>
<td>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). TYPE: Radiofrequency Endovenous</td>
</tr>
<tr>
<td>36478</td>
<td>Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated.  TYPE Laser Endovenous Ablation</td>
</tr>
<tr>
<td>36479</td>
<td>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). TYPE Laser Endovenous Ablation</td>
</tr>
<tr>
<td>37765</td>
<td>Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions. TYPE: Phlebectomy</td>
</tr>
<tr>
<td>37766</td>
<td>Stab phlebectomy of varicose veins, 1 extremity; more than 20 incisions. TYPE: Phlebectomy</td>
</tr>
<tr>
<td>37718</td>
<td>Ligation, division, and stripping, short saphenous vein. TYPE: Stripping</td>
</tr>
<tr>
<td>37722</td>
<td>Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below. TYPE: Stripping</td>
</tr>
<tr>
<td>37735</td>
<td>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. TYPE: Stripping</td>
</tr>
</tbody>
</table>

Table II. Definitions for Utilization Tables

- **Unique members**: Unique, non-duplicated member, reported by agency
- **Count of procedures (CPT)**: Count of annual varicose vein procedures, non-duplicated; methods used ensured that procedures were not double-counted.
- **Average procedures/member**: Total procedures (CPT)/Unique members
- **Dollars paid by (CPT)**: Paid dollars for all varicose vein procedure CPTs – non-duplicated. (See Table I)
- **Total dollars on date of service**: Total paid dollars for any other services received on the date of the varicose vein procedure
- **Average dollars/ CPT**: Dollars paid by procedure (CPT)/ Total procedures (CPT)
- **Average dollars/date of service**: Total dollars incurred on date of service/ Total procedures (CPT)

Demographics

The following graphs depict the study populations, PEBB and HCA Medicaid, and Managed Care Medicaid. Each agency population is analyzed over a five (5) year period.
Total Medicaid Population

Population distribution by year

Distribution by Gender

<table>
<thead>
<tr>
<th>Year</th>
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<th>Male</th>
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<tbody>
<tr>
<td>2012</td>
<td>596,062</td>
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</tr>
<tr>
<td>2013</td>
<td>603,088</td>
<td>469,993</td>
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<tr>
<td>2014</td>
<td>798,070</td>
<td>678,986</td>
</tr>
<tr>
<td>2015</td>
<td>874,797</td>
<td>769,331</td>
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<tr>
<td>2016</td>
<td>897,762</td>
<td>799,786</td>
</tr>
</tbody>
</table>

Five year average by Gender

- Female: 46%
- Male: 54%

Distribution by Age Cohort

<table>
<thead>
<tr>
<th>Year</th>
<th>0 - 17</th>
<th>18 +</th>
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</thead>
<tbody>
<tr>
<td>2012</td>
<td>710,257</td>
<td>351,625</td>
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<tr>
<td>2013</td>
<td>712,309</td>
<td>360,780</td>
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<tr>
<td>2014</td>
<td>736,855</td>
<td>740,204</td>
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<tr>
<td>2015</td>
<td>785,147</td>
<td>858,884</td>
</tr>
<tr>
<td>2016</td>
<td>811,317</td>
<td>886,432</td>
</tr>
</tbody>
</table>

Five year average by Age Cohort

- 0 - 17: 44%
- 18 +: 56%
Total PEBB Population

PEBB Population by Year

Gender Distribution by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>117,612</td>
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<tr>
<td>2013</td>
<td>122,632</td>
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<tr>
<td>2014</td>
<td>125,652</td>
<td>102,235</td>
</tr>
<tr>
<td>2015</td>
<td>128,714</td>
<td>104,453</td>
</tr>
<tr>
<td>2016</td>
<td>134,004</td>
<td>108,314</td>
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</tbody>
</table>

Five year average by Gender

- Female: 45%
- Male: 55%

Age Cohort by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>0 - 17</th>
<th>18 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>179,523</td>
<td>4,046</td>
</tr>
<tr>
<td>2013</td>
<td>184,260</td>
<td>5,541</td>
</tr>
<tr>
<td>2014</td>
<td>191,285</td>
<td>6,002</td>
</tr>
<tr>
<td>2015</td>
<td>195,834</td>
<td>7,333</td>
</tr>
<tr>
<td>2016</td>
<td>203,312</td>
<td>7,006</td>
</tr>
</tbody>
</table>

Five year average by Age Cohort

- 0 - 17: 16%
- 18 +: 84%
### Utilization: Varicose Vein Procedures

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</tr>
</thead>
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<td><strong>HCA Medicaid</strong></td>
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<tr>
<td>Unique Members</td>
<td>35</td>
<td>9</td>
<td>7</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Count of procedure (CPT)</td>
<td>53</td>
<td>18</td>
<td>13</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Average procedures/member</td>
<td>1.5</td>
<td>2</td>
<td>1.9</td>
<td>1.9</td>
<td>2</td>
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<tr>
<td>Dollars paid by CPT</td>
<td>76,965</td>
<td>18,190</td>
<td>11,743</td>
<td>18,820</td>
<td>10,080</td>
</tr>
<tr>
<td>Total dollars on date of service</td>
<td>97,025</td>
<td>22,462</td>
<td>16,763</td>
<td>23,164</td>
<td>21,840</td>
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<tr>
<td>Average dollars/CPT</td>
<td>1,452</td>
<td>1,011</td>
<td>903</td>
<td>650</td>
<td>360</td>
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<tr>
<td>Average dollars/date of service</td>
<td>41,267</td>
<td>17,350</td>
<td>17,108</td>
<td>6,669</td>
<td>15,219</td>
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<td><strong>Managed Medicaid</strong></td>
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<tr>
<td>Unique Members</td>
<td>52</td>
<td>41</td>
<td>322</td>
<td>569</td>
<td>554</td>
</tr>
<tr>
<td>Count of procedure (CPT)</td>
<td>96</td>
<td>80</td>
<td>626</td>
<td>1,133</td>
<td>1,140</td>
</tr>
<tr>
<td>Average procedures/member</td>
<td>1.8</td>
<td>2</td>
<td>1.9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dollars paid by CPT</td>
<td>106,770</td>
<td>96,898</td>
<td>501,767</td>
<td>691,399</td>
<td>660,393</td>
</tr>
<tr>
<td>Total dollars on date of service</td>
<td>128,340</td>
<td>143,757</td>
<td>644,554</td>
<td>871,035</td>
<td>825,727</td>
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<tr>
<td>Average dollars/CPT</td>
<td>1,112</td>
<td>1,211</td>
<td>802</td>
<td>610</td>
<td>579</td>
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<tr>
<td>Average dollars/date of service</td>
<td>6,165</td>
<td>18,019</td>
<td>7,402</td>
<td>3,921</td>
<td>3,728</td>
</tr>
<tr>
<td><strong>PEBB/UMP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique Members</td>
<td>170</td>
<td>174</td>
<td>151</td>
<td>132</td>
<td>80</td>
</tr>
<tr>
<td>Count of procedure (CPT)</td>
<td>406</td>
<td>383</td>
<td>334</td>
<td>284</td>
<td>154</td>
</tr>
<tr>
<td>Average procedures/member</td>
<td>2.4</td>
<td>2.2</td>
<td>2</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Dollars paid by CPT</td>
<td>623,077</td>
<td>655,438</td>
<td>471,072</td>
<td>397,953</td>
<td>202,072</td>
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<tr>
<td>Total dollars on date of service</td>
<td>1,535</td>
<td>1,711</td>
<td>1,410</td>
<td>1,401</td>
<td>1,312</td>
</tr>
<tr>
<td>Average dollars/CPT</td>
<td>1.9</td>
<td>1.8</td>
<td>1.7</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Average dollars/date of service</td>
<td>110</td>
<td>118</td>
<td>111</td>
<td>122</td>
<td>103</td>
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<tr>
<td><strong>Medicare/PEBB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique Members</td>
<td>205</td>
<td>213</td>
<td>190</td>
<td>238</td>
<td>180</td>
</tr>
<tr>
<td>Count of procedure (CPT)</td>
<td>1.9</td>
<td>1.8</td>
<td>1.7</td>
<td>2</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Review Objectives

**Scope**

The scope of this report is defined as:

**Population:** Adult patients being treated for varicose veins

**Interventions:** EVLA, endovascular RFA, sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy)

**Comparisons:** Vein ligation with or without stripping

**Outcomes:**

- Clinical outcomes: Failure of the procedure, second or additional procedures after failure of initial procedure, technical recurrence, symptomatic recurrence, second or additional procedures to treat recurrence, changes in symptom scores measured by validated scales (e.g., VCSS)
- Patient-centered outcomes: Patient satisfaction/QOL; time to return to work or normal activity; pain
- Adverse events: Nerve damage, skin burns, deep venous thermal injury, DVT, pulmonary embolism, transient ischemic attacks, stroke, bleeding, infection, thrombophlebitis, headache, visual disturbance, skin staining, pain at injection site, back pain, anaphylaxis, lymph leak, cellulitis
- Cost/cost-effectiveness outcomes

**Settings:** Inpatient or outpatient

**Study Designs:**

For clinical effectiveness (Key Questions #1 and #3), good-quality systematic reviews and RCTs; for harms (Key Questions #2 and #3) in addition to good-quality systematic reviews and RCTs, large observational studies, including registry data (n ≥ 500), may be employed; similarly, for Key Question #4, observational and modelling studies may be also be employed.

**Key Questions**

The following Key Questions will be addressed:

1. Among patients being treated for varicose veins, what is the clinical effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?
2. Among patients being treated for varicose veins, what are the harms associated with endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

3. Among patients being treated for varicose veins, does the effectiveness or risk of adverse events of laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping vary by clinical history (e.g., comorbidities, previous treatment of varicose veins), patient characteristics (e.g., age, sex, body mass index [BMI], smoking history)?

4. What are the cost implications and cost-effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping for patients being treated for varicose veins?

**Search Strategy and Selection Criteria**
See Appendix I for additional search details.

Systematic Reviews
During the period of topic scoping and Key Question refinement, it was determined that the volume of available literature on the selected treatments for varicose veins was very large. In addition, there have been multiple systematic reviews and meta-analyses published on the topic in recent years. Consequently, a review of reviews methodology was employed for this HTA and a systematic search for systematic reviews and HTAs to answer the Key Questions was conducted. Manual searches of each included review identified relevant bodies of literature and data syntheses for inclusion in this HTA. PubMed and the Centre for Reviews and Dissemination (CRD) electronic databases were searched for relevant systematic reviews on September 6, 2016, and the following electronic databases were searched for additional systematic reviews on December 22, 2016: PubMed, Canadian Agency for Technology and Health (CADTH), Cochrane Library, National Health Service – National Institute for Health Research (NIH-NIHR), National Institute for Health and Care Excellence (NICE), and CRD. After searching each database, duplicates were removed from the results and titles and abstracts were reviewed for relevance according to the predetermined inclusion and exclusion criteria listed below. Full texts of each included systematic review and HTA were reviewed against the same inclusion and exclusion criteria. Relevant data from eligible publications were abstracted into evidence tables for inclusion in this HTA.

Primary Studies
*Following identification and selection of systematic reviews and HTAs, a targeted search of PubMed and relevant primary data studies published subsequent to the review(s) selected for each indication was conducted on September 6, 2016. The initial search was limited to RCTs published in the English language from March 1, 2011, to the search date. Titles, abstracts, and full texts were reviewed using the inclusion and exclusion criteria and data were abstracted into evidence tables for inclusion in this*
HTA. Searches will be updated for the final version of this HTA. A separate search was conducted for additional economic evaluations on February 1, 2017.

Practice Guidelines

In addition to guidelines found through the database and manual searches outlined above, we also searched the National Guidelines Clearinghouse and websites of professional organizations. Guidelines were not abstracted into evidence tables but rather summarized descriptively.

Inclusion/Exclusion Criteria

Detailed inclusion and exclusion criteria, along with their rationale, are presented in Table 5. The inclusion and exclusion criteria were derived in conjunction with the WA HTA program personnel based on feedback from the participating agencies.

Table 5. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong> Adult pts being treated for varicose veins</td>
<td>Pts aged &lt;18 yrs; pts being treated for complications from varicose veins or other forms of venous insufficiency (e.g., ulcer)</td>
</tr>
<tr>
<td><strong>Intervention:</strong> EVLA, RFA, sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy)</td>
<td>Thermal ablation other than laser and RFA (e.g., steam ablation); CHIVA; cryostripping</td>
</tr>
<tr>
<td><strong>Comparator:</strong> Vein ligation w/ or w/o stripping</td>
<td>Placebo/sham, other active comparators, or no comparison group</td>
</tr>
</tbody>
</table>

Outcomes:

Clinical outcomes — Failure of the procedure, second or additional procedures after failure of initial procedure, technical recurrence, symptomatic recurrence, second or additional procedures to treat recurrence, changes in symptom scores measured by validated scales (e.g., VCSS)

Pt-centered outcomes — Pt satisfaction/QOL; time to return to work or normal activity; pain

Safety — Nerve damage, skin burns, deep venous thermal injury, deep vein thrombosis, pulmonary embolism, transient ischemic attacks, stroke, bleeding, infection, thrombophlebitis, headache, visual disturbance, skin staining, pain at injection site, back pain, anaphylaxis, lymph leak, cellulitis

Cost/cost-effectiveness outcomes
### Inclusion Criteria

**Study Design:** For clinical effectiveness (Key Questions #1 and #3), good-quality systematic reviews and RCTs; for harms (Key Questions #2 and #3) in addition to good-quality systematic reviews and RCTs, large observational studies, including registry data (n ≥ 500), may be employed; similarly, for Key Question #4, observational and modelling studies may be also be employed.

**Setting:** Inpatient or outpatient

### Exclusion Criteria

Non-English language, no original data (narrative reviews, editorials, letters), abstracts, and conference posters; for systematic reviews, older reviews that have been updated or superseded by more recent reviews, no meta-analyses

### Quality Assessment

**Systematic Reviews and Primary Studies**

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was employed to determine the quality of selected systematic reviews (Shea et al., 2007; Appendix II). Appendix III outlines the process used by Hayes for assessing the quality of individual primary studies and the quality of bodies of evidence. This process is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good, fair, poor,* or *very poor.*

Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as AHRQ, use the phrase *strength of evidence.* The Hayes Evidence-Grading Guides ensure that assessment of the quality of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies, with an emphasis on the risk of bias within studies.
- Applicability to the population(s), intervention(s), comparator(s), outcome(s), and settings of interest, i.e., applicability to the PICOS statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

**NOTE:** Two terms related to applicability are *directness* and *generalizability.* Directness refers to how applicable the evidence is to the outcomes of interest (i.e., health outcomes versus surrogate or intermediate outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). Generalizability usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICOS (population-interventions-comparator-outcomes-setting) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision,* which refers to findings based on such a small quantity of data that the CI surrounding a pooled estimate includes both clinically
important benefits and clinically important harms, or such a small quantity of data that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of high, moderate, low, or very low quality. These labels can be interpreted in the following manner:

**High:** Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

**Moderate:** Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

**Low:** We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

**Very Low:** Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

**Economic Evaluations**

A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. Sources are listed in Appendix III.

**Guidelines**

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Next Steps Consortium, 2013), along with a consideration of the items related to commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. Use of the AGREE tool was limited to these areas because they relate most directly to the link between guideline recommendations and evidence.

**Search Results**

 Searches yielded 635 citations for abstract and title review. After screening abstracts, 106 articles were selected for full text review. A total of 18 publications were identified for data abstraction and assessment to answer the Key Questions. This includes 8 SRs and 10 publications of primary data not already included in 1 or more of the SRs. Five of the 10 primary publications represent newer data from studies that were included in the SRs based on earlier publications.

See Figure 2 for a summary of the update literature search results.
**Included Studies**

Eight systematic reviews were identified for inclusion (Rigby et al., 2009; Rathbun et al., 2012; Carroll et al., 2013; Dermody et al., 2013; Nesbitt et al., 2014; Pan et al., 2014; O’Donnell et al., 2016; Paravastu et al., 2016). There was considerable overlap of the individual studies included across the 8 reviews; however, none of the reviews includes exactly the same set of studies as another because of variations in search dates and inclusion and exclusion criteria. Consideration was given to the overlap of included primary studies when assessing the body of evidence. The review by Carroll et al. (2013) included studies of EVLA, RFA, and FS. This review included studies of patients with any type of varices. Nesbitt et al. (2014), and Paravastu et al. (2016) each assessed 3 interventions of interest for this HTA: EVLA, RFA, and FS and focused on studies evaluating the selected interventions for GSV and SSV varices, respectively. Dermody et al. (2013) and O’Donnell et al. (2016) assessed studies of EVLA and RFA; Dermody et al. (2013) specifically focused on analyzing data about harms associated with the procedures compared with traditional surgery. Pan et al. (2014) evaluated studies of EVLA only; this review included RCTs and observational studies. Rathbun et al. (2012) and Rigby et al. (2009) focused on sclerotherapy compared with surgery. Rathbun et al. (2012) limited studies to those of FS, whereas Rigby et al. (2009) did not. Details regarding how many studies for each intervention are included in each review are shown in Appendix V. No good-quality systematic reviews evaluating ambulatory phlebectomy alone compared with surgery were identified.

Eight additional publications of primary data were identified.

Two economic analysis studies were identified.

**Excluded Studies**

See Appendix IV for a listing of the 88 studies that were excluded from analysis after full-text review.

**Figure 2. Summary of Search Results**

- 635 citations
- 206 primary study searches
- 374 systematic review (SR) searches
- 106 full-text articles reviewed
- 529 citations excluded based on title/abstract review
- 88 citations excluded at full-text review
  - Ineligible study design, intervention, outcomes, population, or full text not available (11)
  - Ineligible publication type (32)
  - Ineligible comparator (14)
  - Included in an SR (31)
- 18 articles included
  - 8 SRs; 10 recent primary publications (includes 5 follow-up publications)
Literature Review

**Key Question #1**: Among patients being treated for varicose veins, what is the clinical effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

**Study characteristics**

See Appendix V for more details.

**Systematic Reviews**

Seven systematic reviews covering interventions of interest for this HTA were identified for Key Question #1 (Rigby et al., 2009; Rathbun et al., 2012; Carroll et al., 2013; Nesbitt et al., 2014; Pan et al., 2014; O'Donnell et al., 2016; Paravastu et al., 2016). The number of included relevant primary studies ranged from 3 to 25. See Table 6 for a list of individual study references in each of the reviews. Three reviews (Carroll et al., 2013; Nesbitt et al., 2014; Paravastu et al., 2016) assessed EVLA, RFA, and FS compared with traditional surgery. One of the reviews evaluated evidence for EVLA compared with surgery (Pan et al., 2014), 1 evaluated EVLA and RFA compared with surgery (O'Donnell et al., 2016), and 2 evaluated sclerotherapy compared with surgery (Rigby et al., 2009; Rathbun et al., 2012). Most of the reviews included only RCTs for primary data; however, 2 reviews included observational studies (Rathbun et al., 2012; Pan et al., 2014). Rathbun et al. (2012) included 104 studies; however, most of them did not include comparison groups and therefore did not contribute data to meta-analyses comparing treatments. Interventions described in the reviews included EVLA with 810 nm, 980 nm, or 1470 nm lasers; RFA with the Closure PLUS or ClosureFast catheters; and US-guided FS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation or high ligation with or without stripping. Several of the reviews described differences across individual studies with respect to reporting or analyzing data (e.g., randomization was by patient in some studies and by limb in others). As noted by several of the review authors, the use of data randomized by limbs can introduce some bias to pooled analyses (Carroll et al., 2013; Nesbitt et al., 2014). There was considerable overlap of the individual studies included across the 7 reviews; however, none of the reviews includes exactly the same set of studies as another because of variations in search dates and inclusion and exclusion criteria. Overlap of studies between reviews was considered when assessing bodies of evidence to minimize “double counting” of study populations.

**Table 6. Study Characteristics of Systematic Reviews Included for KQ#1**

**Key**: EVLA, endovenous laser ablation; FS, foam sclerotherapy; GSV, great saphenous vein; HTA, health technology assessment; NHS-NIHR, National Health Service – National Institute for Health Research; pt, patient; RCT(s), randomized controlled trial(s); RFA, radiofrequency ablation; SR, systematic review; SSV, small saphenous vein; tx, treatment; tx’d, treated
<table>
<thead>
<tr>
<th>SR Author, Yr</th>
<th>Total # Studies (Design)</th>
<th>Pt Population</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll et al. (2013)</td>
<td>n=34 (RCTs)*</td>
<td>Population: Adults aged ≥16 yrs who are being tx’d for varicose veins</td>
<td>Funding: NIHR HTA program (UK)</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Nesbitt et al. (2014)</td>
<td>n=13 (RCTs)</td>
<td>Population: Males and females of any age w/ varicose veins affecting the GSV system, confirmed on duplex ultrasound imaging, who were suitable for any of the tx options</td>
<td>Funding source: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paravastu et al., (2016)</td>
<td>n=3 (RCTs)</td>
<td>Population: Men and women aged ≥18 yrs who received tx for SSV varices</td>
<td>Funding source: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan et al. (2014)</td>
<td>n=13 (10 RCTs, 3 nonrandomized trials)</td>
<td>Population: Pts being tx’d for varicose veins</td>
<td>Funding source:</td>
</tr>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th># of Studies per Tx vs. Surgery</th>
<th>Author, Yr of Primary Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>EVLA vs surgery</strong> (8 RCTs): de Medeiros and Luccas, 2005; Darwood et al., 2008; Kalteis et al., 2008; Rasmussen et al., 2009; Christenson et al., 2010; Pronk et al., 2010a; Pronk et al., 2010b; Rasmussen et al., 2010; Carradice et al., 2011a; Rasmussen et al., 2011</td>
<td></td>
</tr>
<tr>
<td>• <strong>RFA vs surgery</strong> (6 RCTs): Rautio et al., 2002; Lurie et al., 2003; Lurie et al., 2005a; Perala et al., 2005; Hinchliffe et al., 2006; Balakrishnan et al., 2008; Subramonia and Lees, 2010a; Subramonia and Lees, 2010b; Helmy Elkaffas et al., 2011; Rasmussen et al., 2011</td>
<td></td>
</tr>
<tr>
<td>• <strong>FS vs surgery</strong> (10 RCTs): Bountouroglou et al., 2004; Liams et al., 2005; Bountouroglou et al., 2006; Wright et al., 2006; Abela et al., 2008; Kalodiki et al., 2008; Figueiredo et al., 2009; Jia et al., 2010; Lawaetz et al., 2010; Shadid et al., 2010; Kalodiki et al., 2011; Rasmussen et al., 2011</td>
<td></td>
</tr>
<tr>
<td>• <strong>EVLA vs surgery</strong> (8 RCTs): Beale et al., 2005; Rasmussen et al., 2007; Carradice et al., 2008; Darwood et al., 2008; Carradice et al., 2009; Flessenkamper et al., 2009; Rasmussen et al., 2009; Lawaetz et al., 2010; Pronk et al., 2010a; Rasmussen, 2010; Rasmussen et al., 2010; Carradice et al., 2011a; Carradice et al., 2011b; Rasmussen et al., 2011; Biemans et al., 2012; Carradice et al., 2012; Rass et al., 2012; Biemans et al., 2013; Flessenkamper et al., 2013a; Flessenkamper et al., 2013b; Lawaetz et al., 2013; Rasmussen et al., 2013</td>
<td></td>
</tr>
<tr>
<td>• <strong>RFA vs surgery</strong> (5 RCTs): Rautio et al., 2002; Lurie et al., 2003; Lurie et al., 2005a; Lurie et al., 2005b; Perala et al., 2005; Balakrishnan et al., 2008; Lawaetz et al., 2010; Subramonia and Lees, 2010a; Subramonia and Lees, 2010b; Helmy Elkaffas et al., 2011; Rasmussen et al., 2011</td>
<td></td>
</tr>
<tr>
<td>• <strong>FS vs surgery</strong> (3 RCTs): Lawaetz et al., 2010; Rasmussen, 2010; Shadid et al., 2010; Rasmussen et al., 2011; Biemans et al., 2012; Shadid et al., 2012; Biemans et al., 2013</td>
<td></td>
</tr>
<tr>
<td>• <strong>EVLA vs surgery</strong>: Roopram et al., 2013 (VESPA trial); Samuel et al., 2013 (HELP2 trial)</td>
<td></td>
</tr>
<tr>
<td>• <strong>RFA vs surgery</strong>: No studies identified for this comparison</td>
<td></td>
</tr>
<tr>
<td>• <strong>FS vs surgery</strong>: Brittenden et al., 2014 (CLASS trial);</td>
<td></td>
</tr>
<tr>
<td>SR Author, Yr</td>
<td>Total # Studies (Design)</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Rathbun et al. (2012)</td>
<td>n=104* (20 RCTs, 82 observational studies, 2 not classified)</td>
</tr>
<tr>
<td>Rigby et al. (2009)</td>
<td>n=9 (RCTs)</td>
</tr>
<tr>
<td>O’Donnell et al. (2016)</td>
<td>n=7 (RCTs)</td>
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</tbody>
</table>

*The HTA by Carroll et al. (2013) included a total of 34 studies; some of these studies compared the interventions of interest with treatments other than surgery and are not listed in this table. The systematic review by Rathbun et al. (2012) included studies without comparison groups or with comparisons other than surgery; these studies are not listed in this table.
**Primary Studies**

Seven recent publications evaluating interventions of interest for this HTA, and not included in the systematic reviews described above, were identified for Key Question #1. Five of these are follow-up publications related to previously published studies (Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Flessenkamper et al., 2016; Gauw et al., 2016), and 2 are publications unrelated to previously published studies (Michaels et al., 2006; Mozafar et al., 2014). Five publications compare EVLA with surgery (Basel et al., 2012; Mozafar et al., 2014; Kalteis et al., 2015; Rass et al., 2015; Flessenkamper et al., 2016; Gauw et al., 2016), 1 study compares sclerotherapy with surgery (Michaels et al., 2006), and 1 study compares EVLA and sclerotherapy with surgery (van der Velden et al., 2015). Details about study characteristics can be found in Appendix V.

**Study Quality**

Applying AMSTAR criteria for rating the quality of systematic reviews, all of the included systematic reviews were deemed to be of good quality. Limitations of some of the reviews included not providing a list of excluded studies (presumably because of limited publication space for journal publications) (Rathbun et al., 2012; Pan et al., 2014) and missing details about the quality of individual studies and/or the body of evidence (O’Donnell et al., 2016). Generally, the reviews were well conducted; however, the strength of the conclusions may be limited by the quality of the individual studies and the availability of appropriate data to pool for analyses. Each review described a method for assessing the quality of the individual studies included in the review. Methods included published checklists, the Jadad scale, the Cochrane Collaboration’s tool for assessing risk of bias, and the authors’ own criteria. Most reviews stated that the individual studies were predominantly of fair to poor quality or exhibited high risk of bias in 1 or more domains (e.g., selection or attrition bias).

The quality of the primary studies identified through the update search ranged from fair (n=6) (Michaels et al., 2006; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Flessenkamper et al., 2016; Gauw et al., 2016) to poor (n=2) (Liu et al., 2011; Mozafar et al., 2014). Limitations include lack of blinding, which is a common limitation in this area of research because of the nature of the interventions being studied. Other limitations include potential lack of statistical power or statistical testing, reporting bias, attrition bias, and unclear method of randomization.

**Clinical and Patient-Centered Outcomes**

Meta-analyses or qualitative summaries for the following clinical or patient-centered outcomes were presented in 1 or more of the included systematic reviews (SRs): failure of procedure, technical recurrence, change in VCSS, pain, symptomatic recurrence, QOL, and reintervention (because of technical failure). When meta-analyses could not be done, qualitative summaries were provided.

**Systematic Reviews: EVLA Versus Surgery**

Studies reporting clinical or patient-centered outcomes for EVLA compared with conventional surgery techniques were synthesized in 5 of the included SRs (Carroll et al., 2013; Nesbitt et al., 2014; Pan et al.,...
2014; Lynch et al., 2015; Paravastu et al., 2016), and a sixth review combined EVLA and RFA data to compare endovenous ablation with surgery (O'Donnell et al., 2016).

**Failure of Procedure:** Carroll et al. (2013) defined failure of procedure as “the procedure was incomplete, or occlusion or obliteration was not achieved or was not sustained for more than 1 month” (Carroll et al., 2013 p. 8). The investigators pooled results from 12 studies to determine the percentage of failure events in each study group. The pooled percentage for the EVLA pts was 1% (5/467), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20/681) (Carroll et al., 2013). The statistical significance of this difference was not reported. A meta-analysis conducted by Nesbitt et al. (2014) analyzed results from 6 studies comparing EVLA with surgery and found a statistically significant odds reduction favoring the EVLA group (OR=0.29 [95% CI, 0.14-0.60]; P=0.0009).

Paravastu et al. (2016) analyzed studies of EVLA versus surgery for patients with SSV varices. Results from a meta-analysis of 3 studies reporting recanalization or persistence of reflux at 6 weeks (due to technical failure of the intervention) favored EVLA (OR=0.07 [95% CI, 0.02-0.22]; P<0.00001; I²=51%) (Paravastu et al., 2016). Early technical success (1-12 weeks) was analyzed in the review by Pan et al. (2014). This analysis included 9 studies. Pooled percentages show that the initial technical success rates were 97.3% and 97.6%, respectively for EVLA and high ligation and stripping for treating varicose veins. The meta-analysis of the number of limbs with technical failure also suggests that there is no statistical difference between EVLA and surgery (risk ratio [RR]=1.1 (95% CI, 0.62-1.97); P=0.72; I²=43%) (Pan et al., 2014).

**Technical Recurrence:** Technical recurrence was defined by Carroll et al. (2013) as “the presence of reflux, recanalization or new varicose veins in a treated limb as diagnosed by duplex ultrasound scanning (DUS)” (Carroll et al., 2013 p. 8). A network meta-analysis using data from 23 studies was conducted to compare the hazard of having technical recurrence when treated with EVLA, RFA and FS compared with stripping for 6 months, 1 year, and 2 years. The analysis indicated that EVLA exhibited the greatest effect on technical recurrence relative to stripping, with some decrease over time. The 2-year HR for EVLA compared with stripping was 0.84 (95% CrI], 0.44-1.81), with a probability HR > 1 of 0.257. At 6 months and 1 year, the HRs were 0.70 (95% CrI, 0.27-1.45) [0.150] and 0.77 (CrI, 0.37-1.54) [0.182], respectively. Nesbitt et al. (2014) included 7 studies in a meta-analysis of technical recurrence data. The results suggest no difference between EVLA and surgery (OR=0.72 [95% CI, 0.43-1.22]; P=0.22; I²=60%) when used to treat GSV incompetence. A meta-analysis of 2 studies evaluating EVLA compared with surgery for treating SSV varices found a statistically significant result in favor of EVLA for technical recurrence at 1 year (OR=0.24 [95% CI, 0.07-0.77]; P=0.016; I²=0%) (Paravastu et al., 2016). One study in the Paravastu et al. (2016) review reported 2-year results for technical recurrence. This study found no statistically significant difference between EVLA and surgery for SSV varices (OR=0.43 [95% CI, 0.16-1.15]; P=0.09). Pan et al. (2014) conducted meta-analyses of data on recurrence from studies comparing EVLA with surgery for treating varicose veins and found no statistically significant difference at either 1 or 2 years follow-up. The first analysis included 6 studies and used 1-year follow-up data. The results did not quite reach statistical significance (RR=0.65 [95% CI, 0.41-1.02]; P=0.06; I²=7%). The second analysis used 2-year follow up data from 5 studies and yielded RR=0.65 (95% CI, 0.37-1.12); P=0.12; I²=61%). O'Donnell et al. (2016) conducted a review of RCTs of EVLA or RFA compared with surgery to determine the
incidence of recurrence after endovenous ablation of the GSV. In this review, the authors pooled data from the EVLA and RFA treatment groups and compared it with pooled data from the surgery groups. For duplex recurrence, the pooled percentages were as follows: EVLA (4 studies): 12.5% (95% CI, 8.9-16.5); RFA (3 studies): 12.4% (95% CI, 7.3-18.6); surgery (ligation and stripping) (5 studies): 7.2% (95% CI, 4.4-10.6). There was no statistically significant difference between the 2 types of endovascular ablation procedures and surgery (ligation and stripping) (P=0.32).

Symptomatic Recurrence: Carroll et al. (2013) provided a qualitative summary of studies that provided data on symptomatic occurrence (defined as “patient presentation with symptoms of varicose veins, the diagnosis of which is validated by DUS”). Three studies comparing EVLA with surgery provided data on symptomatic recurrence; Carroll et al. (2013) concluded that the number of patients reporting symptomatic recurrence for any intervention was very small, with no significant difference between treatment groups. Similarly, in a meta-analysis of data from 3 studies, Nesbitt et al. (2014) found no difference between EVLA and surgery for symptomatic recurrence (OR=0.87 [95% CI, 0.47-1.62]; P=0.67; I²=0%). Only 1 study included in the Paravastu et al. (2016) review reported symptomatic recurrence results for EVLA compared with surgery; the results were not statistically significant (OR=0.54 [95% CI, 0.17-1.75]; P=NR). Pan et al. (2014) also analyzed symptomatic (clinical) recurrence and found no difference between groups at 1-year or 2-years follow-up. The meta-analysis with 1-year data included 6 studies, and the RR for EVLA compared with surgery was 0.83 (95% CI, 0.39-1.77); P=0.63; I²=62% for clinical recurrence. The 2-year analysis yielded at RR=0.85 (95% CI, 0.64-1.11); P=0.23), I²=52%. As above with the analyses of duplex recurrence by O’Donnell et al. (2016), there was no statistically significant difference between the endovenous ablation procedures and surgery for clinical recurrence (EVLA [5 studies]: 20.6% [95% CI, 17.0-24.3]; RFA [3 studies]: 21.4% [95% CI, 14.8-28.8]; surgery [6 studies]: 19.2% [95% CI, 15.5-23.2]; P=0.98).

Change in VCSS: A network meta-analysis was conducted by Carroll et al. (2013) using data at 1 year when available and 6-month data when 1-year data was missing. Six studies contributed data for this analysis, which found slightly lower post-intervention VCSS for EVLA than for stripping (mean difference [MD]=−0.10 [95% Crl, −0.89 to 0.73] with a probability of MD > 0 of 0.324).

Pain: Data from 9 studies contributed to a network meta-analysis of pain within 7 to 14 days of treatment as assessed using a visual analog scale (VAS) (Carroll et al., 2013). For EVLA compared with stripping, the MD was 0.10 (95% Crl, −0.49 to 0.64) with a probability of MD > 0 of 0.653. Nesbitt et al. (2014) described results from studies measuring pain as inconclusive because the measures of pain varied between studies. However, the authors commented that 2 trials found increased postoperative pain in the EVLA groups than the surgery groups and suggest that this needs further evaluation. In the Paravastu et al. (2016) review, 2 of the eligible studies used different VAS scales, 1 used 0 (no pain) to 10 (worst pain imaginable), and the other used a 0 to 100 scale. Pain decreased over time in both groups; however, 1 study reported less pain in the EVLA group than the surgery group at each time point, and the other study reported a higher level of pain in the EVLA group than the surgery group in the first 2 weeks, then less pain at 6 weeks. In the review by Pan et al. (2014), the authors provide a qualitative summary of pain data from 8 studies. Three of the 8 studies found higher levels of postoperative pain in...
the high ligation and stripping group, 4 found no difference between EVLA and surgery, and 1 reported significantly more pain in the EVLA group that the surgery group.

Return to Work or Normal Activity: Results from 6 studies were provided in the review by Carroll et al. (2013) as follows: 2 studies found no difference between EVLA and surgery, study found that EVLA patients returned to work or normal activities statistically significantly quicker than surgery patients, 2 studies did not report statistical test results, and 1 study showed significantly less time to return to work or normal activities for the surgery group. In the Nesbitt et al. (2014) review, results from 6 studies were summarized as generally indicating less time needed to return to work or normal activity for the EVLA group compared with surgery; however, the review authors noted that this conclusion is tentative because of the use of different metrics and definitions across the studies. Paravastu et al. (2016) report that 2 studies showed statistically significantly less time needed in the EVLA patients than the surgery patients being treated for SSV varices. Five of the studies included in the Pan et al. (2014) review reported time to return to normal activity; none showed significant differences between treatment groups. Six studies reported time to return to work. One study demonstrated a longer time to return to work in the EVLA group than in the surgery group, 2 studies showed less time needed in the EVLA group, and the other studies reported no difference between EVLA and surgery.

QOL: Nesbitt et al. (2014) did not conduct a meta-analysis for this outcome because the authors noted that the variety of different measures and different reporting formats used in the studies precluded combining the results for meta-analysis. The authors summarized QOL findings from 5 studies comparing EVLA with surgery for treating GSV incompetence as follows, “Qol and disease severity scoring was generally uniform throughout the studies, with worsening within the first few days or weeks followed by an overall improvement over the follow-up period, with no difference between the groups.” (Nesbitt et al., 2014; p. 17) Paravastu et al. (2016) qualitatively summarized or performed meta-analyses with QOL data from these measurement tools: the Aberdeen Varicose Veins Questionnaire (AVVQ), EuroQol Group 5 Dimension Questionnaire (EQ-5D), and the 36-item SF-36 Health Survey (QualityMetric Inc.) (SF-36). The meta-analysis of AVVQ data at 6 weeks from 2 studies suggest no difference between EVLA and surgery (MD=0.15 [95% CI, −1.65−1.95]; $P=0.87; I^2=0\%$). One study also reported 1-year results from the AVVQ, which were also not statistically significant for EVLA compared with surgery (MD=−1.08 [95% CI, −3.39 to 1.23]; $P=\text{NR}$). The investigators did not conduct a meta-analysis of data from the EuroQol Group 5-dimension Questionnaire (EQ-5D); they noted that the 2 studies reporting these data found no difference between treatment groups (Paravastu et al., 2016). Paravastu et al. (2016) reports that results of QOL assessment using the SF-36 was available for patients being treated for SSV varices from 1 study included in their review. This study, known as HELP2 (Samuel et al., 2013), suggested that the EVLA and surgery groups both showed higher scores over time in 5 of the 8 domains. In the other 3 domains (general health, vitality, and mental health), the EVLA group’s scores decreased slightly over time, while the surgery group maintained an improvement in scores.

Reintervention: Data regarding reintervention due to technical failure from 2 studies comparing EVLA with surgery were reported in the review by Nesbitt et al. (2014). One study found 6 of 68 (8.8%) of surgery patients compared with 9 of 69 (13%) EVLA patients experienced reintervention, and the other reported 2 of 143 (1.4%) for the surgery group compared with 3 of 173 (3.5%) for the EVLA group.
Paravastu et al. (2016) described 1 study that reported reintervention due to technical failure. In this study, 4 patients in the EVLA group received further treatment compared with 3 patients in the surgery group (Paravastu et al., 2016). O’Donnell et al. (2016) found no statistically significant difference in the pooled percentages of endovenous ablation (EVLA, RFA) and surgery patients who underwent reintervention after recurrence: EVLA (5 studies): 27.2% (95% CI, 23.3-31.3); RFA (1 study): 16.2% (95% CI, 10.4-35.9); surgery (4 studies): 17.3% (95% CI, 13.6-21.4); P=0.74.

**Additional Primary Studies: EVLA Versus Surgery**

Six recent publications of studies comparing EVLA with surgery were identified (Mozafar et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Flessenkamper et al., 2016; Gauw et al., 2016). Five of these represent recent publications of studies previously included in one or more of the systematic reviews discussed above (Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Flessenkamper et al., 2016; Gauw et al., 2016). One of these represents a study for which earlier publications were not identified (Mozafar et al., 2014). These recent publications add longer term follow-up data to the evidence summarized in existing systematic reviews. The findings are consistent with previous conclusions. Generally, outcomes reported in the longer-term follow-up slightly favor EVLA or are not statistically significantly different between EVLA and surgery.

The 2015 publication by van der Velden et al. (2015) reports 5-year follow-up from the MAGNA trial. The 2015 publication is a follow-up publication to Biemans et al. (2013), which was included in analyses presented in the Nesbitt et al. (2014) review. At the 5-year follow-up, recurrence (defined as flow or reflux of the GSV at mid thigh in the EVLA group, and as presence of the GSV in the saphenous compartment at thigh level in the surgery group as determined by clinical examination and DUS) was present in 10 of 69 (14.5%) in the surgery group and 18 of 78 (23%) in the EVLA group. These values were calculated from the reported Kaplan-Meier estimates of obliteration or absence of the GSV data provided in the publication. Statistical significance of the difference between the surgery group and the EVLA group was not provided. QOL was a secondary outcome in this study. At the 5-year follow-up, there were no significant differences between EVLA and surgery with respect to changes in CIVIQ Venous Quality of Life Questionnaire scores or EQ-5D scores. Clinical improvement was measured using the C category of the CEAP classification; there was no difference in the distribution of class C between legs in the surgery (OR=1.4 [95% CI, 1.2-1.6]) and those treated with EVLA (OR=1.3 [95% CI, 1.1-1.5]). Reintervention and additional treatments were given 1 or more times to 10% of the limbs in the surgery and EVLA groups (van der Velden et al., 2015).

Flessenkamper et al. (2016), published a follow-up to a 2013 publication by Flessenkamper et al. (2013a). The 2013 publication reported results at 2 months; this publication was included in the Nesbitt et al. (2014) review. The 2016 publication reports secondary outcome data for clinical recurrence up to 6 years. Follow-up rates were: 74% at 2 years, 47% at 3 years, 39% at 4 years, 36% at 5 years, and 31% at 6 years. The median time to follow-up was 4.0 years; the mean follow-up time was 3.6 years. There was no significant difference between EVLA and high ligation/stripping with respect to time to clinical recurrence within the 6-year follow-up (log-rank test, P=0.5479).
Five-year results from the RELACS (Randomized study comparing Endovenous Laser Ablation with Crosssection and Stripping of the great saphenous vein) study are presented in the 2015 publication by Rass et al. (2015). Previous RELACS study publications were included in the Nesbitt et al. (2014), Pan et al. (2014), and O’Donnell et al. (2016) reviews. At 5 years, 281 legs (81% of the study population) were evaluated with a median follow-up of 60.4 (EVLA) and 60.7 months (HL/S). Overall recurrence of varicose veins after surgery at 5 years was similar between groups and occurred in 45% of the EVLA group and 54% of the HL/S group ($P=0.152$). However, same-site recurrence occurred significantly more often in the EVLA group ($n=27 [18%]$) than in the HL/S group ($n=7 [5%]$); $P=0.002$. Recurrence at a different site than originally treated occurred more often in the HL/S group (64 [91%]) than in the EVLA group ($n=47 [68%]$); $P=0.002$. Reintervention, or management of recurrence, consisted of “wait and see” sclerotherapy, phlebectomy, SFJ and/or GSV or anterior accessory saphenous vein (AASV) redo treatment, or SSV surgery. More patients in the HL/S group ($n=47$ of 70 [67%]) were given a “wait and see” approach than those in the EVLA group ($n=34$ of 69 [49%]); $P=0.040$. Sclerotherapy was recommended for 23 of 69 (33%) EVLA patients compared with 8 of 70 (11%) HL/S patients ($P=0.004$). There was no significant difference between groups with respect to retreatment with phlebectomy ($P=0.138$). Six of 69 (9%) EVLA patients compared with 0 of 70 (0%) HL/S patients received SFJ and/or GSV or AASV redo treatment ($P=0.028$). There was no significant difference between groups for reintervention with SSV surgery ($P=0.620$). Disease severity (measured with the Homburg Varicose Vein Severity Score [HVVSS]) changed over time in both groups, showing improvement up to 12 months, then stabilizing until 24 months, and declined significantly in both groups at 60 months; there was no difference between groups. HVVSS at 5 years was $3.00 \pm 2.87$ in the EVLA group and $3.16 \pm 3.48$ in the HL/S group ($P=0.789$). Similarly, there was no difference between groups for CIVIQ-2 QOL scores. Patient satisfaction after 5 years was rated $1.28 \pm 0.51$ for EVLA and $1.39 \pm 0.58$ for HL/S ($P=0.078$).

Gauw et al. (2016) reported 5-year results in a follow-up publication to the Pronk et al. (2010) publication, which reported 1-year results. The 2010 Pronk et al. publication was included in the Carroll et al. (2013) and Nesbitt et al. (2014) reviews. Initially, 130 legs (121 patients) were randomized to either EVLA ($n=62$) or saphenofemoral ligation/stripping (SFL/S) ($n=68$). After 5 years, 9 patients were lost to follow-up, 8 from the SFL/S group and 1 from the EVLA group. Recurrence (detected by DUS) was observed in 23% of SFL/S patients and 49% of EVLA patients (log-rank test, $P=0.02$). CEAP classification improved after 1 year and was maintained for up to 5 years with no difference between groups. Disease severity improved for both groups and was not statistically significantly different between them. There was no statistically significant difference between EVLA and SFL/S with respect to the percentage of patients who did not receive a secondary procedure (80% of SFL/S compared with 70% of EVLA, log-rank $P=0.20$). For those that did receive reintervention to treat recurrence, reintervention consisted of high ligation, endovenous thermal ablation, or FS. FS was used in 4 of 10 (7%) of SFL/S patients compared with 15% ($n=9$) of EVLA patients.

A 2015 publication by Kalteis et al. (2015) added 5-year results to an earlier publication also by Kalteis et al. (2008). This study compared HL/S with high ligation + EVLA (HL+EVLA). At 5 years, 75% ($n=72$) of the original study population attended the follow-up visit (HL/S, $n=40$ [83%]; HL+EVLA, $n=32$ [68%]). Patient satisfaction was high in both groups, 88% of HL/S patients rated 5-year outcome good or very good.
compared with 87% of the HL+EVLA group. Similarly, the CIVIQ-2 QOL score was also high in both groups (93 in the HL/S and 94 in the HL+EVLA group). The VCSS scores significantly improved from baseline to 5 years in both groups, and CEAP clinical category also significantly improved from baseline in both groups. Recurrent varicose veins were visible in 55% of the HL/S group and 40% of the HL+EVLA group. Most cases of recurrences were rated mild; however, 14% of the HL/S group had moderate, severe, or very severe cases compared with 20% of the HL+EVLA group. DUS examination revealed no signs of varicosity in 67% of HL/S patients compared with 43% of the HL+EVLA group (P=0.049).

An RCT by Mozafar et al. (2014) compared EVLA (n=30) with high ligation (HL) of the saphenous vein (n=35) for treating varicosities of the GSV. Recurrence rates at 12 months were 6.7% and 11.7% in the EVLA and HL groups, respectively (statistical significance not reported). The Aberdeen Varicose Vein Severity Score (AVVSS) score was lower in the EVLA group at 12 months than in the HL group (P=0.019); this difference was sustained at 18 months (P=0.008). CEAP score and patient satisfaction was similar in both groups.

**Systematic Reviews: RFA Versus Surgery**

Studies reporting clinical or patient-centered outcomes for RFA compared with conventional surgery techniques were synthesized in 2 of the included systematic reviews (Carroll et al., 2013; Nesbitt et al., 2014). A third systematic review (O’Donnell et al., 2016) pooled data from EVLA and RFA groups for comparison with pooled data from surgery groups; results from this review are summarized above in the EVLA versus surgery section.

**Failure of Procedure:** The investigators who conducted the 2013 NHS NIHR review pooled results from 12 studies to determine the percentage of failure events in each study group. The pooled percentage for the RFA patients was 4% (16/431), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20/681) (Carroll et al., 2013). The statistical significance of this difference was not reported. In the review by Nesbitt et al. (2014), a meta-analysis of technical failure data from 5 studies found no difference between RFA and surgery (OR=0.82 [95% CI, 0.07-10.10]; P=0.88; I²=70%).

**Technical Recurrence:** Nesbitt et al. (2014) identified 4 studies comparing RFA with surgery that reported “clinician noted” recurrence. The meta-analysis of these studies suggests no statistically significant difference between treatment groups (OR=0.82 [95% CI, 0.49-1.39]; P=0.47; I²=39%). In a network meta-analysis using data from 23 studies, Carroll et al. (2013) found that the relative likelihood of experiencing a technical recurrence of varicose veins over time was lower for RFA than surgery: at 6 months, HR=0.92 (95% CrI, 0.39-2.11 [probability HR > 1, 0.409]); at 1 year, HR=0.93 (95% CrI, 0.42-2.22); and at 2 years, HR=0.94 (95% CrI, 0.42-2.51 [0.421]). While the relative effect of RFA on recurrence was small, it remained consistent over time.

**Symptomatic Recurrence:** Two studies included in the Carroll et al. (2013) review provided data for symptomatic recurrence for RFA compared with stripping. One study reported no symptomatic recurrence in either group at 4 months, and the other study reported that 4 of 15 patients in the RFA group had symptomatic recurrence at 3 years compared with 2 of 13 in the stripping group; the difference was not statistically significant. Nesbitt et al. (2014) reported symptomatic recurrence results...
for RFA compared with surgery from 1 study. Results were not statistically significant (OR=2.00 [95% CI, 0.30-13.26]; P=NR).

**Change in VCSS:** A network meta-analyses conducted by Carroll et al. (2013) found slightly higher post-intervention VCSS scores for RFA than surgery (MD=0.15 [95% CrI, −0.50 to 0.95]; probability MD > 0, 0.739) based on data available at 1 year (or 6 months if 1-year data was not available) from 6 studies. Based on a qualitative summary of results from 3 studies comparing RFA with surgery, Nesbitt et al. (2014) concluded that disease severity scores generally improved over the length of the follow-up for both treatment groups, with most studies reporting no overall differences between the groups.

**Pain:** Nesbitt et al. (2014) did not conduct a meta-analysis of pain data; however, they summarized findings as generally reporting less pain in the RFA group than the surgery group. Results from 3 out of 4 studies suggested significantly less pain after treatment with RFA compared with surgery, and 1 study found no difference. The network meta-analysis presented in the review by Carroll et al. (2013) used data from 9 studies. Results suggest that relative to stripping, RFA is associated with decreased pain in the first 2 weeks after the procedure (MD=−1.26 [95% CrI, −1.95 to −0.61] [0.001]).

**Return to Work or Normal Activity:** Carroll et al. (2013) summarized findings from 4 studies comparing RFA with surgery as follows. One study found no statistically significant difference, while 3 other studies reported significantly quicker return to work or normal activities for RFA compared with surgery. Nesbitt et al. (2014) noted that while 5 studies reported either time to return to work or time to return to normal activities, the results were reported differently between the studies, precluding meta-analysis for this outcome. All 5 studies reported less time for RFA than for surgery.

**QOL:** Three of the studies described in the Nesbitt et al. (2014) review reported QOL scores, each using different measurement tools: CIVIQ-2 QOL, RAND-36 (a variation of SF-36 validated for Finland), the Venous Insufficiency Epidemiological and Economics Study (VEINES)-QOL/Sym questionnaire, and the AVVSS. Two studies reported no significant differences between the RFA and surgery groups. The third study, which used the CIVIQ-2 tool, reported an initial decrease in QOL for the surgery group compared with an initial increase in the RFA group. At 3 weeks, differences were not significant, but at 1 year there was a significant difference in favor of RFA that persisted at 2 years.

**Reintervention (because of technical failure):** Nesbitt et al. (2014) reported data for this outcome from 2 studies comparing RFA with surgery. One study found that 6 of 81 (7.4%) patients who received surgery had reintervention due to technical failure, compared with 0 of 81 (0%) who received RFA. The second study reported 2 of 13 (15.4%) in the surgery group compared with 2 of 15 (13.3%) in the RFA group received reintervention. Statistical differences were not provided. This outcome was not assessed in the systematic review by Carroll et al. (2013).

**Additional Primary Studies: RFA Versus Surgery**

No additional primary study publications comparing RFA with surgery not already included in 1 or more of the systematic reviews described above were identified for this Key Question.
Systematic Reviews: Sclerotherapy Versus Surgery

Studies reporting clinical or patient-centered outcomes for sclerotherapy compared with conventional surgery techniques were synthesized in 5 of the included systematic reviews (Rigby et al., 2009; Rathbun et al., 2012; Carroll et al., 2013; Nesbitt et al., 2014; Paravastu et al., 2016).

Failure of Procedure: The investigators in the Carroll et al. (2013) review pooled results from 12 studies to determine the percentage of failure events in each study group. The pooled percentage for the FS pts was 7% (21/295), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20/681) (Carroll et al., 2013). The statistical significance of this difference was not reported. A meta-analysis conducted by Nesbitt et al. (2014) analyzed results from 2 studies comparing FS with surgery and found no statistically significant difference between groups for technical failure (OR=0.44 [95% CI, 0.12-1.57]; P=0.20). Paravastu et al. (2016) reported that 1 study of FS versus surgery for patients with SSV varices provided data for recanalization or persistence of reflux at 6 weeks (due to technical failure of the intervention). For this outcome, data were available for 16 of 21 patients randomized to FS and 17 of 21 patients randomized to surgery. There were 2 patients in the FS group compared with 5 patients in the surgery group who experienced recanalization or persistence of reflux at 6 weeks. The findings were not statistically significant (OR=0.34 [95% CI, 0.06-2.10]; P=0.25) (Paravastu et al., 2016). Rathbun et al. (2012) conducted a meta-analysis using data pertaining to anatomical closure from 6 RCTs comparing FS with vein surgery. In this analysis, surgery showed statistically significantly better anatomical closure than FS (RR=0.92 [95% CI, 0.86-0.97]; P=0.0036). A meta-analysis of 4 studies showed no difference between FS and surgery for the outcome of residual saphenofemoral incompetence rates (RR=0.92 [95% CI, 0.56-1.51]; P=0.73) (Rathbun et al., 2012).

Technical Recurrence: A network meta-analysis using data from 23 studies was conducted by Carroll et al. (2013) to compare the hazard of having technical recurrence when treated with EVLA, RFA, and FS compared with stripping for 6 months, 1 year and 2 years. The analysis indicated that FS was worse than stripping over the first year, although there was a small benefit after 2 years (2-year HR=0.92 [95% CrI, 0.43-1.60]). At 6 months and 1 year, the HRs were 1.12 (95% CrI, 0.53-2.27 [0.659]) and 1.02 (95% CrI, 0.49-1.84 [0.524]), respectively. A meta-analysis by Nesbitt et al. (2014) using data from 3 studies suggests that there is no statistically significant difference for technical recurrence between FS and surgery (OR=1.74 [95% CI, 0.97-3.12]; P=0.06; I²=55%). Recurrence of reflux was found to be no different at 6 months between FS and surgery in 1 study included in the Paravastu et al. (2016) review (OR=1.19 [95% CI, 0.29-4.92]; P=NR). Rigby et al. (2009) planned to conduct meta-analyses but found the studies too heterogenous to combine. Results for “treatment success or failure” were reported in terms of follow-up at 1 year and beyond, and definitions of success and failure varied in the individual studies. The narrative summary provided by Rigby et al. (2009) describes a general trend showing sclerotherapy was better than surgery at 1 year as reported in 3 studies, but phlebectomy was better than sclerotherapy in a fourth study at 1 year. Studies reporting results at 2-, 3-, and 5-year follow-up points, either reported that surgery was significantly better than sclerotherapy or there were no differences between groups at these time points.
Symptomatic Recurrence: One study included in the Nesbitt et al. (2014) review found no statistically significant difference for symptomatic recurrence between FS and surgery (OR=1.28 [95% CI, 0.66-2.49]; \(P=\text{NR}\)).

Change in VCSS: A network meta-analysis conducted by Carroll et al. (2013) found that FS exhibited the greatest effect among the 3 interventions analyzed (EVLA, RFA, and FS) relative to stripping (MD=−1.63 [95% CrI, −2.90 to −0.42]; probability MD > 0, 0.015) based on data available at 1 year (or 6 months if 1-year data was not available) from 6 studies. Two studies included in the Nesbitt et al. (2014) review found no difference between FS and surgery for VCSS; in both studies, both groups showed improvement from baseline to the final follow-up time point.

Pain: Results of a network meta-analysis involving 9 studies of EVLA, RFA, and FS compared with surgery or with each other, suggest that FS and RFA exhibit the greatest effects on pain relative to stripping. The results for FS were MD=−0.80 (95% CrI, −1.93 to 0.30) (Carroll et al., 2013). Nesbitt et al. (2014) summarized results for post-procedure pain from 2 studies comparing FS with surgery. One study found that scoring for “more,” “stable,” or “less” pain were similar between the groups at 3, 12, and 24 months. Results from the other study suggest that the FS group experienced significantly less postoperative pain than the surgery group (\(P<0.001\)), and the number of phlebectomies did not influence pain scores (\(P=0.136\)).

Return to Work or Normal Activity: Carroll et al. (2013) summarized findings from 3 studies comparing FS with surgery as follows. One study did not report statistical significance, and the other 2 studies reported significantly quicker return to work or normal activities for FS compared with surgery. Nesbitt et al. (2014) presented data from 1 study comparing FS with surgery. This study found that the FS group took less time to return to work (median, 2.9 versus 4.3 days) and to return to normal activities (median, 1 day versus 4 days) than the surgery group, but statistical significance was not provided.

QOL: The variety of different measures and different reporting formats used in the studies assessed by Nesbitt et al. (214) precluded combining the results for meta-analysis. Three studies used 1 or more of the following QOL or disease severity assessment tools: EQ-5D, CIVIQ-2, CEAP scoring, AVVSS, and the SF-36. Both groups showed similar QOL scores by the final follow-up assessment in all 3 of the studies and no significant differences between groups were evident.

Reintervention (because of technical failure): Nesbitt et al. (2014) reported data for reintervention due to technical failure from 2 studies comparing FS with surgery. Only 1 of these studies provided data for both groups; in the FS 40 of 123 (18.8%) patients needed reintervention compared with 10 of 177 (5.6%) in the surgery group. The second study reported 5 of 144 (3.5%) patients in the FS group had a reintervention (no data were provided for the surgery group).

Additional Primary Studies: Sclerotherapy Versus Surgery

Two publications presenting information about sclerotherapy compared with surgery not already included in 1 or more of the SRs described previously were identified for this Key Question (Michaels et al., 2006; van der Velden et al., 2015). One of these was related to a previously published study (van der
Velden et al., 2015), and 1 was not related to a previously published study (Michaels et al., 2006). Results from these 2 publications are consistent with previous findings.

The 2015 publication by van der Velden et al. (2015) reports 5-year follow-up from the MAGNA trial. The 2015 publication is a follow-up publication to the Biemans et al. (2013) study, which was included in analyses presented in the Nesbitt et al. (2014) review. At the 5-year follow-up, recurrence, was present in 10 of 69 (14.5%) in the surgery group and 59 of 77 (77%) in the US-guided FS (UGFS) group (P<0.001). These values were calculated from the reported Kaplan-Meier estimates of obliteration or absence of the GSV data provided in the publication. At 5 years, patients who received surgery were 4 times more likely to have persisting obliteration of the above-knee GSV than patients who received UGFS, the restricted mean survival time (RMST) ratio was 0.6 (95% CI, 0.5-0.7). QOL was a secondary outcome in this study. The statistical significance of the results of the CIVIQ scores and EQ-5D scores between the surgery and UGFS groups were not reported; those values (reported as regression coefficients) were as follows for the surgery and UGFS groups, respectively: CIVIQ 0.44 (95% CI, –0.41 to 1.29) and 0.98 (95% CI, 0.16-1.79); EQ-5D 0.02 (95% CI, 0.01-0.02) and 0.01 (95% CI, 0.01-0.02). Clinical improvement was measured using the C category of the CEAP classification; there was no difference in the distribution of class C between legs in the surgery group (OR=1.4 [95% CI, 1.2-1.6]) and those treated with UGFS (OR=1.3 [95% CI, 1.1-1.5]). Reintervention and additional treatments were given 1 or more times to 10% of the limbs in the surgery group compared with 32% of legs in the UGFS group (log rank test, P<0.001) (van der Velden et al., 2015).

The REACTIV trial included, among other comparisons, a comparison of liquid sclerotherapy with surgery. Results are presented in a 2006 health technology assessment conducted for the UK Health Technology Assessment Programme (Michaels et al., 2006). This study was in progress at the time of the literature search conducted in 2004 by Rigby et al. for the previously described systematic review of sclerotherapy compared with surgery (Rigby et al., 2009). Therefore, data from the RCT portion of the report was not included in the Rigby et al. (2009) review. The study may have been underpowered to detect significant differences between treatment groups as it included 77 patients, 41 in the sclerotherapy group and 36 in the surgery group. After 1 year, data from 29 people in the sclerotherapy group and 23 people in the surgery group were available for analysis. Symptom improvement was similar between groups at 1 year, with the majority of patients in both groups reporting that symptoms were improved or gone. No visible varicosities were evident in 76% of patients in the surgery group compared with 39% in the sclerotherapy group (P<0.05). There was no statistically significant difference between groups for the development of new varicose veins at 1 year, 2 years, or 3 years. Quality of Life utility as derived from the SF-36 was not statistically significantly different between groups at 1 year (sclerotherapy, n=28, 0.71 [0.11]; surgery, n=24, 0.76 [0.10]) or at 2 years (sclerotherapy, n=15, 0.75 [0.11]; surgery, n=16, 0.76 [0.11]). Quality of Life utility derived from the EQ-5D and VAS were statistically different at 1 year, but not at 2 years. In the sclerotherapy group (n=28), the EQ-5D utility at 1 year was 0.80 (0.14) compared with 0.85 (0.20) for the surgery group (n=22); P<0.05. The utility derived from VAS at 1 year was mean 0.77 (SD 0.18) in the sclerotherapy group (n=27) and mean 0.83 (SD 0.14) in the surgery group (n=22); P<0.05. Patient satisfaction at 1 year was similar in both groups; 4
in each group were dissatisfied with initial treatment. Three people in the sclerotherapy group elected to have surgical treatment (Michaels et al., 2006).

**Key Question #2:** Among patients being treated for varicose veins, what are the harms associated with endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping?

**Study Characteristics**

Seven systematic reviews were identified for this Key Question (Rigby et al., 2009; Rathbun et al., 2012; Carroll et al., 2013; Dermody et al., 2013; Nesbitt et al., 2014; Pan et al., 2014; Paravastu et al., 2016). Three reviews (Carroll et al., 2013; Nesbitt et al., 2014; Paravastu et al., 2016) assessed EVLA, RFA, and FS compared with traditional surgery. One of the reviews evaluated evidence for EVLA compared with surgery (Pan et al., 2014), 2 evaluated EVLA and RFA compared with surgery (Dermody et al., 2013), and 2 evaluated sclerotherapy compared with surgery (Rigby et al., 2009; Rathbun et al., 2012). Most of the reviews included only RCTs for primary data; however, 2 reviews included observational studies (Rathbun et al., 2012; Pan et al., 2014). Rathbun et al. (2012) included 104 studies; however, most of them did not include comparison groups and therefore did not contribute data to meta-analyses comparing treatments. Interventions described in the reviews included EVLA with 810 nm, 980 nm, or 1470 nm lasers; RFA with the Closure PLUS or ClosureFast catheters; and US-guided FS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation or high ligation with or without stripping.

Four additional publications not already included in the systematic reviews described above were also identified for this key question (Rass et al., 2015; Mozafar et al., 2014; Carruthers et al., 2014; Gauw et al., 2016). Two of these are follow-up publications related to studies already included in one or more systematic review (Rass et al., 2015; Gauw et al., 2016), and 2 are not related to previously published studies (Mozafar et al., 2014; Carruthers et al., 2014). Details of included studies are presented in [Appendix V](#).

**Study Quality**

Quality assessment of the systematic reviews and individual studies included for Key Question #2 is described in the Key Question #1 section. The Dermody et al. (2013) review was not included in Key Question #1; however, the same quality assessment description applies. The Carruthers et al. (2014) publication is a fair-quality large observational study.

**Complications**

**EVLA Versus Surgery**

Five systematic reviews synthesized information about adverse events from studies comparing EVLA with surgery (Carroll et al., 2013; Dermody et al., 2013; Nesbitt et al., 2014; Pan et al., 2014; Paravastu
Each review had a different focus. The review by Carroll et al. (2013) had the broadest scope in terms of PICOS, this review sought studies of patients with varicose veins regardless of location of the varicosity, included studies of multiple interventions and comparisons, and sought information on effectiveness and harms. Nesbitt et al. (2013) and Paravastu et al. focused on varicosities of the GSV and SSV respectively. Dermody et al. (2013) evaluated data from studies of EVLA or RFA to treat GSV varicosities and focused on complications. The review by Pan et al. evaluated studies comparing EVLA with surgery and included observational studies as well as RCTs. Literature search dates and publication dates also varied. These factors contributed to variation in the individual studies across the systematic reviews; however, several of the SRs included data from some of the same primary studies. Table 6 includes lists of the individual studies included in each of the SRs. Because the Dermody et al. (2013) review had 8 primary studies in common with the Nesbitt et al. (2014) review and it provided pooled percentages for complication rates, only information from Dermody et al. (2013) is summarized below for the EVLA and RFA comparisons with surgery.

Four additional publications not already included in the systematic reviews described above were also included for this key question (Rass et al., 2015; Mozafar et al., 2014; Carruthers et al., 2014; Gauw et al., 2016). Two of these are follow-up publications related to studies already included in one or more systematic review (Rass et al., 2015; Gauw et al., 2016), and 2 are not related to previously published studies (Mozafar et al., 2014; Carruthers et al., 2014). One of these recent publications represents an observational study (Carruthers et al., 2014) that met inclusion criteria for this key question.

DVT and Pulmonary Embolism (PE): Carroll et al. (2013) identified 1 study that compared EVLA with surgery in which any DVT event was reported. In this study, there were zero DVT events in the EVLA arm and 1 event in the surgery arm (Rasmussen et al., 2011). Carroll et al. (2013) did not identify any studies comparing EVLA with surgery in which any PE events were reported. Dermody et al. pooled the incidences of DVT and PE and found no difference between ligation/stripping (L/S) and EVLA. The analysis included 12 studies with an L/S arm and 10 studies with an EVLA arm. The pooled incidence for L/S was 0.7% (95% CI, 0.2-1.3) compared with 0.4% (95% CI, 0.1-1.0) for EVLA; \( P=0.52 \). Pan et al. (2014) report that 1 case of DVT was reported in each group in 1 study included in their review (Rass et al., 2012). In their review of studies evaluating EVLA compared with surgery for SSV varicosities, Paravastu et al. (2016) found 1 occurrence of DVT in the surgery group of the HELP-2 study and 1 occurrence of DVT in the EVLA group of the VESPA study (Roopram et al., 2013; Samuel et al., 2013).

In a recent publication of primary data, Mozafar et al. (2014) reported zero DVT events in both the HL/S or EVLA group. Carruthers et al. (2014) analyzed data from the American College of Surgeons National Surgical Quality Improvement Program. Data were collect from 2005 to 2011 and represented 4,366 patients, 2,580 received open surgery for varicose veins, and 1,786 received endovenous ablation (EVLA or RFA). The investigators found a 50% decrease in the odds of DVT for patients undergoing open surgery compared with endovenous ablation (adjusted odd ratio = 0.52 [95% CI 0.28-0.97], \( P=0.040 \). Analyses suggested that age, gender, race, BMI, specialty of the treating surgeon, and VU did not significantly affect the odds of postoperative DVT.
Nerve Damage (including paresthesia): Carroll et al. (2013) noted that paresthesia was 1 of the complications most frequently reported in all of the studies evaluated in their review (this includes all interventions and comparisons assessed in the review). The authors summarized data on paresthesia along with events of other types of complications as follows, “For all adverse events the number of events was very small and statistically significant differences were not often reported” (p. 23). The review noted only 1 study that found a significant difference between EVLA and surgery; results favored EVLA (P<0.001) (Kalteis et al., 2008). Other studies that reported data for this event either did not report statistical significance or there was no difference between treatments. Regarding nerve damage, Carroll et al. (2013) identified 1 study comparing EVLA with surgery that reported this outcome but it did not report statistical significance (Pronk et al., 2010a) and Carroll et al. did not report the number of events in each group from this study. Dermody et al. (2013) pooled the incidence of paresthesia from 15 studies with L/S arms (6.7 % [95% CI, 5.3-8.3]) and compared it with the pooled incidence of paresthesia from 12 studies with an EVLA arm (3.3% [95% CI 2.4-4.5]); P<0.001. Results suggest that EVLA is associated with significantly fewer events of paresthesia than surgery. A meta-analysis of 8 studies (1 study with zero events was excluded) comparing EVLA with L/S showed similar results (OR=0.53 [95% CI, 0.34-0.82]; I²=0%) (Dermody et al., 2013). Pan et al. (2014) conducted a meta-analysis using 9 studies, 6 of which were also included in the Dermody et al. (2013) analysis. The result from the Pan et al. (2014) study also indicated a statistically significant difference between EVLA and surgery in favor of EVLA (RR=0.59 [95% CI, 0.45-0.79]; P=0.0003 I²=0%). Paravastu et al. (2016) found 2 studies that reported sural nerve injury. In 1 study, 8% (4/51) of EVLA patients compared with 27% (14/52) of surgery patients experienced sural nerve injury at 6 weeks (no statistical test results were reported) (Samuel et al., 2013). The review authors noted that the second study reported similar percentages, 6% (7/110) in the EVLA group and 31% (16/52) in the surgery group (Roopram et al., 2013). At 52 weeks, 1 study showed a decrease in nerve injury for both groups (4% [2/48] in the EVLA group, and 10% [5/52] in the surgery group) (Samuel et al., 2013).

In the recent publication by Gauw et al. (2016), the authors noted the persistence of pretibial neurosensory deficit for 5 years in one patient (1/66 [2%]) who received saphenofemoral L/S and no occurrences of this in the EVLA group.

Infection: Carroll et al. (2013) noted that infection was 1 of the complications most frequently reported in all of the studies evaluated in their review (this includes all interventions and comparisons assessed in the review). The authors summarized data on infection along with events of other types of complications as follows, “For all adverse events the number of events was very small and statistically significant differences were not often reported” (p.23). One study reported significantly fewer infections in the EVLA group than the surgery group (P<0.05) (Carradice et al., 2011a). Dermody et al. (2013) found a statistically significant difference between the pooled incidence of infection from 12 studies with an L/S arm (2.1% [95% CI 1.3-3.1]) and the pooled incidence of infection from 12 studies with an EVLA arm (0.7% [95% CI 0.3-1.3]); P=0.006. A meta-analysis of 7 comparisons (2 studies with zero events were excluded) comparing EVLA with L/S by Dermody et al. also found a statistically significant difference in favor of EVLA (OR=0.24 [95% CI, 0.10-0.58]; I²=0%). A similar result was found by Pan et al. (2014); their meta-analysis included 6 of the same studies as Dermody et al. (2013). The RR=0.28 (95% CI, 0.11-0.70);
\(I^2=0\)% in favor of EVLA. Paravastu et al. (2016) reported that 2% of surgery patients in 1 study and 11% in another study experienced wound infection (Roopram et al., 2013; Samuel et al., 2013); no infection events were reported for the EVLA arms in these studies.

Carruthers et al. (2014) reported an increased odds of experiencing a superficial surgical site infection in patients undergoing open surgery compared with those who received EVLA (adjusted OR=2.56 [95% CI 1.19-5.50], \(P=0.016\)). Overall, increased odds of superficial surgical site infection were also higher for those with venous ulcers (adjusted OR=2.55 [95% CI 1.4-5.26], \(P=0.011\)) and obese patients (adjusted OR=2.16 [95% CI 1.10-4.24], \(P=0.025\). Age, gender, race, and the specialty of the treating surgeon did not significantly affect the odds of superficial surgical site infection.

Other Complications: Carroll et al. (2013) noted that bruising and skin discoloration, hematoma, and phlebitis were among the complications most frequently reported in all of the studies evaluated in their review (this includes all intervention and comparison types). The authors summarized data on these events along with events of other types of complications as follows, “For all adverse events the number of events was very small and statistically significant differences were not often reported” (p.23). With respect to discomfort due to bruising, Carroll et al. (2013) noted that 1 study found no difference between EVLA and surgery (Carradice et al., 2011a), and another reported better outcomes for EVLA than for surgery (\(P=0.002\)) (Christenson et al., 2010). Out of 12 studies that reported hematoma outcomes, only 5 reported \(P\) values with significant differences; 3 of these compared EVLA with surgery and found a significant difference in favor of EVLA (\(P<0.05\)) (Rautio et al., 2002; Kalteis et al., 2008; Carradice et al., 2011a). This difference did not persist at the 12-week follow up in 1 study (Kalteis et al., 2008). Dermody et al. (2013) found statistically significant differences between L/S and EVLA in the pooled incidences of superficial venous thrombosis or thrombophlebitis (\(P=0.003\) in favor of L/S) and hematoma (\(P<0.001\) in favor of EVLA), but no difference was found for bruising (\(P=0.55\)). A meta-analysis for thrombophlebitis events from 8 comparisons of EVLA and L/S found an OR=1.83 (95% CI, 1.13-2.95), suggesting that L/S is associated with fewer thrombophlebitis events than EVLA (Dermody et al., 2013). The result of the meta-analysis by Pan et al. (2014) for phlebitis did not reach statistical significance, but it also suggests a lower rate of phlebitis for surgery (3.7%) than EVLA (6.0%) (RR=1.54 [95% CI, 0.97-2.44]; \(P=0.06\); \(I^2=46\)). Other meta-analyses conducted by Pan et al. (2014) were for hematoma and bruise. The hematoma analysis suggests a statistically significant difference in favor of EVLA (RR=0.30 [95% CI, 0.15-0.57]; \(I^2=0\)), and the analysis for bruise found no difference between treatments and had high statistical heterogeneity (RR=0.74 [95% CI, 0.33-1.66]; \(I^2=75\)). The review by Paravastu et al. (2016) reported the following other complications: hematoma (1 study, zero events in the EVLA group, and 2/52 events in the surgery group); pigmentation/skin bruising (1 study, 2/51 in EVLA arm, zero in the surgery arm); phlebitis (1 study, 3/51 in the EVLA arm, and 1/52 in the surgery arm).

Mozafar et al. (2014) reported bruising in 12 (34.3%) and 5 (16.7%) of HL/S and EVLA patients respectively (\(P=0.107\)). In the same study at 3, 6, and 18-month follow-up the rate of dysthesia was 6 (17.1%), 4 (11.7%), and 3 (8.6%) respectively in the HL/S group compared with 4 (13.3%), 3 (10%), and 2 (6.7%) in the EVLA group; \(P\) was not significant at any time point. Similarly, there was no difference between groups for dispigmentation at 3, 6, and 18 months. Rass et al., (2015) reported 5-year follow-
up data for the RELACS trial. The authors reported only a few cases of persistent dysthesia (EVLA 3%, HLS 2%) or hyperpigmentation (EVLA 0%, HLS 1%) 5 years after treatment without significant differences.

**RFA Versus Surgery**

Three systematic reviews consolidated information about adverse events from primary studies evaluating RFA compared with surgery (Carroll et al., 2013; Dermody et al., 2013; Nesbitt et al., 2014). The Dermody et al. (2013) and Nesbitt et al. (2014) reviews shared considerable overlap with respect to included primary studies; therefore, only the results from the Dermody et al. (2013) review are described below.

**DVT and PE**: Carroll et al. (2013) identified 1 study comparing RFA with surgery in which 1 DVT event was reported (Rasmussen et al., 2011). This event occurred in the surgery arm. Carroll et al. (2013) did not identify any studies comparing RFA with surgery in which any PE events were reported. Dermody et al. (2013) pooled the incidences of DVT and PE and found no difference between L/S and RFA. The analysis included 12 studies with an L/S arm and 4 studies with an RFA arm. The pooled incidence for L/S was 0.7% (95% CI, 0.2-1.3) compared with 0.5% (95% CI, 0.1-1.2) for RFA; \( P=0.71 \).

**Nerve Damage (including paresthesia)**: Two studies in the Carroll et al. (2013) review showed statistical significance with respect to the occurrence of paresthesia after RFA compared with surgery. Both studies reported more events in the surgery groups than the RFA groups \( (P<0.05) \) (Rautio et al., 2002; Subramonia and Lees, 2010b). Two other studies either reported no \( P \) value or results were not statistically significant (Lurie et al., 2003; Rasmussen et al., 2011). Dermody et al. (2013) pooled the incidence of paresthesia from 15 studies with L/S arms (6.7 % [95% CI, 5.3-8.3]) and compared it with the pooled incidence of paresthesia from 4 studies with an RFA arm (7.8% [95% CI, 5.8-10.1]); \( P=0.43 \). Results suggest no difference between RFA and surgery for paresthesia. Only 1 study directly compared RFA with surgery, the OR=1.15 (95% CI, 0.35-3.85) from this study suggests no difference between surgery and RFA with respect to paresthesia (Rasmussen et al., 2011; Dermody et al., 2013).

**Infection**: No significant differences in rates of infection between RFA and surgery were described in the Carroll et al. (2014) review. Dermody et al. did not find a statistically significant difference between the pooled incidence of infection from 12 studies with an L/S arm (2.1% [95% CI, 1.3-3.1]) and the pooled incidence of infection from 4 studies with an RFA arm (1.0% [95% CI, 0.3-2.0]); \( P=0.094 \). Only 1 study directly compared RFA with surgery, the OR for wound infection from this study was 0.96 (95% CI, 0.06-15.4) and was not statistically significant (Rasmussen et al., 2011; Dermody et al., 2013).

**Other**: Carroll et al. (2013) described only 1 study comparing RFA with surgery that reported a significant difference between the treatments with respect to bruising; this study reported better outcomes for RFA than for surgery \( (P<0.02) \) (Hinchliffe et al., 2006). For rates of hematoma, 1 study reported a significant difference between RFA and surgery and the results favored RFA (Rautio et al., 2002). Surgery was associated with better results than RFA with respect to phlebitis in 1 study (Rasmussen et al., 2011). Dermody et al. (2013) found statistically significant differences between surgery and RFA for superficial venous thrombosis or thrombophlebitis, bruising, and hematoma. The pooled incidences for superficial
venous thrombosis were 2.9% (95% CI, 1.9-4.0) for surgery (12 studies) and 5.2% (95% CI, 3.0-7.8) for RFA (4 studies); \( P = 0.003 \). For hematoma, RFA was associated with better results at 0.2 (95% CI, 0.0-1.3) compared with 13.5% (95% CI, 11.1-16.1) for surgery; \( P < 0.001 \). Results for the pooled incidences of bruising also favored RFA at 3.1% (95% CI 0.12-9.9) compared with 36.1% (95% CI 32.6-39.6) for surgery.

**Sclerotherapy Versus Surgery**

Three systematic reviews reported comparative adverse event data from primary studies comparing sclerotherapy with surgery (Rathbun et al., 2012; Carroll et al., 2013; Nesbitt et al., 2014).

**DVT and PE:** Carroll et al. (2013) identified 3 studies that compared FS with surgery in which any DVT events were reported. Across these studies, there were 13 DVT events in the sclerotherapy groups and 1 event in the surgery groups (Wright et al., 2006; Shadid et al., 2010; Rasmussen et al., 2011). Most of the DVT events (\( n = 11 \)) were reported in 1 study (Wright et al., 2006) and occurred prior to a dose reduction in the FS group. The review authors found 1 study comparing FS with surgery that reported 1 PE event in the sclerotherapy group (Shadid et al., 2010). Nesbitt et al. (2014) did not name specific events in the “major event, requiring intervention” category, but it reports that across 3 studies (Rasmussen et al., 2011; Shadid et al., 2012; Biemans et al., 2013) there were 8 of 363 (2.2%) wound problems in the surgery group compared with 4 of 418 (1%) in the FS group. They also reported 1 of 363 (0.3%) other major events in the surgery groups compared with 3 of 418 in the FS groups from these 3 studies. Rathbun et al. (2012) pooled data from studies comparing FS with surgery and found no difference between treatments (\( RR = 1.45 \) [95% CI, 0.4-4.53]; \( P = 0.52 \)); the number of studies included in the analysis was not clear.

**Nerve Damage (including paresthesia):** Carroll et al. (2013) noted that 1 study reported no \( P \) value or found no difference between FS and surgery for incidence of paresthesia (Rasmussen et al., 2011), and another study found better results for FS than surgery (Shadid et al., 2010). Nesbitt et al. (2014) reported 15 of 363 (4.1%) cases of nerve damage in the surgery groups compared with 3 of 418 (0.7%) in the FS groups from 3 studies (Rasmussen et al., 2011; Shadid et al., 2012; Biemans et al., 2013).

**Infection:** One study identified by the authors of the Carroll et al. (2013) review found higher infection rates in the FS group than in the surgery group (Rasmussen et al., 2011).

**Other:** In the Carroll et al. (2013) review, 2 studies are described as having found that FS had significantly better outcomes with respect to bruising than surgery (Liamis et al., 2005; Abela et al., 2008). In the same review, 2 studies were described as finding better results for surgery than for FS with respect to rates of phlebitis (Shadid et al., 2010; Rasmussen et al., 2011). Hematoma was reported in 2 studies included in the Nesbitt et al. (2014) review; total incidence across these 2 studies was 4 of 295 (1.4%) for the surgery groups and 1 of 341 (0.3%) for the FS groups (Rasmussen et al., 2011; Shadid et al., 2012). With respect to the incidence of phlebitis, Nesbitt et al. (2014) reported 5 of 295 (1.7%) and 34 of 341 (10%) in the surgery and FS groups, respectively, based on data from 2 studies (Rasmussen et al., 2011; Shadid et al., 2012). In the Rathbun et al. (2012) review, a meta-analysis suggested that the rate of superficial thrombophlebitis was higher in the FS group than in the surgery group (\( RR = 16.85 \) [95% CI, 2.27-124.74]; \( P = 0.0057 \)). The authors of this review note that rates of skin pigmentation did not
differ between surgery and FS; however, ecchymosis was significantly lower with FS compared with surgery (RR=0.40 [95% CI, 0.25-0.64]; P=0.0001).

**Key Question #3:** Among patients being treated for varicose veins, does the effectiveness or risk of adverse events of laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping vary by clinical history (e.g., comorbidities, previous treatment of varicose veins), patient characteristics (e.g., age, sex, body mass index [BMI], smoking history)?

Three of the SRs described in Key Questions #1 and #2 focused specifically on varicosities of either the GSV or SSV (Dermody et al., 2013; Nesbitt et al., 2014; O'Donnell et al., 2016; Paravastu et al., 2016). No studies were identified that reported on subgroup analyses by previous treatment, race, comorbidities, or other clinical history or patient characteristics.

**Key Question #4:** What are the cost implications and cost-effectiveness of endovascular laser ablation, radiofrequency ablation, sclerotherapy, or ambulatory phlebectomy compared with ligation with or without stripping for patients being treated for varicose veins?

Three of the SRs identified for Key Questions #1 and #2 also included assessments of cost information (Rigby et al., 2009; Carroll et al., 2013; Nesbitt et al., 2014). No recent publications of primary cost-effectiveness data from a U.S. perspective comparing the interventions of interest with surgery were identified. Two primary studies assessing the cost of varicose vein treatments in U.S. facilities were identified (Eidson et al., 2011; Lin et al., 2014).

**Systematic Reviews – Economic Analyses**

Four economic studies were identified by Carroll et al. (2013); 2 economic analyses conducted along with RCTs (Disselhoff et al., 2009; Subromonia and Lees, 2010a), and 2 modelling studies (Adi et al., 2004; Gohel et al., 2010). One of the RCTs was assigned a poor-quality rating by the review authors and found to contain a critical error in the calculation of the incremental cost-effectiveness ratios (ICERs). Carroll et al. (2013) were able to recalculate the ICERs and assess the study. This study compared EVLA with cryostripping, the other RCT compared RFA with surgery in primary or recurring lower limb varicose veins and also had a major flaw in its calculations. One of the modelling studies compared RFA with surgery using data from a single RCT, and the other used a Markov model to compare EVLA, RFA, and FS with surgery over a 5-year span. From these, the authors of the review conclude that the available economic analyses of endovenous treatments in comparison with conventional treatment for varicose veins were of limited scope and quality. Differences in costs and benefits between treatments are small
and sensitive to assumptions; cost-effectiveness of the different procedures in relation to each other is likely to be uncertain, and vary by local costs.

Nesbitt et al. (2014) found 6 studies (Rautio et al., 2002; Rasmussen et al., 2007; Subromonia and Lees, 2010; ElKaffas et al., 2011; Rasmussen et al., 2011; Shadid et al., 2012) that presented costs analyses. Two studies reported costs for FS compared with surgery and both found decreased costs with FS. Two other studies provided cost comparisons for EVL and surgery. Both found slightly higher costs associated with laser ablation. Three studies reported cost information for RFA compared with surgery. While procedural costs were similar for both treatment groups, 1 study reported slightly higher costs in the RFA group and 2 reported slightly higher costs in the surgical groups. Overall, Nesbitt et al. (2014) concluded that the costs in each of the studies they identified varied, and no study reported estimation of costs of additional procedures for residual or recurrent varices, which may have been of some significance.

Rigby et al. (2009) noted that costs were analyzed in some studies identified for their review, but the data on cost-effectiveness was not adequately reported or was outdated. Based on the cost outcomes reported in the included studies, sclerotherapy was cheaper in terms of cost to the hospital and to the patient, measured in terms of money and days off work.

Limitations of the economic analyses provided in these systematic reviews are related to the quality of the individual studies providing the data synthesized in the review. In addition, the individual studies may not have provided cost information from a U.S. healthcare perspective, limiting the applicability to the U.S.

*Primary Studies – Economic Analyses*

Using the last date in the search conducted by Carroll et al. (2013) as a parameter for the beginning date of an update literature search, 2 retrospective cohort analyses that presented relative cost information from a U.S. perspective for RFA, EVL, phlebectomy, and surgery were identified. One study compared average direct costs of RFA with those of surgery (Eidson et al., 2011) and the other calculated costs per case and net profit/loss for RFA, EVL, phlebectomy, and surgery (Lin et al., 2013). Eidson et al. (2011) used a subset of data from 200 patients undergoing either RFA or stripping and ligation for treatment of varicose veins at a single hospital during a 5-year period. Patients were divided in to 4 groups and 10 records from each group were randomly selected for cost calculations. Average direct costs for each group were: RFA group (in treatment room), $906; RFA group (in operating room), $2533; GSV stripping and ligation group (inpatient), $4241(excludes patients who had > 1 night hospital stay); and GSV stripping and ligation group (outpatient), $2622. There were statistically significant differences in age and percentage of male patients at baseline between the full RFA (n=100) and stripping and ligation groups (n=100). It is not clear if there were differences between the subsets who were analyzed for average direct costs. In the study conducted by Lin et al. (2014) cost data from 2010 and 2011 for EVLA, RFA, phlebectomy, and high ligation and stripping were presented in terms of cost per case and net profit or loss. Treatment groups were divided into 7 subsets based on type of facility (tertiary or community) and whether the procedure was performed in an office or operating room. Details of the
calculated per-case costs and net profit or loss for each treatment strategy in each year are provided in Appendix Va. The authors concluded that vein stripping is associated with higher operating costs than EVLA or RFA. This study is limited to an analysis of the cost of the procedures only and does not provide information about costs for follow-up care or retreatment.

Practice Guidelines

Eight practice guidelines with relevant recommendations were identified. Appendix VI presents the quality rating of each guideline based on assessment using the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors.


The 2011 clinical practice guidelines of the SVS and AVF (Gloviczki et al., 2011) Venous Guideline Committee recommend EVLA, RFA, and FS as effective alternatives to stripping and other modalities. In the jointly issued guidelines on management of venous leg ulcers, SVS/AVF makes recommendations about operative and endovascular management for treating incompetent veins with reflux in patients with venous leg ulcers (O’Donnell et al., 2014). In both sets of guidelines, the recommendations are labeled based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as strong (GRADE 1) if the benefits clearly outweigh the risks, burden, and costs. The suggestions are weak (GRADE 2) if the benefits are closely balanced with risks and burden. The level of available evidence to support the evaluation or treatment can be of high (A), medium (B), or low or very low (C) quality. The recommendations are categorized into 11 groups by procedure or diagnosis. Recommendations from the 2011 guidelines specific to the interventions of interest for this HTA include:

- **Open venous surgery:**
  - High ligation and inversion stripping of the saphenous vein to the level of the knee for treatment of the incompetent GSV is recommended with a GRADE of 2B (guideline 10.1).
  - High ligation of the vein at the knee crease, approximately 3 to 5 cm distal to the SPJ, with selective invagination stripping of the incompetent portion of the vein is recommended for treatment of small saphenous vein incompetence with a GRADE 1B (guideline 10.3).
  - Ablation of the incompetent superficial veins in addition to compression therapy to decrease recurrence of venous ulcers is recommended with a GRADE 1A (guideline 10.4).
  - Ambulatory phlebectomy for treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage is recommended, and if anesthesia is required for phlebectomy the organization suggests concomitant saphenous ablation (GRADE 1B, guideline 10.7).
- Transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence as an alternative to traditional phlebectomy for extensive varicose veins is recommended with a GRADE of 2C (guideline 10.8).
- Ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy, or endovenous thermal ablation, depending on the etiology, source, location, and extent of varicosity is suggested for the treatment of recurrent varicose veins with a GRADE of 2C (guideline 10.9).

- **Endovenous thermal ablation**
  - EVLA and RFA are recommended for the treatment of saphenous incompetence with a GRADE of 1B (guideline 11.1).
  - Because of reduced convalescence and less pain and morbidity, the group recommends endovenous thermal ablation of the incompetent saphenous vein over open surgery (GRADE 1B, guideline 11.2).

- **Sclerotherapy**
  - Liquid or FS for telangiectasia, reticular veins, and varicose veins is recommended with a GRADE of 1B (guideline 12.1).
  - Endovenous thermal ablation is recommended over chemical ablation with foam for treatment of the incompetent saphenous vein (GRADE 1B, guideline 12.2).

- **Treatment of perforating veins**
  - Subfascial endoscopic perforating vein surgery, US-guided sclerotherapy, or thermal ablations are suggested for treatment of “pathologic” perforating veins with a GRADE of 2C (guideline 13.3).

The 2014 guidelines on management of venous leg ulcers aim to address the twofold goal of venous leg ulcer treatment, which includes ulcer healing and prevention of ulcer recurrence. The guideline authors note that in general, they found the quality of the available evidence for operative or endovascular management was largely limited to level “C” because of a lack of RCTs evaluating treatment techniques. An exception was superficial venous treatments. The guidelines generally, with a few exceptions, suggest or recommend the use of ablation followed by compression for specific types of venous incompetence and reflux occurring with venous leg ulcers (O’Donnell et al., 2014).

**National Institute for Health and Care Excellence (NICE): Varicose veins in the legs. The diagnosis and management of varicose veins (2013)**

In 2013, the United Kingdom’s National Clinical Guideline Centre developed guidelines on behalf of NICE regarding the diagnosis and management of varicose veins. The aims of the guidelines were to identify which people should be referred and/or treated; identify which treatment is cost effective; and provide information for people with varicose veins. The guidelines apply to adults older than 18 years of age with varicose veins in the legs; special populations considered were pregnant women and people with recurrent varicose veins. From the full set of recommendations, 4 key priorities were identified. Among these were a recommendation that people with confirmed varicose veins and truncal reflux should first be offered endothermal ablation (EVLA or RFA), if endothermal ablation is not suitable, then patients should be offered US-guided FS, and if US-guided FS is not suitable, then surgery should be offered. NICE
recommends not offering compression hosiery to treat varicose veins unless interventional treatment is not suitable. The full list of recommendations includes a recommendation against interventional treatment for varicose veins during pregnancy other than in exceptional circumstances (National Clinical Guideline Centre, 2013; O’Flynn et al., 2014).


Guidelines from the European SVS issued in 2015 (Wittens et al., 2015) lay out recommendations for an array of treatment of options. The guidelines were rated based on the European Society of Cardiology grading system. For each recommendation, the letter A, B, or C marks the level of evidence with A being the highest (multiple RCTs and meta-analyses) and C being the lowest (consensus opinion, small studies, retrospective studies, registries). Weighing the level of evidence and expert opinion, every recommendation was subsequently marked as either class I, IIa, IIb, or III; class I indicated evidence or general agreement that a treatment is beneficial, useful, and effective and class III reflects evidence or general agreement that a treatment or procedure is not useful/effective, and in some cases may be harmful. Recommendations directly pertaining to the treatments of interest for this HTA are:

- Liquid sclerotherapy or FS is not recommended as the first-choice treatment for CVD (C2-C6 in the CEAP classification) due to saphenous vein incompetence. It should be used only as the primary treatment in selected cases (recommendation 38, IIaA).
- FS is recommended as a second choice treatment of varicose veins (C2 in the CEAP classification) and for more advanced stages of CVD (C3-C6 in the CEAP classification) in patients with saphenous vein incompetence, not eligible for surgery or endovenous ablation (recommendation 39, IA).
- FS should be considered as primary treatment in patients with recurrent varicose veins, and in elderly and frail patients with venous ulcers (recommendation 40, IIaB).
- Liquid sclerotherapy should be considered for treating telangiectasias and reticular veins (C1 in the CEAP classification) (recommendation 41, IIaB).
- For treatment of GSV reflux in patients with symptoms and signs of CVD, endovenous thermal ablation techniques are recommended in preference to surgery (recommendation 43, IA).
- For the treatment of GSV reflux in patients with symptoms and signs of CVD, endovenous thermal ablation techniques are recommended in preference to FS (recommendation 44, IA).
- For the treatment of SSV reflux in patients with symptoms and signs of CVD, endovenous thermal ablation techniques should be considered (recommendation 45, IIaB).
- For non-complicated varicose veins (C2, C3 in the CEAP classification), surgical treatment is recommended instead of conservative treatment, to improve symptoms, cosmetics, and QOL (recommendation 46, IB).
• In cases in which surgical treatment of the refluxing saphenous vein is performed, high ligation and stripping is recommended instead of high ligation only (recommendation 47, IA).

• Surgical stripping of the saphenous vein without high ligation leaving a 2 cm stump may be considered (recommendation 48, IIbB).

• When performing endovenous thermal ablation of a refluxing saphenous trunk, adding concomitant phlebectomies should be considered (recommendation 51, IIaB).

• To treat tributary varicose veins, ambulatory phlebectomy should be considered (recommendation 52, IIaC).

• Endovenous thermal ablation, US-guided FS, or phlebectomies should be considered for the treatment of recurrent varicose veins (recommendation 63, IIaB).

• Extensive redo surgery is not recommended (including re-exploration of the groin or popliteal fossa) is not recommended as a first-choice treatment in patients with recurrent varicose veins (recommendation 64, IIIB).

**American College of Phlebology (ACP): Guidelines – Treatment of Superficial Venous Disease of the Lower Leg (2014)**

In 2014, the ACP published guidelines (American College of Phlebology, 2014) with the goal of creating a summary document that reflects the recommendations described in the 2011 Gloviczki et al. (2011) publication and other sources available at the time. Other recommendations described in the 2014 ACP guidelines are based on the consensus of experts where the evidence-based research is sparse yet the therapy is considered standard of care. The group followed methods suggested by GRADE to develop its guidelines. For each guideline, the letter A, B, or C marks the quality of the evaluated evidence as high, medium, or low quality. The grade of recommendation of a guideline can be strong (1) or weak (2), depending on the risk and burden of a particular diagnostic test or a therapeutic procedure to the patient versus the expected benefit. The organization uses “recommend” for GRADE 1 and “suggest” for GRADE 2 statements. Some of the recommendations from the 2014 ACP guidance are as follows:

• Recommend against compression therapy as a prerequisite therapy for symptomatic venous reflux disease when other definitive treatments such as endovenous ablation are appropriate. (1A)

• Recommend endovenous thermal ablation (laser and RF) as the preferred treatment for saphenous and accessory saphenous (GSV, SSV, AAGSV, PAGSV) vein incompetence (1B).

• Recommend open surgery is appropriate in veins not amenable to endovenous procedures but otherwise is not recommended because of increased pain, convalescent time, and morbidity (1B).
• Suggest that when open surgery of the GSV is performed, it should include high ligation and invagination stripping to the level of the knee (2B), and recommend that when open surgery of the SSV is performed it include high ligation and selective invagination of the proximal portion. (1B).

• Recommend varicose (visible) symptomatic tributary veins can be treated by stab phlebectomy, liquid sclerotherapy, or foam chemical ablation (1B), and recommend non-visible symptomatic tributary veins be treated by US-guided liquid sclerotherapy or foam chemical ablation (1B).

• Suggest treatment of incompetent perforating veins located beneath a healed or open venous ulcer. They should have outward flow of 500 milliseconds (ms), with a diameter of 3.5 mm. (2B).

• Suggest in patients with perforator reflux as the primary or only source of disease, treatment of the perforator with endovenous thermal ablation, ligation, or US-guided sclerotherapy. Subsequent or simultaneous treatment of symptomatic varicosities arising from the incompetent perforator is also considered best practice. (2B).


In their 2016 Guidelines (Gibson et al., 2016), the ACP used the GRADE strength of recommendation method. The strength of recommendation for or against a specific diagnostic or therapeutic intervention was expressed as strong (1) or alternatively as weak or provisional (2). The quality of evidence was rated as high (A), medium (B), or low (C). The group’s recommendation is that patients with symptomatic incompetence of the accessory GSV be treated with endovenous thermal ablation (EVLA or RFA) or with US-guided FS to reduce symptoms (Grade 1, level C).

**Society for Vascular Medicine (SVS), American College of Phlebology (ACP), and Society of Interventional Radiologists (SIR): Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines (2014)**

Quality improvement guidelines issued jointly by SVS, ACP, and SIR in 2014 (Rathbun et al., 2014) state that endovenous FS is effective for treating primary and recurrent GSV, SSV, and accessory varicose veins. However, no RCTs were available for assessment and the group could not draw conclusions about the comparative efficacy or safety of FS and endovenous thermal ablation.


The ACR describes different clinical variants or scenarios and provides a rating (1 through 9) for the appropriateness of different interventions for the given scenario in its 2012 publication of ACR Appropriateness Criteria for Radiologic Management of Lower-Extremity Venous Insufficiency (Rochon et al., 2012). Ratings in different scenarios for the populations and interventions selected for this HTA are shown below.
• Variant 2: Left small saphenous venous insufficiency resulting in intermittent pain and swelling without skin discoloration or ulceration. Rating 8 (usually appropriate) for endoluminal radiofrequency therapy; Rating 7 (usually appropriate) for endoluminal laser therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

• Variant 3: Left great saphenous venous insufficiency with associated lower leg skin ulceration. Rating 8 (usually appropriate) for endoluminal laser therapy and for endoluminal RF therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

• Variant 4: Symptomatic bilateral great saphenous venous insufficiency and large visible varicose veins during pregnancy. Rating 2 (usually not appropriate) for endoluminal laser therapy, endoluminal RF therapy, injection sclerotherapy, and surgical vein stripping.

• Variant 6: Symptomatic bilateral great saphenous venous insufficiency with remote history of DVT with no residual thrombus present. Rating 7 (usually appropriate) for endoluminal laser therapy and endoluminal RF therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

• Variant 7: Right great saphenous venous insufficiency status post vein stripping 1 year ago with persistent lower-extremity swelling. Reflux is noted in the below-knee greater saphenous vein measuring up to 5 mm. Rating 8 (usually appropriate) for endoluminal laser therapy and endoluminal radiofrequency therapy; Rating 4 (may be appropriate) for repeat surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

Selected Payer Policies

At the direction of WA HCA, published coverage policies for the following organizations were sought: Aetna, Centers for Medicare & Medicaid Services (CMS), Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield. The lack of a published coverage policy does not necessarily indicate that a payer does not provide coverage.

Aetna

Doppler or duplex US studies are considered necessary prior to varicose vein treatment to assess the anatomy and to determine whether there is significant reflux at the SFJ or SPJ requiring repair and after completion of the treatment to determine the success of the procedure and to detect thrombosis. Aetna considers these procedures medically necessary for treatment of varicose veins when the following criteria are met: GSV, accessory saphenous vein, or SSV ligation/division/stripping, RF endovenous occlusion, and EVLA of the saphenous vein (also known as endovenous laser treatment).
• Incompetence at the SFJ or SPJ is documented by recent (performed within the past 6 months) Doppler or duplex US scanning, and all of the following criteria are met:
  
  o US documented junctional reflux duration of 500 ms or greater in the saphenofemoral or saphenopopliteal vein to be treated.
  
  o Vein size is 4.5 mm or greater in diameter measured by US immediately below the SFJ or SPJ (not valve diameter at junction).
  
  o Saphenous varicosities result in any of the following: intractable ulceration secondary to venous stasis; more than 1 episode of minor hemorrhage from ruptured superficial varicosity, or a single significant hemorrhage from a ruptured superficial varicosity, especially if transfusion of blood is required; saphenous varicosities result in either recurrent superficial thrombophlebitis or severe and persistent pain and swelling interfering with activities of daily living and requiring chronic analgesic medication when symptoms persist despite a 3-month trial of conservative management* (e.g., analgesics and prescription gradient support compression stockings). (*A trial of conservative management is not required for persons with persistent or recurrent varicosities who have undergone prior endovenous catheter ablation procedures or stripping/division/ligation in the same leg because conservative management is unlikely to be successful in this situation.)

• Endovenous ablation procedures are considered medically necessary for the treatment of incompetent perforating veins with vein diameter measured by recent US of 3.5 mm or greater with outward flow duration of 500 ms duration or more, located underneath an active or healed venous stasis ulcer.

• Endovenous ablation procedures are considered medically necessary adjunctive treatment of symptomatic accessory saphenous veins for persons who meet medical necessity criteria for endovenous ablation above and who are being treated or have previously been treated by 1 of the procedures listed above for incompetence at the SFJ or SPJ and anatomically related persistent junctional reflux is demonstrated after GSV or SSV have been removed or ablated.

Criteria related to initial and subsequent ablation therapies are as identified in the policy.

See the policy for when Aetna considers endovenous ablation procedures not medically necessary and/or investigational.

Aetna considers liquid sclerotherapy or FS (endovenous chemical ablation), ambulatory or transilluminated powered phlebectomy medically necessary adjunctive treatment of symptomatic saphenous veins, varicose tributaries, accessory and perforator veins 2.5 mm or greater in diameter for persons who meet medical necessity criteria for varicose vein treatment (see above) and are being treated or have previously been treated by 1 or more of the procedures noted for incompetence (see above) at the SFJ or SPJ. US-monitored or duplex-guided techniques for sclerotherapy are only considered medically necessary when initially performed to determine the extent and configuration of varicose veins. Criteria related to sclerotherapy injection sessions are identified in the policy, as are criteria related to initial and subsequent stab phlebectomy incisions. See the policy for when Aetna
considers sclerotherapy, ambulatory or transilluminated powered phlebectomy not medically necessary and/or investigational.


**Centers for Medicare & Medicaid Services (CMS)**

No CMS National Coverage Determination (NCD) for treatment of varicose veins was identified on January 10, 2017 (search National Coverage Documents by the keywords varicose or vein in all documents at: [https://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx](https://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

There is a Local Coverage Determination (LCD) for Treatment of Varicose Veins of the Lower Extremities. The LCD was issued by Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington. The LCD states the indications for sclerotherapy, endoluminal RFA (ERFA) and endovenous laser ablation (EVLA) include:

- A 3-month trial of conservative therapy such as exercise, periodic leg elevation, weight loss, compressive therapy, and avoidance of prolonged immobility where appropriate, has failed and;

- The patient is symptomatic and has 1, or more, of the following:
  - Pain or burning in the extremity severe enough to impair mobility.
  - Recurrent episodes of superficial phlebitis.
  - Nonhealing skin ulceration.
  - Bleeding from a varicosity.
  - Stasis dermatitis.
  - Refractory dependent edema.

In addition, the LCD states the indications for ERFA and EVLA also include the patient's anatomy and clinical condition are amenable to the proposed treatment including all of the following:

- Absence of aneurysm in the target segment.
- Maximum vein diameter of 12 mm for ERFA or 20 mm for laser ablation.
- Absence of thrombosis or vein tortuosity which would impair catheter advancement.
- Absence of significant peripheral arterial diseases.

Medicare will cover 1 US or duplex scan prior to the procedure to determine the extent and configuration of the varicosities.
The coverage policy lists a few limitations for ERFA and EVLA, these include:

- Covered only for the treatment of symptomatic varicosities of the lesser or GSVs and their tributaries, which have failed 3 months of conservative therapy.

- Coverage is only for devices specifically FDA-approved for these procedures.

Noridian notes that stab phlebectomy of the same vein performed on the same day as ERFA or EVLA may be covered if the criteria for reasonable and necessary are met. Also, if sclerotherapy is used with ERFA, it may be covered if the criteria for reasonable and necessary are met.

*See* LCD for Treatment of Varicose Veins of the Lower Extremities ([L34010](#)).

**Group Health Cooperative**

The Group Health Cooperative (GHC) policy on treatment of varicose veins (Clinical Review Criteria) states for their Medicare members, they will use the Local Coverage Determination (LCD) for Treatment of Varicose Veins of the Lower Extremities ([L34010](#)).

For their non-Medicare members, Group Health’s policy states coverage for GSV or SSV, stab phlebectomy, endovenous radiofrequency ablation (ERFA) treatment and endovenous laser ablation (ELAS) (also known as endovenous laser treatment [EVLT]), requires all of the following criteria be met:

- The patient is symptomatic and has 1, or more, of the following: pain or burning in the extremity; recurrent episodes of superficial phlebitis; nonhealing skin ulceration; bleeding from a varicosity; stasis dermatitis; and refractory-dependent edema.

- Vein size is 4.5 mm or greater in diameter (not valve diameter at junction).

- Preoperative Doppler demonstrates reflux (reflux duration of 500 ms or greater).

- In addition all of the following are true for ERFA and laser ablation: absence of aneurysm in the target segment; maximum vein diameter of 12 mm for ERFA or 20 mm for laser ablation; absence of thrombosis or vein tortuosity; and the absence of significant peripheral arterial diseases.

Group Health’s policy states sclerotherapy is covered for up to 6 months after a covered stab phlebectomy or endovenous ablation. Sclerotherapy can be approved at these same venous sites if symptoms continue and are associated with persistent varicosities.

*See* Treatment of Varicose Veins ([Clinical Review Criteria](#)).

**Oregon Health Evidence Review Commission (HERC)**

No coverage guidance for treatment of varicose veins was identified on the Oregon HERC website ([Oregon HERC Coverage Guidances](#)).
Regence

The following is a summary from a Regence Group medical policy for Oregon, Idaho, and select counties in Washington that goes in to effect on April 1, 2017. The document makes it clear that member contracts for covered services vary, and member contracts take precedent over medical policy. The medical policy states all of the following general criteria must be met for varicose vein treatment to be considered for coverage:

- At least 1 or more of the following indications must be present:
  - Functional impairment, attributed to varicose veins, which limits performance of instrumental activities of daily living (ADLs). Instrumental ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning. Clinical records must specifically document the specific instrumental ADL(s) that is impaired and a description of how performance of it is limited.
  - US-documented recurrent attacks of superficial phlebitis.
  - Recurrent or persistent hemorrhage from ruptured varix.
  - Ulceration from venous stasis where incompetent varices are a significant contributing factor.

- There is clinical documentation that ongoing medically supervised conservative therapy, including use of compression (minimum 20 millimeters of mercury [mm Hg]) stockings (or compression wrap when stockings cannot be utilized), has been utilized for a minimum of 3 months, is currently being utilized, and did not successfully treat the patient’s indication(s) or clinical condition.

  Clinical documentation requirements are as outlined in the policy.

- Incompetence in the superficial system veins (e.g., long and short saphenous veins, perforator veins, and saphenous tributaries) must be supported by complete venous imaging study documentation obtained no more than 6 months prior to the request for coverage with the diameter of the vein and the reflux in seconds measured at multiple levels in the thigh and calf.

  Request requirements for additional treatment sessions are as outlined in the policy.

- Clear, interpretable photographs are required on any affected areas of the leg and must be consistent with the submitted clinical description.

Regence Group’s policy discusses the following procedures:

- Phlebectomy (i.e., stab, hook, transilluminated powered) of incompetent superficial system veins (including the long and short saphenous veins and saphenous tributaries, including
accessory saphenous veins) and varicose veins 4 mm or greater in diameter may be considered medically necessary when all of the following criteria are met:

- All of the general criteria are met.
- The incompetent superficial veins proximal to the vein to be treated either have been treated or are being treated concurrently.

- ERFA or EVLA of incompetent long or short saphenous veins may be considered medically necessary when all of the following criteria are met:
  
  - All of the general criteria are met.
  
  - Minimum vein diameters where treatment is requested: long saphenous vein diameter 5.5 mm or greater measured via US at the SFJ (or proximal thigh), midthigh, and knee (If below knee ablation requested mid-calf measurement also necessary); or SSV diameter is 4 mm or greater measured via US at the SPJ and mid-calf.
  
  - Significant incompetence exceeding 0.5 seconds is demonstrated at the SFJ and thigh, or at the SPJ and calf.
  
  - Clinical documentation that all incompetent segments of the same vein will be treated in the same session.

Request requirements for additional treatment sessions are as outlined in the policy.

See the policy for vein ablation procedures Regence Group considers not medically necessary and/or investigational.

- Sclerotherapy (liquid, FS, or microfoam) of the following superficial system veins, SSV, and saphenous tributaries, including accessory saphenous veins, and varicose veins 4 mm or greater in diameter may be considered medically necessary when both of the following criteria are met:
  
  - All of the general criteria are met.
  
  - If related superficial system veins proximal to the incompetent vein to be treated are incompetent, those incompetent proximal veins either have been treated or are being treated concurrently.

See the policy for when Regence Group considers sclerotherapy not medically necessary and/or investigational.

Criteria related to initial and subsequent treatment sessions are as identified in the policy.

*See Varicose Vein Treatment (Regence Group Medical Policy No. 104).*
References


Paravastu SCV, Horne M, Dodd PDF. Endovenous ablation therapy (laser or radiofrequency) or foam sclerotherapy versus conventional surgical repair for short saphenous varicose veins. *Cochrane Database Syst Rev.* 2016(11).


APPENDICES

APPENDIX I. Search Strategy

INITIAL SEARCH, SYSTEMATIC REVIEWS

A review of reviews methodology was employed for this HTA and a comprehensive search for systematic reviews and health technology assessments (HTA) to answer the key questions was conducted first. PubMed and the Centre for Reviews and Dissemination (CRD) electronic databases were searched for relevant systematic reviews on September 6, 2016 and the following electronic databases were searched for additional systematic reviews on December 22, 2016: PubMed, Canadian Agency for Technology and Health (CADTH), Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program (EHC), Cochrane Library, National Health Service – National Institute for Health Research (NIH-NIHR), National Institute for Health and Care Excellence (NICE), and CRD.

Search strategies:

PubMed Systematic Review Search (12-22-16)

((varicose vein[All Fields] OR varicose veins[All Fields]) AND
(“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR

Searches of CRD, NHS-NIHR, NICE, CADTH, AHRQ EHC, and Cochrane used the term “varicose veins.”

SEARCHES FOR PRIMARY CLINICAL STUDIES AND ECONOMIC EVALUATIONS

Following identification and selection of systematic reviews and HTAs, a targeted search of PubMed and reference lists of key publications for relevant primary data published subsequent to the review(s) selected for each indication was conducted on September 6, 2016. The initial search was limited to randomized controlled trials published in the English language between March 1, 2011 and the search date. A separate search was conducted for additional economic evaluations on February 1, 2017.

PubMed search on 9/16/2016 for RCTs

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>#10</td>
<td>Search #6 AND #7 Filters: Publication date from 2011/03/01 to 2016/09/16; English</td>
</tr>
<tr>
<td>#9</td>
<td>Search #6 AND #7 Filters: Publication date from 2011/03/01 to 2016/09/16</td>
</tr>
<tr>
<td>#8</td>
<td>Search #6 AND #7</td>
</tr>
<tr>
<td>#7</td>
<td>Search (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))</td>
</tr>
</tbody>
</table>
#6  Search #1 AND #5

#5  Search #2 OR #3 OR #4

#4  Search (((((phlebectomy) OR "stab phlebectomy") OR "stab avulsion") OR microphlebectomy) OR "microextraction phlebectomy") OR "micro-extraction phlebectomy"

#3  Search (((((("laser ablation") OR radiofrequency) OR RFA) OR venacure) OR "pro v laser") OR cooltouch) OR elves) OR "lumenis sharplan") OR medilas) OR "catheter ablation") OR "closure catheter") OR venefit) OR ablation

#2  Search (((("varicose veins/therapy"[MeSH Major Topic]) OR sclerotherapy) OR asclera) OR aethoxysklerol) OR "chromated glycerin") OR cyanoacrylate) OR dermabond) OR polidocanol) OR scleremo) OR sclerodex) OR "sodium chloride") OR "sodium tetradecyl sulfate") OR sotradecol) OR varisolve) OR varithena

#1  Search (((varicose veins[MeSH Terms]) OR varicose vein[Title/Abstract]) OR varicose veins[Title/Abstract]) OR varicosit*[Title/Abstract]

PubMed Search on 2/1/2017 for cost studies

Search  Query

#10  Search #6 AND #7 Filters: Publication date from 2012/06/01 to 2017/02/01; English Sort by: Author

#9   Search #6 AND #7 Filters: English Sort by: Author

#8   Search #6 AND #7

#7   Search (((economic analysis) OR (economic evaluation))) OR (((cost AND (analysis OR benefit OR effective* OR consequence OR minimization))))) OR ("Costs and Cost Analysis"[MeSH] OR "Cost-Benefit Analysis"[MeSH]))

#6   Search #1 AND #5

#5   Search #2 OR #3 OR #4

#4   Search (((((phlebectomy) OR "stab phlebectomy") OR "stab avulsion") OR microphlebectomy) OR "microextraction phlebectomy") OR "micro-extraction phlebectomy"

#3   Search (((("laser ablation") OR radiofrequency) OR RFA) OR venacure) OR "pro v laser") OR cooltouch) OR elves) OR "lumenis sharplan") OR medilas) OR "catheter ablation") OR "closure catheter") OR venefit) OR ablation

#2   Search (((("varicose veins/therapy"[MeSH Major Topic]) OR sclerotherapy) OR asclera) OR aethoxysklerol) OR "chromated glycerin") OR cyanoacrylate) OR dermabond) OR polidocanol) OR scleremo) OR sclerodex) OR "sodium chloride") OR "sodium tetradecyl sulfate") OR sotradecol) OR varisolve) OR varithena

#1   Search (((varicose veins[MeSH Terms]) OR varicose vein[Title/Abstract]) OR varicose veins[Title/Abstract]) OR varicosit*[Title/Abstract]
SEARCH FOR GUIDELINES

In addition to guidelines found through the database and manual searches outlined above, we also searched the National Guidelines Clearinghouse and websites of professional organizations. The National Guidelines Clearinghouse (https://guideline.gov/) and websites of professional organizations were searched using the terms “endovascular laser ablation”, “endovenous radiofrequency”, “phlebectomy”, “sclerotherapy”, and “varicose veins”. Professional organizations included: American Venous Forum; Society for Vascular Surgery; and American College of Phlebology.
### APPENDIX II.

#### The Assessment of Multiple Systematic Reviews (AMSTAR) Tool

The following key steps describe the AMSTAR tool (Shea et al., 2007):

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Systematic Review Appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate the quality of each systematic review using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). This step is only necessary when data synthesis such as meta-analysis is conducted within the review and used in addition to or in place of individual study data.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Individual Study Appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. Initial rating according to study design</td>
</tr>
<tr>
<td></td>
<td>Good: Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Fair: Nonrandomized trial (controlled, parallel-group, quasi-randomized)</td>
</tr>
<tr>
<td></td>
<td>Poor: Observational analytic studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group)</td>
</tr>
<tr>
<td></td>
<td>Very poor: Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data])</td>
</tr>
<tr>
<td></td>
<td>b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</td>
</tr>
<tr>
<td></td>
<td>c. Repeat for each study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Evaluation of Each Body of Evidence by Outcome, Key Question, or Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. Initial quality designation according to best study design in a body of evidence</td>
</tr>
<tr>
<td></td>
<td>b. Downgrade/upgrade</td>
</tr>
<tr>
<td></td>
<td>c. Downgrade factors: Study weaknesses (Quality Checklists), lack of applicability, inconsistency of results, small quantity of data, publication bias (if adequate information is available)</td>
</tr>
<tr>
<td></td>
<td>d. Possible upgrade factors: Strong association, dose-response effect, bias favoring no effect</td>
</tr>
<tr>
<td></td>
<td>e. Assign final rating: High-Moderate-Low-Very Low</td>
</tr>
<tr>
<td></td>
<td>f. Repeat for each outcome/question/application</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Evaluation of Overall Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a. Rank outcomes by clinical importance</td>
</tr>
<tr>
<td></td>
<td>b. Consider overall quality of the evidence for each critical outcome</td>
</tr>
<tr>
<td></td>
<td>c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low</td>
</tr>
<tr>
<td>Step 5</td>
<td>Evidence-Based Conclusion</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>Overall quality of the evidence + balance of benefits and harms</td>
</tr>
</tbody>
</table>
## APPENDIX III.

### Overview of Evidence Quality Assessment Methods

**Clinical Studies**

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Individual study appraisal:</th>
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<tbody>
<tr>
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<td>Initial rating according to study design</td>
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<td></td>
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<td><strong>Poor:</strong> Observational analytic studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group)</td>
</tr>
<tr>
<td></td>
<td><strong>Very poor:</strong> Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data])</td>
</tr>
<tr>
<td>b.</td>
<td>Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</td>
</tr>
<tr>
<td>c.</td>
<td>Repeat for each study</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Evaluation of each body of evidence by outcome, key question, or application:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Initial quality designation according to best study design in a body of evidence</td>
</tr>
<tr>
<td>b.</td>
<td>Downgrade/upgrade</td>
</tr>
<tr>
<td></td>
<td><strong>Downgrade factors:</strong> Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias</td>
</tr>
<tr>
<td></td>
<td><strong>Possible upgrade factors:</strong> Strong association, dose-response effect, bias favoring no effect</td>
</tr>
<tr>
<td>c.</td>
<td>Assign final rating: High-Moderate-Low-Very Low</td>
</tr>
<tr>
<td>d.</td>
<td>Repeat for each outcome/question/application</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Evaluation of overall evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Rank outcomes by clinical importance</td>
</tr>
<tr>
<td>b.</td>
<td>Consider overall quality of evidence for each <strong>critical</strong> outcome</td>
</tr>
<tr>
<td>c.</td>
<td>Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low</td>
</tr>
</tbody>
</table>

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<tr>
<th>Step 4</th>
<th>Evidence-based conclusion:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Overall quality of evidence + Balance of benefits and harms</td>
</tr>
</tbody>
</table>
Practice Guidelines

(Checklist taken from AGREE Tool and approach to scoring used in this report)

Rank each item on a scale of 1-7.

Decide on overall quality (1 = lowest to 7 = highest), giving strongest weight to items 7-14 (Rigor of Development Domain) and items 22-23 (Editorial Independence).

For qualitative labels:
- Very poor = 1
- Poor = 2 - 3
- Fair = 4 - 5
- Good = 6 - 7

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

**Economic Evaluations**

A tool developed by Hayes for internal use guides interpretation and critical appraisal of economic evaluations. The tool includes a checklist of items addressing issues such as the reliability of effectiveness assumptions, transparency of reporting, quality of analysis, generalizability/applicability, and conflicts of interest. The following publications served as sources of best practice.


**Books**


Other

APPENDIX IV.

Excluded Studies

The following 88 studies were excluded during full-text review.

Ineligible study design, intervention, outcomes, population, or full text not available (11)


Ineligible publication type (32)


Ineligible comparator (14)


**Included in a SR (31)**


APPENDIX V. Evidence Tables

APPENDIX Va. Primary Studies

Key: EE, economic evaluation; f/u, follow-up; grp(s), group(s); HR, hazard ratio; hx, history; mm Hg, millimeter of mercury; NA, not applicable; NR, not reported; pt(s), patient(s); QALY, quality-adjusted life-years; QOL, quality of life; RCT, randomized controlled trial; tx, treatment (or therapy); USD, U.S. dollars

<table>
<thead>
<tr>
<th>Authors/Study Design</th>
<th>Study Population</th>
<th>Treatment</th>
<th>Results</th>
<th>Quality/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eidson et al. (2011) Scott &amp; White Hospital, Texas A and M College of Medicine, Temple, TX Economic analysis (retrospective cohort) F/u: 6 months Time frame: August 2002 – October 2007 Funding source: Non-industry</td>
<td>n= 200 n = 100 Open GSV/SSV stripping and ligations (SL grp) n= 100 RFA (RFA grp) Cost analysis based on 10 randomly selected records from each of 4 subgroups (RFA in treatment room; RFA in OR; SL inpatient; SL outpatient)</td>
<td>Tx setting: Community hospital, mixed inpatient and outpatient Intervention: RFA Control: Open GSV/SSV stripping and ligations</td>
<td>Average direct cost: RFA grp (in treatment room): $906 RFA grp (in OR): $2533 GSV SL (inpatient): $4241; excludes pts who had &gt;1 night hospital stay GSV SL (outpatient): $2622</td>
<td>Limitations: Cost analysis is limited by statistically significant baseline differences b/t grps; small sample size Conflicts of interest: One author was a is a proctor/consultant for VNUS Inc.</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: NR Exclusion criteria: NR Clinical hx/pt characteristics (Intervention grp; Control grp): Mean age (yrs): RFA grp, 57.7 yrs; SL grp, 52.8 yrs (P=0.002) % men: RFA grp, 14%; SL grp, 34% (P&lt;0.05) % smoker: NR CEAP 5/6: RFA grp, 26%; SL grp, 18% (P=NS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors/Study Design</td>
<td>Study Population</td>
<td>Treatment</td>
<td>Results</td>
<td>Quality/Comments</td>
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<tr>
<td>Lin et al. (2014)</td>
<td>n=181 procedures in 2010; n=195 procedures in 2011</td>
<td>Tx setting: Community hospital and a tertiary care hospital</td>
<td>Costs per case (2010, US dollars)</td>
<td>Limitations:</td>
</tr>
<tr>
<td>Henry Ford Hospital, Detroit, MI</td>
<td>Inclusion criteria: Pts undergoing vein stripping, vein ablation procedures using EVLT or RFA, and miniphlebectomy of varicosities</td>
<td>Intervention: RFA (tertiary, office); RFA (community, OR); EVLA (tertiary, office); Phlebectomy (tertiary, office); Phlebectomy (community, OR)</td>
<td>RFA (tertiary, office): $1,074</td>
<td>Conflicts of interest: None</td>
</tr>
<tr>
<td>Economic analysis (retrospective cohort)</td>
<td>Exclusion criteria: NR</td>
<td>Control: HL/S of GSV (tertiary, OR); HL/S (community, OR)</td>
<td>EVLA (tertiary, office): $1,534</td>
<td></td>
</tr>
<tr>
<td>F/u: NR</td>
<td>Clinical hx/pt characteristics (Intervention grp; Control grp):</td>
<td>Outcome measures: Retrospective analysis of the professional and technical portions for the total charges, net revenue, total costs, variable costs, and direct costs of procedures</td>
<td>Phlebectomy (tertiary, office): $3,217</td>
<td></td>
</tr>
<tr>
<td>Time frame: January 1, 2010 – December 31, 2011</td>
<td>Mean age (yrs): NR</td>
<td></td>
<td>Phlebectomy (community, OR): $5,458</td>
<td></td>
</tr>
<tr>
<td>Funding source: NR</td>
<td>% men: NR</td>
<td></td>
<td>HL/S (tertiary, OR): $12,788</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% smoker: NR</td>
<td></td>
<td>HL/S (community, OR): $4,280</td>
<td></td>
</tr>
<tr>
<td>Authors/Study Design</td>
<td>Study Population</td>
<td>Treatment</td>
<td>Results</td>
<td>Quality/Comments</td>
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</table>
| van der Velden et al. (2015) MAGNA trial Erasmus University Medical Center, Rotterdam, The Netherlands | n=240 (224 legs analyzed at 5 yrs)
Inclusion criteria: symptomatic pts with SFJ reflux and a refluxing GSV above the knee with a diameter of at least 5mm (measured mid-thigh)
Exclusion criteria: previous tx of ipsilateral GSV, post-thrombotic syndrome, agenesis of the deep venous system, vascular malformations, use of anticoagulant tx, pregnancy, heart failure, known allergy to local anaesthetics or sclerosing agents, immobility, arterial disease (ankle: brachial pressure index of less than 0.6), age under 18 yrs and inability to provide written informed consent
Clinical hx/pt characteristics (Intervention grp; Control grp):
Mean age (yrs): EVLA, 50.2; surgeru, 52.5; UGFS 56.4
F:M ratio: EVLA, 49:21; surgery, 45:20; 44:20 UGFS
% smoker: NR | Intervention: EVLA, UGFS
Control: surgery
Outcome measures: Obliteration or absence of the treated part of the GSV 5 yrs after tx; absence of above-knee GSV reflux (categories 3 and 4), disease-specific and generic HRQoL scores, class C, SFJ reflux, presence of neovascularization at the SFJ, progression of venous disease and number of reinterventions or additional txs | Clinical outcomes:
Recurrence:
10 of 69 (14.5%) in the surgery grp and 18 of 78 (23%) in the EVLA grp; P=NR (calculated from the reported Kaplan-Meier estimates of obliteration or absence of the GSV data provided in the publication)
10 of 69 (14.5%) in the surgery grp and 59 of 77 (77%) in the US-guided FS (UGFS) grp (P<0.001)
QOL:
NS differences between EVLA and surgery with respect to changes in CIVIQ Venous Quality of Life Questionnaire scores or EQ-5D scores
Disease severity:
no difference in the distribution of class C between legs in the surgery (OR=1.4 [95% CI, 1.2-1.6]) and those treated with EVLA (OR=1.3 [95% CI, 1.1-1.5])
no difference in the distribution of class C between legs in the surgery group (OR=1.4 [95% CI, 1.2-1.6]) and those treated with UGFS (OR=1.3 [95% CI, 1.1-1.5])
Reintervention:
Reintervention and additional txs were given 1 or more times to 10% of the limbs in the surgery and EVLA groups | Study quality: Fair
Conflicts of interest: none |
<table>
<thead>
<tr>
<th>Authors/Study Design</th>
<th>Study Population</th>
<th>Treatment</th>
<th>Results</th>
<th>Quality/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flessenkamper et al. (2016) (f/u to Flessenkamper et al., 2013) Center for Vascular Medicine, Helios Klinikum Emil von Behring, Berlin, Germany</td>
<td>n=449 randomized Inclusion criteria: Ps with varicosity of the GSV Exclusion criteria: Clinical hx/pt characteristics (Intervention grp; Control grp): Mean age (yrs): % men: % smoker:</td>
<td>Intervention: EVLA/HL; EVLA Control: HL/S</td>
<td>given 1 or more times to 10% of the limbs in the surgery group compared with 32% of legs in the UGFS group (log rank test, P&lt;0.001) Complications (Intervention grp; Control grp):</td>
<td>Study quality: Fair Conflicts of interest: none</td>
</tr>
<tr>
<td>Rass et al. (2015) RELACS trial (f/u to Rass et al., 2012) Affiliation: Saarland University Hospital, Homburg, Germany</td>
<td>n=400 randomized (281 at 5yrs) Inclusion criteria: Exclusion criteria: Clinical hx/pt characteristics (Intervention grp; Control grp): Mean age (yrs):</td>
<td>Intervention: EVLA Control: HL/S</td>
<td>Clinical outcomes (Intervention grp; Control grp): Recurrence: No difference in time to clinical recurrence within 6 yr f/u (log rank test P=0.5479) Complications (Intervention grp; Control grp):</td>
<td>Study quality: Fair Conflicts of interest: one author received honoraria for lecturing and travel reimbursement by Covidien</td>
</tr>
<tr>
<td>Authors/Study Design</td>
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</table>
| **Mozafar et al. (2014)** Shohada-e Tajrish Medical Center, Tajrish Sq, Tehran, Iran | n=65  
*Inclusion criteria:* Age 18 to 65; insufficiency of GSV and the SFJ with reflux at least up to the knee; Sxs of GSV insufficiency or CVI  
*Exclusion criteria:* Pregnancy; active malignancy; arterial occlusive disease with ankle brachial index below 0.8; acute DVT; thrombophilia or high risk of thromboemboli; history of inguinal surgery except hernia; insufficiency of the lesser saphenous vein in same limb requiring tx | Intervention: EVLA  
Control: HL/S  
*Outcome measures:* recurrence, AVVSS | Reintervention:  
Types of reintervention for recurrence (n=69 EVLA; n=70 HL/S): “Wait and see” – EVLA, 49%; HL/S 67%; P=0.040  
Sclerotherapy – EVLA, 33%; HL/S, 11%; P=0.004  
Phlebectomy – EVLA, 14%; HL/S, 26%; P=0.138  
Redo tx (SFJ, GSV, AASV) – EVLA, 9%; HL/S, 0%; P=0.000  
SSV surgery – EVLA, 1%; HL/S 4%; P=0.620 | Study quality: Poor  
Conflicts of interest: NR |
| **Carruthers et al. (2014)** Boston Medical Center, Boston, MA | n=4364  
*Inclusion criteria:* Patients treated for CVI in the American College of Surgeons National Surgical Quality Improvement Program data set (2005-2011) | Intervention: Endovenous ablation (EVLA/RFA)  
Control: open surgery DVT | Complications (Intervention grp; Control grp):  
50% decrease in the odds of DVT for patients undergoing open surgery compared with endovenous ablation (adjusted odd ratio = 0.52 [95% CI 0.28-0.97], P=0.040) | Study quality: Fair  
Conflicts of interest: none |
<table>
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<td><strong>Time frame: 2005-2011</strong></td>
<td><strong>Exclusion criteria: NR</strong></td>
<td><strong>Outcome measures: surgical site infection, DVT</strong></td>
<td>Surgical site infection: adjusted OR=2.56 [95% CI1.19-5.50], P=0.016 those with venous ulcers (adjusted OR=2.55 [95% CI 1.4-5.26], P=0.011) and obese patients (adjusted OR=2.16 [95% CI 1.10-4.24], P=0.025</td>
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<tr>
<td><strong>Funding source: none</strong></td>
<td><strong>Clinical hx/pt characteristics (Intervention grp; Control grp):</strong> Mean age (yrs): Overall, 52.4; EVLA/RFA, 53.3; surgery, 51.8 (P&lt;0.001) % men: 33.6%</td>
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<tr>
<td><strong>Fauw et al. (2016)</strong></td>
<td>n=130 legs (112 at Syrs) <strong>Inclusion criteria:</strong> length of the incompetent GSV of at least 15 cm measured from the SFJ downward, with a diameter of greater than 3 mm and less than 1.5 cm. <strong>Exclusion criteria:</strong> having a previous surgical treatment or an infrafascial GSV length of less than 15 cm, pregnancy, and immobility</td>
<td>Intervention: EVLA Control: SFL/S <strong>Outcome measures:</strong> recurrence at 10 yrs (publication reports 5-yr data), EuroQoL-5D questionnaire, relief of venous symptoms, postoperative complications, CEAP stage, and patient satisfaction, long-term post-treatment complications such as paresthesia and hyperpigmentation</td>
<td>Clinical outcomes (Intervention grp; Control grp): Recurrence: EVLA 49%; SFL/S, 23%; log-rank test P=0.02 Reintervention: Did not receive reintervention: EVLA 70%; 80% SFL; log-rank P=0.20 Complications (Intervention grp; Control grp): Nerve damage: persistence of pretibial neurosensory deficit for 5 years in one patient (1/66 [2%]) who received saphenofemoral L/S and no occurrences of this in the EVLA group</td>
<td>Study quality: Fair Conflicts of interest: none</td>
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<tr>
<td><strong>(5-yr f/u to Pronk, 2010)</strong></td>
<td>Affiliation: Centrum Oosterwal, The Netherlands Study design: RCT</td>
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<tr>
<td><strong>F/u: 5 yrs</strong></td>
<td><strong>Funding source: none</strong></td>
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<tr>
<td><strong>Kalteis et al. (2015)</strong></td>
<td>n=100 randomized <strong>Inclusion criteria:</strong> primary truncal varicosity of the GSV (CEAP-C Class 2–4)</td>
<td>Intervention: EVLA/HL Control: HL/S</td>
<td>Clinical outcomes (Intervention grp; Control grp): Recurrence: No recurrence in 43% of the HL+EVLA; 67% of HL/S, P=0.049 Symptomatic recurrence: Visible recurrence: HL+EVLA, 40%; HL/S 40%, P=NR</td>
<td>Study quality: Fair Conflicts of interest: none</td>
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<tr>
<td><strong>(5-yr f/u to Kalteis, 2008)</strong></td>
<td>Affiliation: BHS Hospital, Ried im Innkreis, Austria Study design: RCT</td>
<td><strong>Exclusion criteria:</strong> needing additional treatment for an insufficient small saphenous vein or perforating vein</td>
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<tr>
<td>Authors/Study Design</td>
<td>Study Population</td>
<td>Treatment</td>
<td>Results</td>
<td>Quality/Comments</td>
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<td><strong>Funding source: NR</strong></td>
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<tr>
<td><strong>Michaels et al. (2006)</strong></td>
<td>n=77 (52 at 1yr)</td>
<td>Intervention: sclerotherapy (liquid)</td>
<td><strong>Clinical outcomes (Intervention grp; Control grp):</strong></td>
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<tr>
<td>Affiliation: Academic Vascular Unit, University of Sheffield, UK</td>
<td><strong>Inclusion criteria:</strong> pts referred with a diagnosis of varicose veins</td>
<td>Control: surgery</td>
<td><strong>Recurrence:</strong> No difference at 1, 2, or 3 yrs</td>
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<tr>
<td>Study design: RCT</td>
<td><strong>Exclusion criteria:</strong> Patients with deep venous insufficiency confirmed by duplex; Allergy to sclerosant; Diameter of varicose veins &gt;2 cm; Pre-existing co-morbidities that would make them unsuitable for surgery; BMI &gt;32</td>
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<td><strong>Symptomatic recurrence:</strong> At 1 yr, no visible varicocities in 76% of surgery grp vs. 39% of LS grp (P&lt;0.05)</td>
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<td>F/u: 1 yr</td>
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<td><strong>Pain:</strong> VAS at 1 yr, mean (SD): LS, 0.77 (0.18); surgery 0.83 (0.14); P&lt;0.05</td>
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<td>Funding source: National Health Technology Assessment Programme</td>
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<td><strong>QOL:</strong> SF-36 1 yr: no difference</td>
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<td>SF-36 2 yrs: no difference</td>
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<td>EQ-5D 1 yr: LS, 0.80 (0.14); surgery, 0.85 (0.20); P&lt;0.05</td>
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<td><strong>EQ-5D 2 yrs: no difference</strong></td>
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<td>Study quality: Fair</td>
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<td>Conflicts of interest: none</td>
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**APPENDIX Vb. Systematic Reviews**

**Key:** BMI, body mass index; CADTH, Canadian Agency for Drugs and Technologies in Health; COI, conflict of interest; CRD, Centre for Reviews and Dissemination; Crl, credible interval; DVT, deep vein thrombosis; ES, effect size; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; f/u, follow-up; GL, guidelines; GQ, good quality; grp(s), group(s); GSV, great saphenous vein; HL/S, high ligation and stripping; hx, history; HR, hazard ratio; HTA, health technology assessment; IQR, interquartile range; ITT, intention to treat; L&S, ligation and stripping; LS, liquid sclerotherapy; MA, meta-analysis; mmHg, millimeter of mercury; NA, not available; NHS, National Health Service; NIHR, National Institute for Health Research; NR, not reported; NS, not statistically significant; OR, odds ratio; PE, pulmonary embolism; PQ, poor quality; pt(s), patient(s); QOL, quality of life; RCT(s), randomized controlled trial(s); retx, retreatment; REVAS, recurrence of varicose veins after surgery; RFA-CF, ClosureFAST catheter; RFA-CP, ClosurePLUS catheter; RoB, risk of bias; RR, risk ratio; SR, systematic review; SVT, superficial venous thrombosis or thrombophlebitis; tx, treatment (or therapy); UGFS, ultrasound-guided foam sclerotherapy; UK, United Kingdom; VAS, visual analog score; VCSS, Venous Clinical Severity Score

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<th>Systematic Review (Author and Date)</th>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusions / Limitations</th>
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<tr>
<td><strong>Carroll et al. (2013)</strong></td>
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<tr>
<td><strong>Aim:</strong> To evaluate the clinical effectiveness, safety, and cost-effectiveness of the minimally invasive techniques of FS, EVLA, and RFA compared with other techniques, including traditional surgical techniques, LS, and conservative management, in the management of varicose veins</td>
<td><strong>Search dates:</strong> Inception to July 2011</td>
<td><strong>Study design:</strong> RCTs</td>
<td><strong>Sample size:</strong> 3873 participants across all 34 RCTs included in the review; number of randomized participants in a single trial ranged from 28-710 for these 34 studies</td>
<td><strong>Effectiveness and patient-centered outcomes:</strong></td>
<td><strong>Authors’ conclusions:</strong> The evidence reviewed suggests that each of the minimally invasive procedures assessed offers a viable, clinical alternative to stripping. Cost data reviewed suggests that only FS offers a cost-effective alternative to stripping.</td>
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<td><strong>EVLA vs surgery studies Carradice et al., 2011a and Carradice et al.,</strong></td>
<td><strong>Data sources:</strong> MEDLINE; Embase; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library; Biological Abstracts; Science Citation Index (SCI); Social Sciences Citation Index; Conference Proceedings Citation Index-Science; UK</td>
<td><strong>EVLA vs surgery:</strong> Total: 1221 Range: 20-276</td>
<td><strong>Initial failure of the procedure and retx (within 1 mo); technical and symptomatic recurrence (defined as the technical or symptomatic identification of retrograde flow anywhere in a treated vein, i.e., reflux, recanalization or residual varicose veins after successful occlusion, ablation or stripping); retx following recurrence; VCSS; pain; time to return to work or normal activity; and adverse events</strong></td>
<td><strong>Failure of procedure (12 studies):</strong> EVLA: 5/467 (1%) RFA: 16/431 (4%) FS: 2/295 (7%) Stripping: 20/681 (3%) P=NR</td>
<td><strong>Return to work or normal activity (12 studies):</strong> EVLA vs surgery: No difference or not reported in 4 studies; results favored EVLA in 1 study and surgery in 1 study (note data from Kalteis et al. 2008 was incorrectly reported in**</td>
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<td><strong>RFA vs surgery:</strong> Total: 642 Range: 16-249</td>
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<td><strong>Limitations:</strong> Analyses used aggregate data and not adjusted for observations that were not independent (i.e., different limbs within the same pt); the results of individual studies and**</td>
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<td><strong>FS vs surgery:</strong></td>
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<td>Systematic Review (Author and Date)</td>
<td>Primary Data (Author and Date)</td>
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<td>2011b (n=276)</td>
<td>Christenson et al., 2010</td>
<td>Clinical Research Network; Current Controlled Trials; and ClinicalTrials.gov</td>
<td>Total: 1351</td>
<td>The following outcomes were subjected to formal network MA: Technical recurrence, VCSS, and pain score</td>
<td>Carroll et al [2013]) RFA: No difference in 1 study; results favored RFA in 3 studies</td>
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<td>2008 (n=200)</td>
<td>Darwood et al., 2008</td>
<td>Inclusion criteria: RCTs assessing EVLA, RFA, FS compared with other techniques in terms of recurrence of varicose veins, retx and clinical symptoms, as measured by the VCSS, pain and quality of life</td>
<td>Interventions: EVLA, RFA, FS, FS+ligation</td>
<td>Economic outcomes in terms of cost-effectiveness, cost-utility or cost-benefit</td>
<td>FS: No difference in 1 study; results favored FS in 1 study (2 studies not relevant to this HTA)</td>
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<td>2005; Rasmussen et al., 2009; Rasmussen et al., 2010 (n=137)</td>
<td>De Medeiros et al., 2011</td>
<td>Eligible comparators: Traditional surgical techniques, LS, and conservative management</td>
<td>Comparator: Traditional surgery</td>
<td>Results of network MA:</td>
<td>Quality of review: Good</td>
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<td>2011 (n=249)</td>
<td>ElKaffas et al., 2011</td>
<td>Exclusion criteria: Non-RCT study designs; trials comparing different forms of the same intervention; RCTs of comparison interventions; RCT of co-interventions</td>
<td>F/u: Network MAs were done using 6 mos, 1 yr, and 2 yr f/u data when available</td>
<td>Technical recurrence (23 studies) HR [95% Cr] [probability HR &gt;1]:</td>
<td>Conflicts of interest: The authors do not have any COI</td>
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<td>2006 (n=16)</td>
<td>Hinchcliffe et al., 2006</td>
<td>Quality assessment: Quality assessment criteria adapted from a published checklist for surgical interventions; the</td>
<td>Study quality: The authors concluded that “The majority of the trials used in the network meta-analyses (e.g. those reporting technical recurrence data for EVLA vs. stripping or EVLA vs. RFA, etc.) were at risk of either selection or attrition bias due to inadequate randomization, allocation concealment or intention-to-treat analysis.” (p. 22)</td>
<td>EVLA vs surgery: 6 mos: 0.70 (0.27-1.45) [0.150]; 1 yr: 0.77 (0.37-1.54) [0.182]; 2 yrs: 0.84 (0.44-1.81) [0.257]</td>
<td>EVLA vs surgery: 6 mos: 0.92 (0.39-2.11) [0.409]; 1 yr: 0.93 (0.42-2.22); 2 yrs: 0.94 (0.42-2.51) [0.421]</td>
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<td>2010 (n=249)</td>
<td>Rasmussen et al., 2011 and Lawaetz et al., 2010</td>
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<td>FS vs surgery: 6 mos: 1.12 (0.53-2.27) [0.659]; 2 yrs: 0.92 (0.43-1.60) [0.359]</td>
<td>FS vs surgery: 6 mos: 1.12 (0.53-2.27) [0.659]; 2 yrs: 0.92 (0.43-1.60) [0.359]</td>
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<td>2011 (n=28)</td>
<td>Rautio et al., 2002 and Perala et al., 2005</td>
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<td>EVLA at 1 yr (6 studies, includes 2 studies comparing EVLA with RFA), median [95% Cr] [probability of MD &gt;0]:</td>
<td>EVLA vs surgery: 0.10 (-0.94 to 0.73) [0.324]</td>
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<td>2003 (n=81)</td>
<td>Lurie et al., 2003</td>
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<td>2010 and Balakrishnan et al., 2008 (n=88)</td>
<td>Subramonia et al., 2010</td>
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<td>2008 (n=90)</td>
<td>FS vs surgery Abela et al., 2008</td>
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<td>Systematic Review (Author and Date)</td>
<td>Systematic Review Characteristics</td>
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<td>Outcomes</td>
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<td>Bountouroglou et al., 2004 and Bountouroglou et al., 2006 (n=58)</td>
<td>authors note that blinding of pts and outcome assessors were not retained as criteria because the techniques generally did not permit such blinding, so the risk of detection bias was often inherently high.</td>
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<td>RFA vs surgery: 0.15 (−0.50 to 0.95) [0.739] FS vs surgery: -1.63 (−2.90 to −0.42) [0.015] Pain (within 7-14 days of tx) (9 studies, includes 3 studies comparing EVLA with RFA), median (95% CrI [probability of MD &gt;0]) EVLA vs surgery: 0.10 (-0.49-0.64) [0.653] RFA vs surgery: -1.26 (-1.95 to -0.61) [0.001] FS vs surgery: -0.80 (-1.93 to 0.30) [0.062] Harms: DVT and PE (11 studies): EVLA: 1 DVT RFA: 1 PE FS: 13 DVT; 2 PE Surgery: 1 DVT P=NR</td>
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<td>Figuereido et al., 2010 (n=56)</td>
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<td>Jia et al., 2010 (n=60)</td>
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<td>Kalodiki et al., 2008 and Kalodiki et al., 2011 (n=82)</td>
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<td>Liamis et al., 2005 (n=60)</td>
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<td>Rasmussen et al., 2011 and Lawaetz et al., 2010 (n=248)</td>
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<td>Shadid et al., 2010 (n=425)</td>
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<td>Wright et al., 2006 (n=272)</td>
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<td>(studies of other comparisons are not listed)</td>
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Funding source: NIHR HTA program (UK)
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<th>Systematic Review (Author and Date)</th>
<th>Primary Data (Author and Date)</th>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusions/Limitations</th>
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<tr>
<td>Dermody et al. (2013)</td>
<td>Aim: Analyze the current literature for short-term complications of EVLA compared with L&amp;S</td>
<td># included studies: 17 (7 EVLA vs L&amp;S; 5 RFA vs L&amp;S; 4 RFA vs EVLA; 1 comparing EVLA/RFA/L&amp;S)</td>
<td>Study design: RCTs</td>
<td>Harms</td>
<td>Harms (short term [&lt;1 yr]), results from MA:</td>
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<td>Almeida et al., 2009; Carradice et al., 2011; Christenson et al., 2010;</td>
<td>Search dates: January 2008 – January 8, 2013</td>
<td>Sample size: 2349</td>
<td>Interventions: EVLA (wavelength ranged from 810-1470 nm across studies), RFA (6 studies used RFA-CP, and 4 used RFA-CF [NOTE: RFA-CP]</td>
<td>Wound infection, OR (95% CI): RFA vs L&amp;S (1 study): 0.96 (0.06-15.4) EVLA vs L&amp;S (7 studies, 9 comparisons; I²=0%): 0.24 (0.10-0.58)</td>
<td>Authors’ conclusions: The majority of complications for endovenous thermal ablation and L&amp;S procedures to treat GSV incompetence are benign and self-limited. L&amp;S has a higher rate of wound</td>
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Economic outcomes: From review of 4 economic studies, the authors conclude that economic analyses of endovenous txs in comparison with conventional tx for varicose veins are of limited scope and quality. Differences in costs and benefits between txs are small and sensitive to assumptions; cost-effectiveness of the different procedures in relation to each other is likely to be uncertain, and vary by local costs.
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<th><strong>Systematic Review (Author and Date)</strong></th>
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<th><strong>Results</strong></th>
<th><strong>Conclusions/ Limitations</strong></th>
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<tr>
<td>Darwood et al., 2008; Disselhoff et al., 2008; ElKaffas et al., 2011; Gale et al., 2010; Lurie et al., 2014; Nordon et al., 2011; Pronk et al., 2010; Rasmussen et al., 2007; Rasmussen et al., 2011; Rass et al., 2012; Rautio et al., 2002; Shepherd et al., 2010; Stotter et al., Subramonia et al., 2010</td>
<td>the Cochrane Central Trials Registry, and individual journals</td>
<td>studies not included in meta-analyses.)</td>
<td>Paresthesia, OR (95% CI): RFA v. L&amp;S (1 study): 1.15 (0.35-3.85) EVLA vs L&amp;S (7 studies, 9 comparisons; I²=0%): 0.53 (0.34-0.82)</td>
<td>Infection vs EVLA. EVLA has a higher rate of thrombophlebitis than L&amp;S. EVLA has a lower rate of paresthesia than RFA and L&amp;S. The rate of venous thromboembolic events is low in the RCT literature.</td>
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<tr>
<td><strong>Funding source:</strong> None reported</td>
<td>Inclusion criteria: RCTs comparing RFA and/or EVLA and/or L&amp;S to treat GSV incompetence</td>
<td>Comparator: L&amp;S</td>
<td>Thrombophlebitis, OR (95% CI): RFA vs L&amp;S (1 study): 2.29 (0.86-6.1) EVLA vs L&amp;S (6 studies, 8 comparisons [I²=51%]): 1.83 (1.13-2.95)</td>
<td>Limitations: The authors noted a lack of good-quality data for an analysis of complications, and single or no complications were reported in each study, which precluded a robust estimate of relative event rates.</td>
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<td><strong>Exclusion criteria:</strong> FS studies, and studies of redo GSV surgery, and studies of the addition of high GSV ligation to an EVLA procedure</td>
<td>Eligible comparators: L&amp;S</td>
<td>F/u: &lt;1 yr</td>
<td>Harms, pooled incidences, % limbs (95% CI) (P is significance compared with L&amp;S):</td>
<td>Quality of review: Good</td>
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<td><strong>Quality assessment:</strong> A list of 6 criteria (combination of Jadad scale and author’s own criteria)</td>
<td>Study quality: ITT analyses were carried out in only 25% of the RFA-CF and 50% of the EVLA trials. 25% of trials utilized blinding of the outcome assessor; 1 study reported &gt;20% attrition; 25% of trials did not specify protocol for examining pts for complications; all studies lack sufficient descriptions of complications; most events were unblended, subjective assessments; RCTs underpowered to analyze most complications</td>
<td>DVT: EVLA (10 studies): 0.4 (0.1-1.0); P=0.52 RFA-CF (4 studies): 0.5 (0.1-1.2); P=0.71 L&amp;S (12 studies): 0.7 (0.2-1.3)</td>
<td>Infection: EVLA (12 studies): 0.7 (0.3-1.3); P=0.006 RFA-CF (4 studies): 1.0 (0.3-</td>
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<td>infection vs EVLA.</td>
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<td>EVLA has a higher rate of thrombophlebitis than L&amp;S. EVLA has a lower rate of paresthesia than RFA and L&amp;S. The rate of venous thromboembolic events is low in the RCT literature.</td>
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<td>Limitations: The authors noted a lack of good-quality data for an analysis of complications, and single or no complications were reported in each study, which precluded a robust estimate of relative event rates.</td>
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<td>Quality of review: Good</td>
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<td>Conflicts of interest: None reported</td>
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<td>Systematic Review (Author and Date) Primary Data (Author and Date)</td>
<td>Systematic Review Characteristics</td>
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<td>2.0); ( P=0.71 )</td>
<td>L&amp;S (12 studies): 2.1 (1.3-3.1)</td>
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<td>Paresthesia:</td>
<td>EVLA (12 studies): 3.3 (2.4-4.5); ( P&lt;0.001 ) RFA-CF (4 studies): 7.8 (5.8-10.1); ( P=0.43 ) L&amp;S (15 studies): 6.7 (5.3-8.3)</td>
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<td>SVT:</td>
<td>EVLA (11 studies): 5.5 (4.2-7.0); ( P=0.003 ) RFA-CF (4 studies): 5.2 (3-7.8); ( P=0.003 ) L&amp;S (12 studies): 2.9 (1.9-4.0)</td>
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<td>Bruising:</td>
<td>EVLA (8 studies): 34.5 (31.2-38.0); ( P=0.55 ) RFA-CF (1 study): 3.1 (0.12-9.9); ( P&lt;0.001 ) L&amp;S (8 studies): 36.1 (32.6-39.6)</td>
</tr>
</tbody>
</table>
| | | | | Hematoma: | EVLA (6 studies): 2.1 (1.1-3.5); \( P<0.001 \) RFA-CF (2 studies): 0.2 (0-1.3); \( P<0.001 \) L&S (11 studies): 13.5 (11.1-
<table>
<thead>
<tr>
<th>Systematic Review (Author and Date) Primary Data (Author and Date)</th>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
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</thead>
<tbody>
<tr>
<td>Nesbitt et al. (2014)</td>
<td># included studies: 8 studies added with update for a total of 13 studies (FS 3 studies (n=870); EVLA 8 studies (n=1760); RFA 5 studies (n=642)</td>
<td>Study design: RCTs</td>
<td>Primary outcomes: Recurrence; recanalization; neovascularization; technical failure and reintervention; QOL; postoperative complications</td>
<td>16.1</td>
<td>Skin burn: EVLA (6 studies): 0.7 (0.2-1.4); P=not calculated RFA-CF (2 studies): 0.7 (0.04-2.3); P=not calculated</td>
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<td></td>
<td>Search dates: Update search done January 2014</td>
<td>Sample size: Total randomized 3081 and total analyzed 2489 (range 33-500); (NOTE: In order to achieve congruity, sample sizes were considered in terms of “number of pts” rather than “number of limbs,” although in some cases this was not possible.)</td>
<td>Secondary outcomes: Length of the procedure or operative time; duration of hospital stay; procedural costs</td>
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<td>L&amp;S (none):</td>
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<td>Data sources: Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN register, and reference lists from relevant studies and reviews</td>
<td>Intervention: FS, RFA, EVLA (810-470 nm)</td>
<td>Other outcomes: Time to return to work or normal activities; type of anesthetic required; post-procedure pain</td>
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<td>Comparator:</td>
<td>F/u: 3 mos in all studies; 1-2 yrs in most studies</td>
<td>Study quality: All studies deemed to have low risk</td>
<td>Primary outcomes: (Only results for outcomes eligible for this HTA are shown.)</td>
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<tr>
<td></td>
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<td>Study quality: All studies deemed to have low risk</td>
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<td>Darwood et al., 2008 EVOLVeS Study (Lurie et al., 2003 and 2005a) Flessenkaemper et al., 2013 FOAM-Study (Shadid et al., 2010 and 2012) Helmy ElKaffas et al., 2011 HELP-1 (Carradice et al., 2008, 2009, 2011a, 2011b, 2012)</td>
<td></td>
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<td></td>
<td>Authors’ conclusions: Current data suggest that FS and endovenous ablation (EVLA and RFA) have similar overall outcomes as open surgery involving HL/S. However, these findings still lack robustness due to a paucity of compatible data.</td>
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<td>Limitations: The authors note that, &quot;Despite an apparent congruity in the outcome measures of the studies there was a serious lack of compatible data, including differences in the outcome definitions, metrics</td>
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<tr>
<td>Systematic Review (Author and Date)</td>
<td>Systematic Review Characteristics</td>
<td>Individual Study Characteristics</td>
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<td>Magna 2007 (Biemans et al., 2012 and 2013) Pronk et al., 2010 Rasmussen et al., 2007 Rasmussen et al., 2011 Rautio et al., 2002 RELACS Study (Rass et al., 2012) Subramonia et al., 2010</td>
<td>Inclusion criteria: RCTs evaluating UGFS of the GSV, RFA and EVLT GSV ablation  Eligible comparators: Open GSV HL/S Exclusion criteria: Studies that included pts who had undergone tx of both GSVs and SSVs and did not provide any subanalyses of these grps were excluded Quality assessment: Cochrane Collaboration’s tool for assessing RoB</td>
<td>of selection bias based on allocation concealment, but about half had unclear risk of selection bias based on randomization; all studies had high risk of performance/detection bias; most studies had low risk of attrition and reporting bias; some studies were considered statistically underpowered; most studies were assigned an unclear RoB for other sources of bias. The authors noted that on the whole, individual studies were well conducted, but the availability of comparable evidence was a limiting factor for conducting meta-analyses.</td>
<td>recurrence, $(I^2=39%): 0.82 (0.49-1.39); P=0.47$ 1 study reported symptomatic recurrence: $2.00 (0.30-13.26); P=NR$ Technical failure of procedure, OR (95% CI): FS vs surgery (2 studies, $(I^2=14%): 0.44 (0.12-1.57)); $P=0.20$ EVLA vs surgery (6 studies, $(I^2=22%): 0.29 (0.14-0.60)); $P=0.0009$ RFA vs surgery (5 studies, $(I^2=70%): 0.82 (0.07-10.10)); $P=0.88$ QOL: No MA conducted. FS vs surgery: Both tx grps showed very similar QOL and disease improvements by the final f/u time point. EVLA vs surgery: QOL and disease severity scoring was generally uniform throughout the studies, with worsening within the first few days or wks followed by an overall improvement over the f/u period, with and f/u time points, with which any meaningful meta-analysis could be performed. This has seriously limited the overall effectiveness of this Cochrane review” (p. 18). In addition, inclusion of pts with bilateral varicose veins and presentation of data by numbers of limbs introduced a potential confounding bias.</td>
<td>Quality of review: Good Conflicts of interest: 2 of the authors co-edited a textbook on vascular surgery; no other COI reported</td>
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<tr>
<td>Systematic Review (Author and Date)</td>
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<td>no difference between the grps. RFA vs surgery: General improvements over the length of the f/u for both tx grps, with most studies reporting no overall differences between the grps. Complications: No MA conducted. FS vs surgery: Complications were few and generally equal between the grps. However, early hematoma and saphenous nerve injury were more frequent in the surgical grp and the foam grp had a higher rate of phlebitis. Major complications were very few. EVLA vs surgery: Early and late complications were distributed between the grps and with very few major adverse events. RFA vs surgery: Higher rates of hematoma and wound problems in the</td>
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<tr>
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<td>Surgical grp compared with RFA; and the increased rate of hematoma and saphenous vein injury in the surgical grp were still evident in later complications. Overall, #s of complications were low, especially for major complications.</td>
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*Secondary outcomes:*

**Procedural costs:**
6 studies provided costs analyses, and costs in each study varied. No study reported estimation of costs of additional procedures for residual or recurrent varices.

**Other outcomes:**

**Time to return to work or normal activities:** No MA was conducted.

FS vs surgery: Reported in 1 study, showed less recovery time for FS than surgery.

EVLA vs surgery:
<table>
<thead>
<tr>
<th>Systematic Review (Author and Date)</th>
<th>Primary Data (Author and Date)</th>
<th>Systematic Review Characteristics</th>
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<tr>
<td>Paravastu et al. (2016)</td>
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<td>Reported in 6 studies, most showed less recovery time for EVLA than surgery. RFA vs surgery: 5 studies reported less recovery time for RFA grp than surgery grp. Post-procedural pain: No MA conducted. FS vs surgery: Reported in 2 studies, 1 showed no large change in pain for either grp, 1 study reported less pain during procedure for FS than surgery. EVLA vs surgery: No overall conclusion; 2 robust studies found increased pain in EVLA grp. RFA vs surgery: Studies generally reported less pain in RFA grp than surgery grp.</td>
</tr>
<tr>
<td>Aim: To compare the effectiveness of EVLA, RFA and UGFS vs conventional surgery</td>
<td># included studies: 3 (EVLA 3 [n=311]; UGFS 1 [n=42])</td>
<td>Study design: RCTs</td>
<td>Sample size: EVLA vs surgery: 311; UGFS vs surgery: 42</td>
<td>Primary outcomes: Recanalization or persistence of reflux at 6 wks; recurrence of reflux at 1 yr; clinical evidence of</td>
<td>Primary outcomes: Recanalization or persistence of reflux at 6 wks (tx failure), OR (95% CI)</td>
<td>Authors' conclusions: Low- to moderate-quality evidence exists to suggest that recanalization or persistence of reflux</td>
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Selected treatments for varicose veins: Draft evidence report - Appendices
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<th>Systematic Review (Author and Date)</th>
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<td>in the tx of SSV varices</td>
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<td>recurrence; reintervention</td>
<td>studies, $I^2=51%$): 0.07 (0.02-0.22), $P&lt;0.00001$</td>
<td>at 6 wks and recurrence of reflux at 1 yr are less frequent when EVLA is performed, compared with conventional open surgery. For the UGFS vs conventional surgery comparison, we assessed the quality of evidence as low; consequently, the effectiveness of UGFS compared with conventional surgery in the tx of SSV varices is uncertain.</td>
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<tr>
<td>CLASS (Brittenden et al., 2014 and 2015; Tassie et al., 2014) HELP 2 (Samuel et al., 2011 and 2013; Nandhra et al., 2015) VESPA (Roopram et al., 2013)</td>
<td>Data sources:Specialised Register, Cochrane Register of Studies, World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Register, reference lists of relevant articles and reviews,</td>
<td>Intervention: EVLA, UGFS Comparator: Surgery F/u: 6 wks – 2 yrs Study quality: Low risk of selection bias for all 3 studies; risk of performance bias was high for all 3 studies; low risk of attrition bias for 2 studies and unclear for 1 study; no evidence of reporting bias in any study; the risk of other bias was low in 1 study, unclear in another, and high in the third study.</td>
<td>Secondary outcomes: QOL; postoperative pain; complications; healing of ulcers</td>
<td>Recurrence of reflux at 1 yr (determined by recanalization on US), OR (95% CI): EVLA vs surgery (2 studies, $I^2=0%$): 0.24 (0.07-0.77); $P=0.02$ Recurrence at 2 yrs (reported in 1 study): 0.43 (0.16-1.15); $P=0.09$ FS vs surgery (1 study): 1.19 (0.29-4.92) $P=NR$</td>
<td>Limitations: The review contained a small number of studies, and results for several outcomes from 1 study were not stratified and therefore unusable in this review.</td>
</tr>
<tr>
<td>Funding source: None</td>
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<td>Quality of review: Good</td>
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<td>Conflicts of interest: 1 author is a director of a specialist vascular</td>
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Selected treatments for varicose veins: Draft evidence report - Appendices

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<tr>
<td>Available</td>
<td>EVLA vs surgery (2 studies, I^2=0%, 6 wks f/u): 0.15 (-1.65-1.95) P=0.87</td>
<td>Secondary outcomes:</td>
<td>services provider and has received sponsorship to attend training for ClariVein and VenaSeal devices. No COI reported for other authors.</td>
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<tr>
<td>QOL (AVVQ), MD (95% CI)</td>
<td>EVLA vs surgery (1 study, 1 yr f/u): 1.08 (-3.39-1.23) FS vs surgery: No results</td>
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<td>QOL (EuroQol Group 5 Dimension questionnaire):</td>
<td>EVLA vs surgery (2 studies): No MA; both studies reported no difference between grps</td>
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<tr>
<td>QOL (36-Item SF-36 Health Survey):</td>
<td>FS vs surgery: No results</td>
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<tr>
<td>EVLA vs surgery (1 study): No MA, both grps achieved higher scores over time in 5 of 8 categories, EVLA grp improved in general health domain from 1 wk-6 wks, score was</td>
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Available services provider and has received sponsorship to attend training for ClariVein and VenaSeal devices. No COI reported for other authors.
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<th>Systematic Review (Author and Date)</th>
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<td>slightly lower at 1 yr than 6 wks, EVLA grp scores decreased after wk 12 in vitality and mental health domains. Surgery grp maintained improvement up to 1 yr. FS vs surgery: No results</td>
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<td>Postoperative pain (VAS scores): EVLA vs surgery (2 studies): No MA; 1 study reported statistically significant differences between grps for days 4-7 (day 4, $P=0.025$; day 5, $P=0.008$; day 6, $P=0.033$; day 7, $P=0.042$), the other study reported lower scores for the surgery grp at 1 wk (18 vs 31), and slightly lower score for the EVLA grp at 6 wks (6 vs 9); significance not provided FS vs surgery: No results</td>
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<td>Postoperative complications: EVLA vs surgery (2 studies): No MA, both studies reported few</td>
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### Systematic Review (Author and Date)

**Primary Data (Author and Date)**
- O'Donnell et al. (2016)
- Christenson et al.,

**Aim:** To define the overall incidence of REVAS as well as both the sites of reflux and the causes of REVAS through an SR and MA of RCTs for endovascular ablation

### Systematic Review Characteristics

- **# Included studies:** 7 studies (8 comparisons: 3 RFA vs L&S; 4 EVLA vs L&S; 1 EVLA vs cryoablation)
- **Search dates:** January 1, 2000-July 1, 2014
- **Data sources:** MEDLINE, Embase, Cochrane, and Clinical Trials Registry

### Individual Study Characteristics

- **Study design:** RCTs
- **Sample size:** >1500 limbs
- **Intervention:** EVLA (810 nm-910 nm), RFA (Closure PLUS catheter or ClosureFast catheter)
- **Comparator:** 7 L&S, 1 cryoablation

### Outcomes

**Outcomes:** Recurrence (duplex and clinical); site of recurrence; cause of recurrence; tx of REVAS

### Results

- **Duplex recurrence, pooled percentage (95% CI):**
  - EVLA (4 studies): 12.5 (8.9-16.5)
  - RFA (3 studies): 12.4 (7.3-18.6)
  - L&S (5 studies): 7.2 (4.4-10.6); P=0.32

### Conclusions/ Limitations

- **Authors’ conclusions:** No difference in the overall incidence of REVAS between EVLA and L&S, and REVAS appeared progressive over time.
- **Limitations:** Authors describe quality assessment; however, a discussion of neurological complications, neurological complications were similar at 6 wks but a higher percentage of surgery pts had neurological complications and 1 study reported more wound infections in the surgery grp.

**Return to work:**
- EVLA vs surgery (2 studies): No MA, both studies reported that the EVLA grp returned to work faster than the surgery grp.
### Systematic Review (Author and Date) Primary Data (Author and Date)

<table>
<thead>
<tr>
<th>Study</th>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
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| 2010 (n=200, limbs) Dissanohoff et al., 2008 (n=120, limbs) Lurie et al., 2005a (n=79, pts) Perala et al., 2005 (n=28, pts) Rasmussen et al., 2013a (n=121, pts) Rasmussen et al., 2013b (n=346) | **Inclusion criteria:** RCTs evaluating endovenous ablation (EVLA or RFA) of GSV incompetence  
**Eligible comparators:** L&S or an alternative form of stripping, such as cryostripping  
**Exclusion criteria:** FS; repeated GSV surgery or addition of high GSV ligation to endovascular ablation procedure; f/u <2 yrs; no postoperative duplex scan; did not report incidence of recurrent varicosities; tx of SSV or anterior accessory saphenous veins  
**Quality assessment:** A list of 6 criteria (combination of Jadad scale and authors’ own criteria) | **F/u:** 2 yrs  
**Study quality:** NR | Clinical recurrence pooled percentage (95% CI):  
EVLA (5 studies): 20.6 (17.0-24.3)  
RFA (3 studies): 21.4 (14.8-28.8)  
L&S (6 studies): 19.2 (15.5-23.2); P=0.98  
Reoperation, pooled percentage (95% CI):  
EVLA (5 studies): 27.2 (23.3-31.3)  
RFA (1 study): 16.2 (10.4-35.9)  
L&S (4 studies): 17.3 (13.6-21.4); P=0.74 | individual study and body of evidence quality is missing.  
**Quality of review:** Good  
**Conflicts of interest:** 1 author previously served as a consultant for Covidien, Tactile Medical, and BTG International. No other COI reported |
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<th>Systematic Review (Author and Date)</th>
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<tr>
<td>surgery or sclerotherapy should be recommended for the management of primary varicose veins</td>
<td>surgery; 1 compared sclerotherapy with ambulatory phlebectomy; 1 compared endovascular sclerotherapy with general anesthetic surgery or local anesthetic surgery and sclerotherapy; 1 compared general anesthetic surgery with local anesthetic surgery and sclerotherapy</td>
<td>Intervention: Sclerotherapy (liquid or foam) alone or in combination with other tx (e.g., L&amp;S+sclerotherapy); Comparator: Surgery (e.g., ligation, ambulatory phlebectomy)</td>
<td>economic analyses (cost-effectiveness)</td>
<td>that sclerotherapy was significantly better than surgery. After 1 yr, the effectiveness of sclerotherapy rapidly declined so that by 2 yrs, no significant differences were seen. At 3 yrs, 1 study reported that surgery was significantly better than sclerotherapy. By 5 yrs, 3 trials reported that surgery had significantly better outcome than sclerotherapy.</td>
<td>terms of tx success, complication rates, and cost at 1 yr, but surgery was better after 5 yrs. However, the evidence was not of very good quality and more research is needed. There was insufficient evidence to preferentially recommend the use of sclerotherapy or surgery. There needs to be more research that specifically examines both costs and outcomes for surgery and sclerotherapy.</td>
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<td>Belcaro et al., 2000 Belcaro et al., 2003 Chant et al., 1972 Doran et al., 1975 Einarsson et al., 1993 Hobbs et al., 1968 Jakobsen et al., 1979 Rutgers et al., 1994 deRoos et al., 2003</td>
<td>Search dates: Database inception through June 2004</td>
<td>Study quality: The overall quality of the trials was generally poor. Few studies described method of randomization, none of the trials estimated sample sizes or included a power calculation, many outcome measures were subjective and may not be reproducible or comparable between studies, quality of reporting of the results was also variable. Internal validity was a problem with many of the studies, mainly due to poor reporting and concurrent changes in practice.</td>
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<td>Funding source: Sheffield Vascular Institute, UK; NHS R&amp;D HTA Programme, UK; Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK; Chief Scientist Office, Scottish Government Health Directorates, the Scottish Government, UK</td>
<td>Data sources: 13 electronic databases, including the Cochrane Peripheral Vascular Diseases Review Group’s Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library Issue 2, 2004, MEDLINE and Embase, as well as manual searches of relevant journals</td>
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**Selection criteria:**
- Inclusion: Studies comparing varicose vein treatments.
- Exclusion: Studies comparing non-varicose vein treatments.

**Inclusion criteria:**
- Studied the treatment of varicose veins.
- Provided sufficient data for analysis.

**Exclusion criteria:**
- Studied non-varicose vein treatments.
- Provided insufficient data for analysis.

**Quality assessment:**
- The overall quality of the trials was generally poor. Few studies described method of randomization, none of the trials estimated sample sizes or included a power calculation, many outcome measures were subjective and may not be reproducible or comparable between studies, quality of reporting of the results was also variable. Internal validity was a problem with many of the studies, mainly due to poor reporting and concurrent changes in practice.

**Outcomes:**
- Economic analyses (cost-effectiveness).

**Results:**
- Sclerotherapy was significantly better than surgery. After 1 yr, the effectiveness of sclerotherapy rapidly declined so that by 2 yrs, no significant differences were seen. At 3 yrs, 1 study reported that surgery was significantly better than sclerotherapy. By 5 yrs, 3 trials reported that surgery had significantly better outcome than sclerotherapy.

**Conclusions/ Limitations:**
- Terms of tx success, complication rates, and cost at 1 yr, but surgery was better after 5 yrs. However, the evidence was not of very good quality and more research is needed. There was insufficient evidence to preferentially recommend the use of sclerotherapy or surgery. There needs to be more research that specifically examines both costs and outcomes for surgery and sclerotherapy.

**Limitations:**
- No MA possible due to nature of data available; comparisons between txs were not always clear in the summary of complication rates.

**Quality of review:**
- Good

**Conflicts of interest:**
- 2 authors were
<table>
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<tr>
<td><strong>Inclusion criteria:</strong> RCTs of pts being tx'd for cosmesis and/or symptomatic primary varicose veins (e.g., ache, itch, etc.)</td>
<td>to a lack of reporting adequate methods of randomization and concealment of allocation.</td>
<td>DVT: 1 occurrence in 1 study (grp not specified)</td>
<td>undertaking a study of the txs of varicose veins, funded by the NHS Health Technology Assessment Programme</td>
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<td><strong>Eligible comparators:</strong> Any surgical tx for primary varicose veins</td>
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<td>Wound infection: Ranged from 6%-7.25% in 1 study</td>
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<td><strong>Exclusion criteria:</strong> Trials including pts undergoing tx for complications of varicose veins, venous ulceration, and chronic venous insufficiency or pts undergoing tx for recurrent varicose veins</td>
<td></td>
<td>Nerve injury: Reported in 3 studies; the rate was 10% in 2 studies in which the vein was stripped to the knee, and 33% in a study where it was stripped to the ankle</td>
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<tr>
<td><strong>Quality assessment:</strong> Jadad</td>
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<td>Overall: The overall complication rate for sclerotherapy in 1 study was 6.6%, but went as high as 22% for phlebitis</td>
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<td>Costs: Costs were analyzed in some studies but the methodology was not adequately stated in 1 study and the figures were outdated in 1 study. Sclerotherapy was cheaper in terms of cost to the hospital and to</td>
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<tr>
<td>Systematic Review (Author and Date)</td>
<td>Systematic Review Characteristics</td>
<td>Individual Study Characteristics</td>
<td>Outcomes</td>
<td>Results</td>
<td>Conclusions/ Limitations</td>
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<tr>
<td>Rathbun et al. (2012)</td>
<td># Included studies: 104</td>
<td>Study design: 20 RCTs, 82 observational studies, 2 not classified</td>
<td></td>
<td>Effectiveness outcomes:</td>
<td>Authors’ conclusions: Endovenous FS was found to be effective with similar vein occlusion rates to laser therapy, but less effective than surgery. In addition, major adverse events were rare. Low study numbers and poor quality also limited conclusions about comparative safety; however, it appears that FS is associated with a low-risk profile that is no greater than other varicose vein txs.</td>
</tr>
<tr>
<td></td>
<td>Search dates: Searches completed in 2010, dates varied depending on database</td>
<td>Sample size: Range 1-1200, median 60, avg 153</td>
<td></td>
<td>Anatomical closure, RR (95% CI): Surgery vs FS (6 studies, I²=NR: 0.92 (0.86-0.97); P=0.0036</td>
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<td>Data sources: Included MEDLINE (January 1948 – April 2010), Embase (January 1980 – April 2010), and Evidence-Based Medicine Reviews (through April 2010): Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database using OVID, and manual searches</td>
<td>Intervention: Endovenous FS; dose and tx type varied; FS used as adjuvant tx to either EVLA, surgery, or liquid sclerotherapy in 16 studies; 17 grps of pts tx’d with liquid sclerotherapy</td>
<td></td>
<td>Residual saphenofemoral incompetence, RR (95% CI): FS vs surgery (4 studies, I²=NR): 0.92 (0.56-1.51); P=0.73</td>
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<td>Comparator: EVLA (5 grps), surgery (12 grps), some included studies did not include comparators</td>
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<td>Harms, RR (95% CI): DVT: 1.45 (0.47-4.53); P=0.52</td>
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<td>F/u: Range 1 day-37 yrs, mean 52.5 wks</td>
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<td>Superficial thrombophlebitis: 16.85 (2.27-124.74), P=0.0057</td>
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<tr>
<td></td>
<td></td>
<td>Study quality: Low overall</td>
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<td>Skin pigmentation: FS vs surgery: No difference</td>
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<td>Paresthesia: FS vs surgery: No difference</td>
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</tbody>
</table>

**Aim:** To systematically and comprehensively evaluate the literature to provide accurate estimates of safety and efficacy outcomes for this procedure

(104 studies included in the review; list of primary studies omitted from this table)

**Funding source:** American College of Phlebology Foundation
### Systematic Review (Author and Date)

**Primary Data (Author and Date)**

<table>
<thead>
<tr>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
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</thead>
<tbody>
<tr>
<td>Inclusion criteria: Studies with pts &gt;19 yrs of age tx’d using endovenous FS; tx of varicose veins, congenital malformations, or venous ulcers of the skin; and studies that reported safety or efficacy data. RCTs, case reports, and observational studies</td>
<td>Eligible comparators:</td>
<td>Ecchymosis: FS vs surgery: 0.44 (0.25-0.64); P=0.0001</td>
<td>studies not provided.</td>
<td>Quality of review: Good</td>
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<tr>
<td></td>
<td>Exclusion criteria: Studies that did not report original findings, such as review articles or editorials</td>
<td>Pain: FS vs surgery (1 study): 0.32 (0.17-0.62); P=0.0006</td>
<td></td>
<td>Conflicts of interest: NR</td>
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<tr>
<td></td>
<td>Quality assessment: Method used NR</td>
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</table>

Pan et al. (2014)

**Aim:** To evaluate the efficiency and safety of EVLA for primary lower extremity varicosities compared with HLS

**Medeinos et al., 2005;**

<table>
<thead>
<tr>
<th># Included studies: 13</th>
<th>Study design: Prospective non-randomized studies and RCTs</th>
<th>Outcomes</th>
<th>Clinical Outcomes</th>
<th>Authors’ conclusions: EVLA is a safe and effective alternative for tx of varicose veins.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search dates: May 2012</td>
<td>Sample size: 2245 limbs (EVLA n=1128; HLS n=1117)</td>
<td>Technical success; duplex-detected recurrence at 1 and 2-yr f/u; clinical recurrence and 1 and 2-yr f/u; common complications</td>
<td>Technical success: Meta-analyses based on data for number of limbs with technical failure</td>
<td>Initial Technical Success (9 studies): RR 1.11 (95%)</td>
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<tr>
<td>Data Sources: Medline, PubMed, Cochrane Library</td>
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<tr>
<td>Systematic Review (Author and Date)</td>
<td>Systematic Review Characteristics</td>
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<tr>
<td>Funding Source: NR</td>
<td><strong>Inclusion criteria:</strong> Prospective clinical studies comparing EVLA and HLS for txg varicose veins. All f/u periods were allowed. All wavelengths and energy parameters.</td>
<td><strong>Intervention:</strong> EVLA</td>
<td>(phlebitis, bleeding, haematoma, petechial, wound infection, or paresthesia)</td>
<td>CI 0.62-1.97, ( P=0.72 ) Initial technical success rates were 97.3% (EVLA) and 97.6% (HLS)</td>
</tr>
<tr>
<td>Mekako et al., 2006; Vuylsteke et al., 2006; Darwood, et al., 2008; Kalteis et al., 2008; Theivacumar et al., 2009; Christenson, et al., 2010; Pronk et al., 2010; Rasmussen et al., 2010; Carradice et al., 2011; Disselhoff et al., 2011; Rasmussen et al. 2011; Rass et al., 2012</td>
<td><strong>Eligible comparators:</strong> HLS</td>
<td><strong>Comparator:</strong> HLS</td>
<td><strong>Technical success at 1 yr (6 studies):</strong> RR 2.52 (95% CI 1.20-5.28), ( P=0.01 ); favors HLS The procedural failure rates after EVLA and HLS at one year were 2.6% and 2.1%, respectively</td>
<td>Quality of review: Good</td>
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<td><strong>Exclusion criteria:</strong> Retrospective studies, investigations on EVLA alone, studies comparing EVLA with other endovenous therapies other than HLS and studies in languages other than English.</td>
<td><strong>F/u:</strong> ranged from 3 mos – 5 yrs</td>
<td><strong>Technical success at 2 yrs (5 studies):</strong> RR 2.79 (95% CI 1.24-6.27), ( P=0.01 ); favors HLS</td>
<td>Conflicts of interest: NR</td>
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<tr>
<td></td>
<td><strong>Study quality:</strong> ranged from Sackett’s classification I – II (3 were classified as II and 10 were classified as I)</td>
<td><strong>Initial technical success rates were 97.3% (EVLA) and 97.6% (HLS)</strong></td>
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### Conclusions/Limitations

- **Long term recurrence:**
  1 study (Disselhoff 2011) found no statistical difference between the five-year recurrence rates of 62% and 51% for EVLA and HLS, respectively.

- **Time to return to work or normal activity:**
  1 study reported longer time to return to work in EVLA grp than HLS grp ($P=0.054$); other studies showed shorter recovery times for the EVLA grp, 2 of which reported statistically significant differences.

- **Pain:**
  3 studies (Rasmussen 2009; Carradice 2011; Vuylsteke 2006) found postoperative pain higher in the HLS grp than EVLA grp; 4 studies (Rass 2012; Rasmussen 2011; Darwood 2008; ...)
<table>
<thead>
<tr>
<th>Systematic Review (Author and Date)</th>
<th>Systematic Review Characteristics</th>
<th>Individual Study Characteristics</th>
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<td>Christenson 2010) showed no difference; 1 study (Pronk, 2010) found significantly more pain in EVLA grp than HLS grp</td>
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<td>Complications</td>
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<td>Phlebitis (8 studies): RR 1.54 (95% CI 0.97-2.44), P=0.06</td>
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<td>Hematoma (6 studies):</td>
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<td>RR 0.30 (0.15-0.57), P=0.0003; favors EVLA</td>
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<td>Bruise (6 studies):</td>
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<td>RR 0.74 (95% CI 0.33-1.66), P=0.47</td>
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<td>Infection (7 studies):</td>
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<td>RR 0.28 (95% CI 0.11-0.70), P=0.006; favors EVLA</td>
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<td>Paresthesia (9 studies):</td>
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<td>RR 0.59 (95% CI 0.45-0.79), P=0.0003; favors EVLA</td>
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</table>
APPENDIX VI.

Summary of Practice Guidelines

Key: CEAP, Clinical, Etiologic, Anatomic, Pathophysiologic; CVD, chronic venous disease; EVLA, endovenous laser ablation; FS, foam sclerotherapy; GSV, great saphenous vein; HTA, health technology assessment; RCT, randomized controlled trial; RF, radiofrequency; RFA, radiofrequency ablation; SPJ, saphenopopliteal junction; US, ultrasound; UGFS, ultrasound-guided foam sclerotherapy

<table>
<thead>
<tr>
<th>Sponsor (Year), Title</th>
<th>Relevant Recommendations</th>
<th>Quality*/Main Limitations</th>
</tr>
</thead>
</table>
| Society for Vascular Surgery and the American Venous Forum (Gloviczki et al., 2011) | • Open venous surgery:  
  o High ligation and inversion stripping of the saphenous vein to the level of the knee for treatment of the incompetent GSV is recommended with a GRADE of 2B (guideline 10.1).  
  o High ligation of the vein at the knee crease, approximately 3 to 5 cm distal to the SPJ, with selective invagination stripping of the incompetent portion of the vein is recommended for treatment of small saphenous vein incompetence with a GRADE 1B (guideline 10.3).  
  o Ablation of the incompetent superficial veins in addition to compression therapy to decrease recurrence of venous ulcers is recommended with a GRADE 1A (guideline 10.4).  
  o Ambulatory phlebectomy for treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage is recommended, and if anesthesia is required for phlebectomy the organization suggests concomitant saphenous ablation (GRADE 1B, guideline 10.7).  
  o Transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence as an alternative to traditional phlebectomy for extensive varicose veins is recommended with a GRADE of 2C (guideline 10.8)  
  o Ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy, or endovenous thermal ablation, depending on the etiology, source, location, and extent of varicosity is suggested for the treatment of recurrent varicose veins with a GRADE of 2C (guideline 10.9).  
  o Endovenous thermal ablation | 5.8 - Good  

Limitations: No mention of external review of guidelines or a procedure for updating
<table>
<thead>
<tr>
<th>Sponsor (Year), Title</th>
<th>Relevant Recommendations</th>
<th>Quality*/Main Limitations</th>
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</thead>
<tbody>
<tr>
<td>o EVLA and RFA are recommended for the treatment of saphenous incompetence with a GRADE of 1B (guideline 11.1).</td>
<td>6.2 – Good</td>
<td>Limitations: Criteria for selecting evidence is not clearly described; need to update mentioned, but the method for updating was not identified</td>
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<tr>
<td>o Because of reduced convalescence and less pain and morbidity, the group recommends endovenous thermal ablation of the incompetent saphenous vein over open surgery (GRADE 1B, guideline 11.2).</td>
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<td>o Sclerotherapy</td>
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<td>o Liquid sclerotherapy or foam sclerotherapy (FS) for telangiectasia, reticular veins, and varicose veins is recommended with a GRADE of 1B (guideline 12.1).</td>
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<tr>
<td>o Endovenous thermal ablation is recommended over chemical ablation with foam for treatment of the incompetent saphenous vein (GRADE 1B, guideline 12.2).</td>
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<td>o Treatment of perforating veins</td>
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<td>o Subfascial endoscopic perforating vein surgery, US-guided sclerotherapy, or thermal ablations are suggested for treatment of “pathologic” perforating veins with a GRADE of 2C (guideline 13.3).</td>
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<tr>
<td>Society for Vascular Surgery and the American Venous Forum (O’Donnell et al., 2014)</td>
<td>Recommendations specific to operative/endovascular management</td>
<td></td>
</tr>
<tr>
<td>Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum</td>
<td>Guideline 6.1: Superficial Venous Reflux and Active Venous Leg Ulcer – Ulcer Healing: In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, guidelines suggest ablation of the incompetent veins in addition to standard compressive therapy to improve ulcer healing. [GRADE – 2; LEVEL OF EVIDENCE – C]</td>
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<td>Guideline 6.2: Superficial Venous Reflux and Active Venous Leg Ulcer – Prevent Recurrence: In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, guidelines recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE – 1; LEVEL OF EVIDENCE – B]</td>
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<td>Guideline 6.3: Superficial Venous Reflux and Healed Venous Leg Ulcer: In a patient with a healed venous leg ulcer (C5) and incompetent superficial veins that have axial reflux directed to</td>
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<td>Sponsor (Year), Title</td>
<td>Relevant Recommendations</td>
<td>Quality*/Main Limitations</td>
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<td>the bed of the ulcer, we recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE – 1; LEVEL OF EVIDENCE – C]</td>
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Guideline 6.4: Superficial Venous Reflux With Skin Changes at Risk for Venous Leg Ulcer (C4b): In a patient with skin changes at risk for venous leg ulcer (C4b) and incompetent superficial veins that have axial reflux directed to the bed of the affected skin, guidelines suggest ablation of the incompetent superficial veins in addition to standard compressive therapy to prevent ulceration. [GRADE – 2; LEVEL OF EVIDENCE – C]

Guideline 6.5: Combined Superficial and Perforator Venous Reflux With or Without Deep Venous Reflux and Active Venous Leg Ulcer: In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, guidelines suggest ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence. [GRADE – 2; LEVEL OF EVIDENCE – C]

Guideline 6.6: Combined Superficial and Perforator Venous Reflux With or Without Deep Venous Disease and Skin Changes at Risk for Venous Leg Ulcer (C4b) or Healed Venous Ulcer (C5): In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, guidelines suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. [GRADE - 2; LEVEL OF EVIDENCE - C] Treatment of the incompetent perforating veins can be performed simultaneously with correction of axial reflux or can be staged with reevaluation of perforator veins for persistent incompetence after correction of axial reflux. [GRADE – 2; LEVEL OF EVIDENCE – C]

Guideline 6.7: Pathologic Perforator Venous Reflux in the Absence of Superficial Venous Disease, With or Without Deep Venous Reflux, and a Healed or Active Venous Ulcer: In a
<table>
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<th>Sponsor (Year), Title</th>
<th>Relevant Recommendations</th>
<th>Quality*/Main Limitations</th>
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<td>patient with isolated pathologic perforator veins (outward flow of &gt;500 ms duration, with a diameter of &gt;3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed regardless of the status of the deep veins, guidelines suggest ablation of the “pathologic” perforating veins in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE – 2; LEVEL OF EVIDENCE – C]</td>
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<tr>
<td>Guideline 6.8: Treatment Alternatives for Pathologic Perforator Veins: For those patients who would benefit from pathologic perforator vein ablation, guidelines recommend treatment by percutaneous techniques that include US-guided sclerotherapy or endovenous thermal ablation (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]</td>
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<tr>
<td>Guideline 6.9: Infrainguinal Deep Venous Obstruction and Skin Changes at Risk for Venous Leg Ulcer (C4b), Healed (C5) or Active (C6) Venous Leg Ulcer: In a patient with infrainguinal deep venous obstruction and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), guidelines suggest autogenous venous bypass or endophlebectomy in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE – 2; LEVEL OF EVIDENCE – C]</td>
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<td>Guideline 6.10: Deep Venous Reflux With Skin Changes at Risk for Venous Leg Ulcer (C4b), Healed (C5) or Active (C6) Venous Leg Ulcer – Ligation: In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), guidelines suggest against deep vein ligation of the femoral or popliteal veins as a routine treatment. [GRADE – 2; LEVEL OF EVIDENCE – C]</td>
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<td>Guidelines 6.11 – 6.17 do not mention the interventions of interest for this HTA.</td>
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<tr>
<td>National Institute for Health and Care Excellence (NICE)</td>
<td><strong>Major recommendations for treatment for people with confirmed varicose veins and truncal reflux:</strong>&lt;br&gt;• Offer endothermal ablation (RFA or EVLA)&lt;br&gt;• If endothermal ablation is unsuitable, offer USGFS.</td>
<td>6.4 – Good&lt;br&gt;&lt;i&gt;Limitations: Process for external review not described&lt;/i&gt;</td>
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<tr>
<td>Sponsor (Year), Title</td>
<td>Relevant Recommendations</td>
<td>Quality*/Main Limitations</td>
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</table>
| (National Clinical Guideline Centre, 2013)  
Diagnosis and management of varicose veins in the legs: NICE guideline | • If UGFS is unsuitable, offer surgery.  
• If incompetent varicose tributaries are to be treated, consider treating them at the same time.  
• Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.  
Management during pregnancy:  
• Give pregnant women presenting with varicose veins information on the effect of pregnancy on varicose veins.  
• Do not carry out interventional treatment for varicose veins during pregnancy other than in exceptional circumstances.  
Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy. |  
| European Society for Vascular Surgery  
(Wittens et al., 2015)  
Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) | • Liquid sclerotherapy or FS is not recommended as the first-choice treatment for CVD (C2-C6 in the CEAP classification) due to saphenous vein incompetence. It should be used only as the primary treatment in selected cases (recommendation 38, IIIA).  
• FS is recommended as a second-choice treatment of varicose veins (C2 in the CEAP classification) and for more advanced stages of CVD (C3-C6 in the CEAP classification) in patients with saphenous vein incompetence, not eligible for surgery or EVLA (recommendation 39, IA)  
• FS should be considered as primary treatment in patients with recurrent varicose veins, and in elderly and frail patients with venous ulcers (recommendation 40, IIaB).  
• Liquid sclerotherapy should be considered for treating telangiectasias and reticular veins (C1 in the CEAP classification) (recommendation 41, IIaB)  
• For treatment of GSV reflux in patients with symptoms and signs of chronic venous disease, endovenous thermal ablation techniques are recommended in preference to surgery (recommendation 43, IA).  
• For the treatment of GSV reflux in patients with symptoms and signs of CVD, endovenous thermal ablation techniques are recommended in preference to FS (recommendation 44, IA) | 5.6 – Good  
Limitations: Methods for formulating recommendations included considering expert opinion, the process for external review was not described, and process for updating was not described |
<table>
<thead>
<tr>
<th>Sponsor (Year), Title</th>
<th>Relevant Recommendations</th>
<th>Quality*/Main Limitations</th>
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<tbody>
<tr>
<td></td>
<td>• For the treatment of SSV reflux in patients with symptoms and signs of CVD, endovenous thermal ablation techniques should be considered (recommendation 45, IIaB).</td>
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<td>• For non-complicated varicose veins (C2, C3 in the CEAP classification), surgical treatment is recommended instead of conservative treatment, to improve symptoms, cosmetics, and quality of life (recommendation 46, IB).</td>
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<td></td>
<td>• In cases in which surgical treatment of the refluxing saphenous vein is performed, high ligation and stripping is recommended instead of high ligation only (recommendation 47, IA).</td>
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<td>• Surgical stripping of the saphenous vein without high ligation leaving a 2 cm stump may be considered (recommendation 48, IIbB).</td>
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<td>• When performing endovenous thermal ablation of a refluxing saphenous trunk, adding concomitant phlebectomies should be considered (recommendation 51, IIaB).</td>
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<td>• To treat tributary varicose veins, ambulatory phlebectomy should be considered (recommendation 52, IIaC).</td>
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<td></td>
<td>• Endovenous thermal ablation, ultrasound-guided foam sclerotherapy UGFS, or phlebectomies should be considered for the treatment of recurrent varicose veins (recommendation 63, IIaB).</td>
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<td>• Extensive redo surgery is not recommended (including reexploration of the groin or popliteal fossa) is not recommended as a first-choice treatment in patients with recurrent varicose veins (recommendation 64, IIIB).</td>
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<tr>
<td>American College of</td>
<td>The group’s recommendation is that patients with symptomatic incompetence of the accessory GSV be treated with endovenous thermal ablation (EVLA or RFA) or with UGFS to reduce symptoms (Grade 1, level C).</td>
<td>4.3 – Fair</td>
</tr>
<tr>
<td>Phlebology (Gibson et</td>
<td></td>
<td>Limitations: Criteria for selecting evidence not described, limited discussion of the strength and limitations of the evidence, methods for formulating recommendations not well described, external</td>
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<td>Sponsor (Year), Title</td>
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<td><strong>American College of Phlebology (Rathbun et al., 2014)</strong>&lt;br&gt;Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines</td>
<td>The quality improvement guidelines state that endovenous FS is effective for treating primary and recurrent GSV, SSV, and accessory varicose veins. However, no randomized controlled trials were available for assessment and the group could not draw conclusions about the comparative efficacy or safety of FS and endovenous thermal ablation.</td>
<td>5 – Fair&lt;br&gt;&lt;i&gt;Limitations: Criteria for selecting evidence not thoroughly described, limited discussion of the strengths and limitations of the evidence, procedure for updating not described, and competing interests of guideline authors not recorded and addressed&lt;/i&gt;</td>
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<td><strong>American College of Phlebology (ACP, 2014)</strong>&lt;br&gt;Treatment of Superficial Venous Disease of the Lower Leg</td>
<td>• Recommend against compression therapy as a prerequisite therapy for symptomatic venous reflux disease when other definitive treatments such as endovenous ablation are appropriate. (1A)&lt;br&gt;• Recommend endovenous thermal ablation (laser and radiofrequency) as the preferred treatment for saphenous and accessory saphenous (GSV, SSV, AAGSV, PAGSV) vein incompetence. (1B)&lt;br&gt;• Recommend open surgery is appropriate in veins not amenable to endovenous procedures but otherwise is not recommended because of increased pain, convalescent time, and morbidity. (1B)&lt;br&gt;• Suggest that when open surgery of the GSV is performed it should include high ligation and invagination stripping to the level of the knee (2B), and recommend that when open surgery of the SSV is performed it include high ligation and selective invagination of the proximal portion (1B).&lt;br&gt;• Recommend varicose (visible) symptomatic tributary veins can be treated by stab phlebectomy, liquid sclerotherapy, or foam chemical ablation (1B), and recommend non-visible symptomatic tributary veins be treated by US-</td>
<td>3.2 – Poor&lt;br&gt;&lt;i&gt;Limitations: Limitations evident in all Rigor of Development domain items&lt;/i&gt;</td>
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### Relevant Recommendations

- **American College of Radiology (Rochon et al., 2012)**

  - **ACR Appropriateness Criteria: Radiologic Management of Lower-extremity Venous Insufficiency**

  Ratings in different scenarios described within the guidelines for the populations and interventions selected for this HTA are shown below.

  - **Variant 2:** Left SSV insufficiency resulting in intermittent pain and swelling without skin discoloration or ulceration. Rating 8 (usually appropriate) for endoluminal radiofrequency therapy; Rating 7 (usually appropriate) for endoluminal laser therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

  - **Variant 3:** Left GSV insufficiency with associated lower leg skin ulceration. Rating 8 (usually appropriate) for endoluminal laser therapy and for endoluminal radiofrequency therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.

  - **Variant 4:** Symptomatic bilateral GSV insufficiency and large visible varicose veins during pregnancy. Rating 2 (usually not appropriate) for endoluminal laser therapy, endoluminal radiofrequency therapy, injection sclerotherapy, and surgical vein stripping.

  - **Variant 6:** Symptomatic bilateral great saphenous venous insufficiency with remote history of deep venous thrombosis with no residual thrombus present. Rating 7 (usually appropriate) for endoluminal laser therapy and endoluminal radiofrequency therapy; Rating 5 (may be appropriate) for surgical vein stripping.

### Quality*/Main Limitations

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<td>guided liquid sclerotherapy or foam chemical ablation (1B).</td>
<td>3.9 – Fair</td>
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<td>- Suggest treatment of incompetent perforating veins located beneath a healed or open venous ulcer. They should have outward flow of 500 ms, with a diameter of 3.5 mm. (2B)</td>
<td><strong>Limitations:</strong> Criteria for selecting evidence not described, process for external review not described, procedure for updating not described, and competing interests of authors not recorded or addressed</td>
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<td>- Suggest in patients with perforator reflux as the primary or only source of disease, treatment of the perforator with endovenous thermal ablation, ligation or US-guided sclerotherapy. Subsequent or simultaneous treatment of symptomatic varicosities arising from the incompetent perforator is also considered best practice. (2B)</td>
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Selected treatments for varicose veins: Draft evidence report - Appendices

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<td>appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.</td>
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<td>• Variant 7: Right GSV insufficiency status post vein stripping 1 year ago with persistent lower-extremity swelling. Reflux is noted in the below-knee GSV measuring up to 5 mm. Rating 8 (usually appropriate) for endoluminal laser therapy and endoluminal radiofrequency therapy; Rating 4 (may be appropriate) for repeat surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy.</td>
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*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on a scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).