

Selected treatments for varicose veins

Final evidence report

April 14, 2017

Health Technology Assessment Program (HTA)

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A Health Technology Assessment

Prepared for Washington State Health Care Authority

Final REPORT

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Acknowledgement

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List of Abbreviations

AGREE	Appraisal of Guidelines Research and Evaluation tool
AVVSS	Aberdeen Varicose Vein Symptom Severity
CEAP	Clinical, Etiologic, Anatomic, Pathophysiologic
CHIVA	Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire
CIVIQ	Chronic Venous Insufficiency Quality-of-Life Questionnaire
CVD	chronic venous disease
CVI	chronic venous insufficiency
DVT	deep vein thrombosis
EVLA	endovenous laser ablation
FDA	Food and Drug Administration
FS	foam sclerotherapy
GSV	great saphenous vein
HL&S or HL/S	high ligation and stripping
(HR)QOL	(health related) quality of life
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
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. Potential benefits of sclerotherapy and endoluminal occlusion using radiofrequency or laser light energy for the treatment of varicose veins due to GSV, SSV, or saphenofemoral junction (SFJ) reflux include reduced postoperative morbidity and improved recovery time compared with conventional surgical options, but these techniques 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 of reflux and varicose veins may reform 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. Various devices or other products associated with these procedures may be regulated by the U.S. Food and Drug Administration (FDA); an evaluation of specific devices or products is not within the scope of this health technology assessment (HTA).

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 the vein when reflux is present. The goal of EVLA is to use laser energy to seal off the damaged portions of a vein 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 may be 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. This therapy is also intended primarily for the treatment of varicose veins that result from GSV, SSV, or accessory vein reflux. 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. The presence of thrombus in the vein segment to be treated is a contraindication for endovenous RFA.

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. FDA-approved liquid 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. FS products may be 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 treatment sessions may be needed depending on the extent and severity of the condition. After treatment, compression bandages or stockings are worn for several days. Varithena, a prescribed proprietary canister that generates a sterile, uniform, stable, low-nitrogen polidocanol 1% microfoam sclerosant intended for US-guided intravenous (IV) injection received FDA approval in 2013. Methods using liquid sclerosants to make foam sclerosants at the time of treatment by physicians have also been employed. Physician compounded foam involves mechanically agitating a mixture of a liquid sclerosant and a gas (usually room air). Safety concerns have been raised regarding the variability and potentially high concentration of nitrogen in physician compounded FS products. Contraindications to sclerotherapy 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.

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. Treatments for varicose veins represent an area of substantial utilization in plans managed by the Washington state agencies. 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

Review Objectives

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., 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 ($n \geq 500$), 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 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. An update search of PubMed for systematic reviews was conducted on March 6, 2017. Following identification and selection of systematic reviews and HTAs, a targeted search of PubMed and relevant primary data sources 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. Update searches of the PubMed and Embase databases were conducted on March 6, 2017, and March 9, 2017, to identify additional primary studies. In addition to the database and manual searches described, the National Guidelines Clearinghouse and websites of professional organizations were searched for practice guidelines.

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).

Intervention: Thermal ablation other than laser and RF (e.g., steam ablation); Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire (CHIVA); cryostripping.

Comparator: Placebo/sham, other active comparators, or no comparison group.

Study design/publication type: 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 23 publications were identified through searches for systematic reviews and additional publications of primary data to answer the Key Questions. This includes 8 systematic reviews and 15 publications of primary data not already included in 1 or more of the systematic reviews. Eight of the 15 primary publications represent newer data from studies that were included in the systematic reviews based on earlier publications.

See [Appendix IV](#) for a list of the 92 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 11 in the Technical Report for a list of individual studies evaluated 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; studies without comparison groups 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 included 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 ClosurePLUS or ClosureFast catheters (note the ClosurePLUS device is no longer available in the U.S.); and liquid or FS or in various doses and numbers of injections. Comparisons included open surgical procedures such as vein 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 and/or data analysis was by patient in some studies and by limb in others. As noted by several of the systematic review authors, the use of data randomized by limbs can introduce some bias into pooled analyses.

Primary Studies

Eleven recent publications evaluating interventions of interest for this HTA, and not included in the systematic reviews described above, were identified for Key Question #1. Eight of these are follow-up publications related to previously published studies, and 3 are publications unrelated to previously published studies. Nine publications compare EVLA with surgery, and 5 publications compare sclerotherapy with surgery. One recent publication of primary data comparing RFA with surgery was identified. No recent publications of primary data comparing phlebectomy alone with surgery were identified. 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=10) to poor (n=1). 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 through 8 follow the narrative summaries for each outcome 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 systematic reviews 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 low-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 of 431), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20 of 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 statistically significant difference between RFA and surgery (odds ratio [OR]=0.82 [95% CI, 0.07-10.10]; $P=0.88$; $I^2=70\%$).

Sclerotherapy Versus Surgery: The evidence from quantitative analyses presented in 4 systematic reviews 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 heterogeneous body of evidence. Two of the included systematic reviews 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 and reported the outcome as “treatment success or failure.” The review authors 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.

Table 1. Summary of Findings, Key Question 1: Clinical Outcome – Failure of Procedure

Key: EVLA, endovenous laser ablation; GQ, good quality; HL/S, high ligation and stripping; KQ, key question; L/S, ligation and stripping; NR, not reported; NS, not statistically significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; RFA, radiofrequency ablation; RR, risk ratio; SF, saphenofemoral; S/L stripping and ligation; SR, systematic review

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ #1. Clinical outcome: Failure of procedure, EVLA vs surgery			
4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014	OVERALL: Moderate Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	Reduced w/ EVLA or similar	Carroll, 2013 (n=12 studies) Pooled percentage: EVLA 1% (5/467); S/L 3% (20/681); $P=NR$ Nesbitt, 2014 (n=6 studies) $OR=0.29$ (95% CI, 0.14-0.60); $P=0.0009$

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
No additional primary studies			<p>Paravastu, 2016 (n=3 studies) OR=0.07 (95% CI, 0.02-0.22); P<0.00001</p> <p>Pan, 2014 (n=9 studies) Pooled percentage (1-12 wks): EVLA 97.3%; HL/S 97.6%; P=NS Meta-analysis: RR=1.1 (95% CI, 0.62-1397); P=0.72</p>
KQ #1. Clinical outcome: Failure of procedure, RFA vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014 No additional primary studies	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	<p>Carroll, 2013 (n=12 studies) Pooled percentage: RFA 4% (16/431); S/L 3% (20/681); P=NR</p> <p>Nesbitt, 2014 (n=5 studies) OR=0.82 (95% CI, 0.07-10.10); P=0.88</p>
KQ #1. Clinical outcome: Failure of procedure, sclerotherapy vs surgery			
4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Rathbun, 2012	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	<p>Carroll, 2013 (n=12 studies) Pooled percentage: Foam sclerotherapy 7% (7/295); S/L 3% (20/681); P=NR</p> <p>Nesbitt, 2014 (n=2 studies) OR=0.44 (95% CI, 0.12-1.57); P=0.20</p> <p>Paravastu, 2016 (1 study) OR=0.34 (95% CI, 0.06-2.10); P=0.25</p> <p>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</p>

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% credible 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 (95% CrI, 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 at one year. 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. One publication of primary data contributed 5-year follow-up to 1 of the studies included in 1 of the systematic reviews. 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. 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 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]; $P=0.47$; $I^2=39\%$). 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 2 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 no 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 no 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.

Table 2. Summary of Findings, Key Question 1: Clinical Outcome – Technical Recurrence

Key: CrI, credible interval; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; f/u, follow-up; GQ, good quality; HL, high ligation; HL/S, high ligation and stripping; HR, hazard ratio; KQ, key question; L/S, ligation and stripping; MA, meta-analysis; NR, not reported; NS, not significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; PQ, poor quality; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, risk ratio; SFL/S, saphenofemoral ligation/stripping; SR, systematic review

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ #1. Clinical outcome: Technical recurrence, EVLA vs surgery			
5 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014; O'Donnell, 2016 3 FQ RCTs van der Velden, 2015 (5-yr f/u from MAGNA trial) Gauw, 2016 (5-yr f/u) Kalteis, 2015 (5-yr f/u) 1 PQ RCT Mozafar, 2014	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% CrI, 0.44-1.81) 1 yr HR=0.77 (95% CrI, 0.37-1.54) 6 mo HR=0.70 (95% CrI, 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 w/ L/S van der Velden, 2015 (n=135 pts; 147 legs at 5yrs) EVLA, 23%; surgery, 14.5%; P=NR 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: EVLA 6.7% EVLA; HL 11.7% HL; P=NR
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% CrI, 0.42-2.51) 1 yr HR=0.93 (95% CrI, 0.42-2.22) 6 mo HR=0.92 (95% CrI, 0.39-2.11) Nesbitt, 2014 (n=4 studies) OR=0.82 (95% CI, 0.49-1.39)

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ #1. Clinical outcome: Technical recurrence, sclerotherapy vs surgery			
4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Rigby, 2009 2 FQ RCTs 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 w/ 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 Michaels, 2006 No difference at 1, 2, or 3 yrs

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 reported statistically significant differences between EVLA and surgery with respect to symptomatic recurrence. In a 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 ($P=0.152$). Another 5-year follow-up publication did not report statistical significance, but found a lower rate of visible recurrence in the EVLA group. A third 5-year follow-up publication reported statistically significantly less recurrence in the surgery group ($P=0.04$). In a 6-year follow-up publication, there was no significant difference between EVLA and HL/S with respect to time to clinical recurrence.

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 (26%) patients in the RFA group had symptomatic recurrence at 3 years compared with 2 of 13 (15.4%) patients 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 between FS and surgery (OR=1.28 [95% CI, 0.66-2.49]; $P=NR$). Another study, not included in the systematic review, reported no visible varicosities in 76% of surgery group versus 39% of the LS grp ($P<0.05$) at 1 year. Three-year follow-up data from 1 study suggests no difference in medium-term recurrence of varicose veins between sclerotherapy and surgery.

Table 3. Summary of Findings, Key Question 1: Clinical Outcome – Symptomatic Recurrence

Key: EVLA, endovenous laser ablation; FQ, fair quality; f/u, follow-up; GQ, good quality; grp(s), group(s); HL, high ligation; KQ, key question; LS, liquid sclerotherapy; NR, not reported; NS, not significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, risk ratio; SR, systematic review; UGFS, ultrasound-guided foam sclerotherapy

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Clinical outcome: Symptomatic recurrence, EVLA vs surgery			
5 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014; O'Donnell, 2016 4 FQ RCTs Kalteis, 2015 (5-yr f/u); Rass, 2015 (5-yr f/u); Flessenkamper, 2016 (6-yr f/u); Gauw, 2016 (5-yr f/u)	OVERALL: Moderate Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	Carroll, 2013 (n=3 studies) <i>Differences between grps NS</i> Nesbitt, 2014 (n=3 studies) <i>OR=0.87 (95% CI, 0.47-1.62); $P=0.67$</i> Paravastu, 2016 (n=1 study) <i>OR=0.54 (95% CI, 0.17 to 1.75); $P=NR$</i> Pan, 2014 (n=5 & 6 studies) <i>1 yr RR=0.83 (95% CI, 0.39-1.77); $P=0.63$</i> <i>2 yr RR=0.85 (95% CI, 0.64-1.11); $P=0.23$</i> O'Donnell, 2016 <i>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 w/ surgery</i> Rass, 2015 (RELACS) (n=281 legs at 5 yrs) <i>EVLA 45% EVLA; HL/S 54% HL/S ; ($P=0.152$)</i> Flessenkamper, 2016 (n=81 pts at 72 mos) <i>No difference in time to clinical recurrence w/in 6-yr f/u (log rank test $P=0.5479$)</i>

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
			Kalteis, 2015 (n=72 at 5 yrs) Visible recurrence: HL+EVLA 40%; HL/S 55%; P=NR Gauw, 2016 (n=112 pts at 5 yrs) Clinical recurrence at 5 yrs, 33% EVLA, 17% SFL/S, P=0.04
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 between grps NS Nesbitt, 2014 (n=1 study) OR=2.00 (95% CI, 0.30-13.26); P=NR
KQ1. Clinical outcome: Symptomatic recurrence, sclerotherapy vs surgery			
1 GQ SRs Nesbitt, 2014 2 FQ RCTs Michaels, 2006; Rasmussen, 2013b (3-yr f/u)	OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown	Mixed	Nesbitt, 2014 (n=1 study) OR=1.28 (95% CI, 0.66-2.49); P=NR Michaels, 2006 At 1 yr, no visible varicosities in 76% of surgery grp vs 39% of LS grp (P<0.05) Rasmussen, 2013b (n=247 pts; 284 legs at 3 yrs) Recurrence, n (Kaplan Meier estimate): UGFS 20 (19.1%); surgery 22 (20.2%); P=NS

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], probability MD > 0, 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 (HVCSS) 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). In 1 follow-up publication of 3-

year results, there was no difference between EVLA patients and surgery patients with respect to VCSS scores; both groups showed statistically significant improvement from baseline.

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 systematic review 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. In 1 follow-up publication of 3-year results, there was no difference between RFA patients and surgery patients with respect to VCSS scores; both groups showed statistically significant improvement from baseline.

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]). In 1 follow-up publication of 3-year results, there was no difference between UGFS patients and surgery patients with respect to VCSS; both groups showed statistically significant improvement from baseline. Another study also reported no difference between groups in change in disease severity (VCSS) scores at 6 months; however, the difference was statistically significant at 12 months suggesting better outcome with UGFS ($P=0.006$).

Table 4. Summary of Findings, Key Question 1: Clinical Outcome – Change in VCSS

Key: AVVSS, Aberdeen Varicose Vein Symptom Severity; CND, cannot determine; CrI, credible interval; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; f/u, follow-up; GQ, good quality; grp(s), group(s); HL, high ligation; HL/S, high ligation and stripping; IQR, interquartile range; KQ, key question; MA, meta-analysis; MD, mean difference; NS, not statistically significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; PQ, poor quality; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, risk ratio; SR, systematic review; SSV, small saphenous vein; tx, treatment; UGFS, ultrasound-guided foam sclerotherapy; VCSS, Venous Clinical Severity Score

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Clinical outcome: Change in VCSS or other measure of disease severity, EVLA vs surgery			
1 GQ SR Carroll, 2013 3 FQ RCT Rasmussen, 2013 (3-yr f/u) van der Velden, 2015 (5-yr f/u for the MAGNA trial) Rass, 2015 (5-yr f/u from RELACS trial) 1 PQ RCT Mozafar, 2014	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 to 0.73) 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 Rasmussen, 2013 (n=247 pts; 284 legs at 3 yrs) VCSS, mean (SD): EVLA 0.34 (1.3); surgery 0.3 (0.5); P=NS 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. Clinical outcome: Change in VCSS or other measure of disease severity, RFA vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014 1 FQ RCT Rasmussen, 2013b (3-yr f/u)	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	Carroll, 2013 (n=6 studies, network MA) MD=0.15 (95% CrI, -0.50 to 0.95) Nesbitt, 2014 (3 studies) No overall differences between grps Rasmussen, 2013b (n=247 pts; 287 legs at 3 yrs) VCSS, mean (SD): RFA 0.44 (1.82); surgery 0.3 (0.5)
KQ1. Clinical outcome: Change in VCSS or other measure of disease severity, sclerotherapy vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014 3 FQ RCTs Rasmussen, 2013b (3-yr f/u) van der Velden, 2015; Yin, 2017	OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown	Mixed	Carroll, 2013 (n=6 studies, network MA) MD=-1.63 (95% CrI, -2.90 to -0.42) Nesbitt, 2014 (2 studies) No difference Rasmussen, 2013b (n=247 pts; 284 legs at 3 yrs) VCSS, mean (SD): FS 0.15 (0.4); surgery 0.3 (0.5) van der Velden, 2015 (n=129 pts; 146 legs) No difference at 5 yrs in C class distribution between the tx grps Yin, 2017 VCSS, median (IQR) at 6 mos: UGFS 4 (4); surgery 4 (3); P=0.869

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
			VCSS, median (IQR) at 12 mos: UGFS 2 (1); 3 surgery (2); $P=0.006$

Pain

EVLA Versus Surgery: The quality of evidence for postoperative pain was determined to be very low due to inconsistencies 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, 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 than the surgery group.

RFA Versus Surgery: There is moderate quality evidence that RFA is associated with less postprocedural 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] [probability of MD > 0, 0.001]).

Sclerotherapy Versus Surgery: A very-low-quality body of evidence suggests that FS may be no different in terms of postoperative pain than surgery. With respect to pain, a network meta-analysis of 9 studies found no statistically significant difference between FS and surgery. Another review found conflicting results in 2 studies. One of the 2 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 ($P=0.136$).

Table 5. Summary of Findings, Key Question 1: Patient-Centered Outcome – Pain

Key: CrI, credible interval; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; GQ, good quality; grp(s), group(s); HL/S, high ligation and stripping; KQ, key question; MA, meta-analysis; MD, mean difference; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, risk ratio; SR, systematic review

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Patient-centered outcome: Pain, EVLA vs surgery			
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 w/in 7-14 days: MD=0.10 (95% CrI, -0.49 to 0.64) Nesbitt, 2014 Described results from studies measuring pain as inconclusive Paravastu, 2016 (n=2 studies) Mixed results Pan, 2014 (n=8 studies) 3 studies found >pain in HL/S grp than EVLA grp; 4 studies found no difference; 1 study reported significantly >pain in the EVLA grp
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 w/ RFA	Carroll, 2013 (n=9 studies, network MA) MD=-1.26 (95% CrI, -1.95 to -0.61) Nesbitt, 2014 (4 studies) 3 studies less pain in RFA grp (P<0.001); 1 study no statistically significant difference
KQ1. Patient-centered outcome: Pain, sclerotherapy vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014	OVERALL: Very low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	Carroll, 2013 (n=9 studies, network MA) MD=-0.80 (95% CrI, -1.93 to 0.30) Nesbitt, 2014 (2 studies) 1 study, no difference; 1 study significantly less pain in FS grp (P<0.001)

Time to 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. In a publication of results from the CLASS trial, results suggest that for 13 of 15 behaviors, EVLA patients returned significantly faster than patients treated with surgery.

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: 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 systematic reviews 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. In a publication of results from the CLASS trial, results suggest that for 13 of 15 behaviors, UGFS patients returned significantly faster than patients treated with surgery. A recent RCT enrolling patients with severe lower extremity varicosities reported that UGFS patients returned to normal activities faster than patients in the surgery group ($P<0.001$).

Table 6. Summary of Findings, Key Question 1: Patient-Centered Outcome – Return to Activity

Key: BRAVVO, Behavioral Recovery After treatment for Varicose Veins; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; GQ, good quality; grp(s), group(s); KQ, key question; NR, not reported; PICOS, population, intervention, comparator, outcomes, setting; RCT, randomized controlled trial; RFA, radiofrequency ablation; SR, systematic review; UGFS, ultrasound-guided foam sclerotherapy

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Patient-centered outcome: Return to work or normal activity, EVLA vs surgery			
4 GQ SRs Carroll, 2013; Nesbitt, 2014; Paravastu, 2016; Pan, 2014	OVERALL: Low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown	Reduced with EVLA	Carroll, 2013 (n=6 studies) 1 study, < time in surgery grp; 1 study, < time in EVLA grp; 2 studies, no difference; 2 studies, P=NR Nesbitt (2014) (n=6 studies)

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
1 FQ RCT Cotton, 2016 (CLASS trial)			<p>6 studies summarized as generally < time for the EVLA grp</p> <p>Paravastu (2016) (n=2 studies) < time for EVLA grp</p> <p>Pan (2014) (n=7 studies) Time to return to normal activities (5 studies): No difference Time to return to work: 2 studies, < time in EVLA grp; 3 studies, no difference; 1 study, < time in surgery grp</p> <p>Cotton, 2016 (n=415 at 6 wks) BRAVVO: < time for EVLA grp for 13 of 15 behaviors</p>
KQ1. Patient-centered outcome: Return to work or normal activity, RFA vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	Reduced w/ RFA	<p>Carroll, 2013 (n=4 studies) 1 study, P=NS; 3 studies, < time in RFA grp</p> <p>Nesbitt (2014) (n=5 studies) < time in RFA grp; P=NR</p>
KQ1. Patient-centered outcome: Return to work or normal activity, sclerotherapy vs surgery			
2 GQ SRs Carroll, 2013; Nesbitt, 2014 2 FQ RCTs Cotton, 2016 (CLASS trial); Yin, 2017	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	Reduced w/ FS	<p>Carroll, 2013 (n=3 studies) 1 study; P=NR 2 studies, < time in FS grp; P<0.001</p> <p>Nesbitt, 2014 (n=1 study) Return to work < time in FS grp, median 2.9 vs 4.3 days; P=NR Return to normal activities < time in FS grp, median 1 vs 4 days; P=NR</p> <p>Cotton, 2016 (n=473 at 6 wks) BRAVVO: < time for UGFS grp for 13 of 15 behaviors</p> <p>Yin, 2017 (n=177) Avg time to return to normal activities, days (range): UGFS 5.4 (3-14); surgery 9.6 (7-18); P<0.001</p>

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. In 1 publication of 3-year results, analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for EVLA and surgery; no between-group analysis was provided. The AVVSS improved for all groups from 3 days to 3 years with no significant between-group differences. In another study, results of patients' survey responses at 2 months suggest no statistical difference at 2 months posttreatment between those who received EVLA and those who received surgery in any of the categories measured.

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. In 1 publication of 3-year results, analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for RFA and surgery; no between-group analysis was provided. The AVVSS improved for all groups from 3 days to 3 years with no significant between-group differences.

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 with an increased utility for patients randomized to surgery at 1 year based on EQ-5D scores and EuroQOL VAS scores, but there were no significant differences in SF-36 scores at 1 or 2 years or in EuroQOL VAS or EQ-5D at 2 years. In 1 publication of 3-year results, analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for UGFS and surgery; no between-group analysis was provided. The AVVSS improved for all groups from 3 days to 3 years with no significant between-group differences. Another study reported no difference between UGFS plus HL and

HL/S plus phlebectomy with respect to change in AVVQ at 6 or 12 months or patient satisfaction at 12 months.

Table 7. Summary of Findings, Key Question 1: Patient-Centered Outcome – Quality of Life

Key: AVVSS, Aberdeen Varicose Vein Symptom Severity; AVVQ, Aberdeen Varicose Veins Questionnaire; CND, cannot determine; CrI, credible interval; CIVIQ, Chronic Venous Insufficiency Quality-of-Life Questionnaire; EQ-5D, EuroQoL Group 5-dimension Questionnaire; EVLA, endovenous laser ablation; FLQA, Freiburg Life Quality Assessment; FQ, fair quality; f/u, follow up; GQ, good quality; HL/S, high ligation and stripping; KQ, key question; LS, liquid sclerotherapy; MD, mean difference; NR, not reported; NS, not statistically significant; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; RCT, randomized controlled trial; RFA, radiofrequency ablation; SR, systematic review; UGFS, ultrasound-guided foam sclerotherapy;

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Patient-centered outcome: Quality of life/patient satisfaction, EVLA vs surgery			
2 GQ SRs Nesbitt, 2014; Paravastu, 2016 5 FQ RCTs Rasmussen, 2013b (3-yr f/u) Flessenkamper, 2014 (2 mos) van der Velden, 2015 (5-yr f/u for the MAGNA trial) Rass, 2015 (5-yr f/u from RELACS trial) Kalteis, 2015 (5-yr f/u)	OVERALL: Moderate Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	Nesbitt, 2014 (n=5 studies) <i>No difference</i> Paravastu, 2016 AVVQ at 6 wks (2 studies): MD=0.15 (95% CI, -1.65 to 1.95); P=0.87 AVVQ at 1 yr (1 study): MD=-1.08 (95% CI, -3.39 to 1.23); P=NR EQ-5D (2 studies): <i>No difference</i> Rasmussen, 2013b (n=247 pts; 284 legs at 3 yrs) AVVSS, mean (SD): EVLA 4.61 (5.8); surgery 4.0 (4.87) Flessenkamper, 2014 (n=343) FLQA-V: <i>No difference</i> van der Velden, 2015 (n=114 pts) CIVIQ and EQ-5D scores: <i>No difference at 5 yrs</i> Rass, 2015 (n=281 legs at 5 yrs) CIVIQ-2 scores: <i>No difference</i> Pt satisfaction: EVLA 1.28±0.51; HL/S 1.39±0.58; P=0.078 Kalteis, 2015 (n=72 at 5 yrs) CIVIQ-2: EVLA 94; HL/S 93; P=NR Pt satisfaction: EVLA 87%; HL/S 88% rated good or very good; P=NR

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Patient-centered outcome: Quality of life/patient satisfaction, RFA vs surgery			
1 GQ SR Nesbitt, 2014 1 FQ RCT Rasmussen, 2013b (3-yr f/u)	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 Rasmussen, 2013b (n=247 pts; 287 legs at 3 yrs) AVVSS, mean (SD): 4.43 (6.58); surgery 4.0 (4.87)
KQ1. Patient-centered outcome: Quality of life/patient satisfaction, sclerotherapy vs surgery			
1 GQ SR Nesbitt, 2014 4 FQ RCTs Michaels, 2006; Rasmussen, 2013b (3-yr f/u) van der Velden, 2015 (5-yr f/u for MAGNA trial); Yin, 2017	OVERALL: Low Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown	No difference	Nesbitt, 2014 (n=3 studies) NS differences Michaels, 2006 (n=49 pts at 1 yr) SF-36 1 yr: No difference SF-36 2 yrs: No difference EQ-5D 1 yr, mean (SD) : LS 0.80 (0.14); surgery 0.85 (0.20); P<0.05 EQ-5D 2 yrs, mean (SD): LS 0.74 (0.11); surgery 0.84 (0.32); P=NS EuroQOL VAS 1 yr, mean (SD): LS 0.77 (0.18); surgery 0.83 (0.14); P<0.05 EuroQOL VAS 2 yrs, mean (SD): LS 0.77 (0.13); surgery 0.83 (0.13); P=NS Rasmussen, 2013b (n=247 pts; 284 legs at 3 yrs) AVVSS, mean (SD): 4.76 (5.71), surgery 4.0 (4.87) van der Velden, 2015 (n=111) CIVIQ: FS 0.98 (95% CI, 0.16-1.79); surgery 0.44 (95% CI, -0.41 to 1.29); P=NR EQ-5D: FS 0.01 (95% CI, 0.01-0.02); surgery 0.02 (95% CI, 0.01-0.02); P=NR Yin, 2017 AVVQ: No difference at 6 or 12 mos Pt satisfaction (12 mos): UGFS 92.3%; surgery 86.5%; P=NS

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 because of technical failure or 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. A third 5-year follow-up publication reported that a higher percentage of patients with recurrent varicose veins who initially received surgery were managed with a “wait and see” approach than patients with recurrent varicose veins who initially received EVLA ($P=0.04$).

RFA Versus Surgery: There is very-low-quality evidence of mixed results for reintervention after varicose vein treatment with RFA compared with conventional surgery. According to 1 systematic review, 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 systematic review 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, $P<0.001$). One study reported 3-year follow-up results suggesting that more legs ($n=37$) in the UGFS group received retreatment compared with those in the surgery group ($n=18$); $P<0.0001$. The authors attributed the difference to more recanalization events in the UGFS than the surgery group; retreatment was not necessarily given because of symptoms or recurrent varicose veins. A recent RCT that enrolled patients with severe lower extremity varicosities (C4-C6) and compared UGFS combined with HL with HL/S combined with phlebectomy, reported that 29 patients in the UGFS group compared with 34 patients in the surgery group ($P=0.506$) experienced additional procedures because of technical failure.

Table 8. Summary of Findings, Key Question 1: Clinical Outcome – Reintervention

Key: AASV, anterior accessory saphenous vein; CND, cannot determine; EVLA, endovenous laser ablation; FQ, fair quality; FS, foam sclerotherapy; f/u, follow up; GQ, good quality; GSV, greater saphenous vein; HL/S, high ligation and stripping; KQ, key question; MA, meta-analysis; MD, mean difference; NR, not reported; NS, not significant; OR, odds ratio; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; PQ, poor quality; RCT, randomized controlled trial; RFA,

radiofrequency ablation; SFJ, saphenofemoral junction; SF/L, saphenofemoral ligation; SR, systematic review; SSV, small saphenous vein; tx, treatment; UGFS ultrasound-guided foam sclerotherapy

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Clinical outcome: Reintervention, EVLA vs surgery			
<p>3 GQ SRs Nesbitt, 2014; Paravastu, 2016; Pan, 2014; O'Donnell, 2016</p> <p>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)</p>	<p>OVERALL: Low Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown</p>	No difference	<p>Nesbitt, 2014 (n=2 studies) <i>Reintervention due to technical failure:</i> EVLA, 13%; surgery 8.8%; P=NR EVLA 3.5%; 1.4% surgery; P=NR</p> <p>Paravastu, 2016 (n=1 study) <i>Reintervention due to technical failure:</i> EVLA 4 pts; surgery 3 pts; P=NR</p> <p>O'Donnell, 2016 <i>No difference for EVLA and RFA combined compared w/ surgery</i> <i>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.</i></p> <p>van der Velden, 2015 (n=135 pts; 147 legs) <i>Reintervention at 5 yrs: 10% in EVLA and surgery grps</i></p> <p>Rass, 2015 (n=281 legs at 5 yrs) <i>Types of reintervention for recurrence (n=69 EVLA; n=70 HL/S):</i> <i>"Wait and see" – EVLA 49%; HL/S 67%; P=0.040</i></p> <p>Gauw, 2016 (n=121 legs at 5 yrs) <i>Did not receive reintervention: EVLA 70%; SF/L 80%; P=0.20</i></p>
KQ1. Clinical outcome: Reintervention, RFA vs surgery			
<p>2 GQ SR Nesbitt, 2014; O'Donnell, 2016</p>	<p>OVERALL: Very Low Consistency: CND Applicability to PICOS: ✓ Publication bias: Unknown</p>	CND	<p>Nesbitt, 2014 (n=2 studies) <i>Reintervention due to technical failure:</i> RFA, 0%; surgery 7.4%; P=NR RFA 13.3%; 15.4% surgery; P=NR</p> <p>O'Donnell, 2016 <i>No difference for EVLA and RFA combined compared w/ surgery for reoperation</i> <i>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.</i></p>

Number, Type, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ1. Clinical outcome: Reintervention, sclerotherapy vs surgery			
1 GQ SR Nesbitt, 2014 3 FQ RCT Rasmussen, 2013b (3-yr f/u); van der Velden, 2015 (5-yr f/u for MAGNA trial); Yin, 2017	OVERALL: Very low Consistency: CND Applicability to PICOS: ✓ Publication bias: Unknown	CND	Nesbitt, 2014 (n=2 studies) <i>Reintervention due to technical failure:</i> FS 18.8%; surgery 5.6%; P=NR FS 3.5%; no data for surgery grp; P=NR Rasmussen, 2013b (n=247 pts; 284 legs at 3 yrs) <i>Retreatment, n (Kaplan Meier estimate):</i> UGFS 37 (31.6%); surgery 18 (15.5%); P<0.0001 van der Velden, 2015 (129 pts; 146 legs at 5 yrs) FS 32%; surgery, 10% (limbs); log rank test P<0.001 Yin, 2017 (n=177) <i>Reintervention due to technical failure:</i> UGFS 29; surgery 34; P=0.506

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 of 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; however, 2 reviews also included observational studies. One review included 104 studies; 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 ClosurePLUS or ClosureFast catheters (NOTE: The ClosurePLUS device is no longer available in the United States.); and UGFS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation, HL, or HL/S.

Six additional publications not already included in the systematic reviews described above were also identified for Key Question #2. Two of these are follow-up publications related to studies already

included in 1 or more systematic reviews, and 4 are not related to previously published studies. Two of these recent publications are observational studies 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 systematic reviews 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 percentage of patients in each group with DVT was 0.8% in the surgery group and 1.6% in the endovenous ablation group ($P=0.027$), and another large observational study reported rates of DVT higher than those reported in RCTs and some pooled analyses. 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 systematic reviews, 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 collected 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, sex, ethnicity, 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. In another large observational study using diagnosis codes from a claims database, the rate of diagnosed DVT within 30 days of EVLA was 701 of 22,980 (3.05%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins ($P=NR$). In this same study, the rate of diagnosed PE within 30 days of EVLA was 58 of 22,980 (0.25%) and was 33 of 11,529 (0.29%) within 30 days of surgery ($P=NR$).

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 to 2

systematic reviews. One large observational study reported that the rate of diagnosed DVT within 30 days of RFA was 954 of 21,637 (4.41%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins ($P=NR$). The rate of diagnosed PE within 30 days of RFA was 68 of 21,637 (0.31%) and was 33 of 11,529 (0.29%) within 30 days of surgery ($P=NR$).

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. Results from a large observational study suggest that the rate of DVT is low among those who received sclerotherapy; the rate of diagnosed DVT within 30 days of sclerotherapy was 104 of 12,708 (0.82%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins ($P=NR$). The rate of diagnosed PE within 30 days of sclerotherapy was 19 of 12,708 (0.15%) and was 33 of 11,529 (0.29%) within 30 days of surgery ($P=NR$). In 1 recent RCT, no cases of PE were recorded in either the UGFS or surgery group; 1 case of DVT was recorded in the UGFS group and there were 2 cases in the surgery 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 statistically significant difference suggesting worse outcomes after surgery than RFA; the other 2 studies did not find a difference between the groups. Analyses conducted in the other review concluded that 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 of 363 [4.1%]) than among those who received FS (3 of 418 [0.7%]), but statistical significance is not reported. One recent RCT reported paresthesia in 0 UGFS patients compared with 9 surgery patients.

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 often not 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 comparisons with zero events were excluded) comparing EVLA with L/S also found a statistically significant difference in favor of EVLA (OR=0.24 [95% CI, 0.10-0.58]; $I^2 = 0\%$). 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); $I^2 = 0\%$ 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. In a recent publication of results from an RCT, there were 0 reported cases of incision/puncture site infections in the UGFS group and 5 cases 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. For hematoma, analyses suggest better outcomes associated with EVLA than with surgery. 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]; $P = 0.0001$). In a recent RCT, the overall rate of minor complications was

27.7% in the UGFS group and 21.6% in the HL/S group ($P=0.406$). The overall rate of major complications was also not statistically significantly different between the groups (UGFS, 3.1% and HL/S, 2.7% [$P=0.897$]). In the UGFS group, there were 0 patients with hematoma compared with 5 patients in the surgery group. Patients with pain needing oral analgesics ($n=5$), saccular thrombophlebitis ($n=10$), and hyperpigmentation ($n=3$) were reported in the UGFS group but none of these events were reported in the surgery group.

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 systematic reviews 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, ethnicity, 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 systematic reviews 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 systematic 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 2 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 9**. 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 9. 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

Quality of Individual GLs, Title (Author, Year)	Recommendations
Good <i>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</i> (Gloviczki et al., 2011)	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.
Good <i>Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF):</i> (O'Donnell et al., 2014)	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.

Quality of Individual GLs, Title (Author, Year)	Recommendations
<p>Good</p> <p><i>Diagnosis and management of varicose veins in the legs: National Institute for Health and Care Excellence (NICE) guideline</i> (National Clinical Guideline Centre, 2013)</p>	<p>The NICE recommended a treatment hierarchy for confirmed varicose veins and truncal reflux: RFA/EVLA > UGFS > surgery. During pregnancy, consideration should be given to compression hosiery instead of interventional treatment (except in exceptional circumstances).</p>
<p>Good</p> <p><i>Management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS)</i> (Wittens et al., 2015)</p>	<ul style="list-style-type: none"> • 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. • 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.
<p>Fair</p> <p><i>American College of Phlebology Guidelines – treatment of refluxing accessory saphenous veins</i> (Gibson et al., 2016)</p>	<p>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.</p>
<p>Fair</p> <p><i>Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines</i> (Rathbun et al., 2014)</p>	<p>The GLs 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.</p>
<p>Poor</p>	<ul style="list-style-type: none"> • 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

Quality of Individual GLs, Title (Author, Year)	Recommendations
<i>Treatment of superficial venous disease of the lower leg</i> (ACP, 2014)	<p>for symptomatic venous disease when treatments such as endovenous ablation are appropriate.</p> <ul style="list-style-type: none"> • 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.
<p>Fair</p> <p><i>ACR Appropriateness Criteria: Radiologic management of lower-extremity venous insufficiency</i> (Rochon et al., 2012)</p>	<p>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.”</p>

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 was 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. However, results from 2 large observational studies suggest that the risk of DVT after procedures such as EVLA and RFA may need further investigation. 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 systematic reviews or primary data publications. Three systematic reviews 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 systematic reviews. 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 2 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 are needed that address the methodological limitations of individual studies such as variation in outcome definitions and metrics, more consistent performance and reporting of statistical analyses, 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). Various devices or other products associated with these procedures have received FDA approval or clearance; an evaluation of specific devices or products is not within the scope of this health technology assessment (HTA).

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): E_c, congenital; E_p, primary; E_s, secondary (e.g., postthrombotic syndrome, trauma); E_n, no venous cause identified.
- Anatomic (A): A_s, superficial; A_d, deep; A_p, perforator; A_n, no venous location identified.
- Pathophysiologic classification (P): P_r, reflux; P_o, obstruction; P_{r,o}, reflux and obstruction; P_n, 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

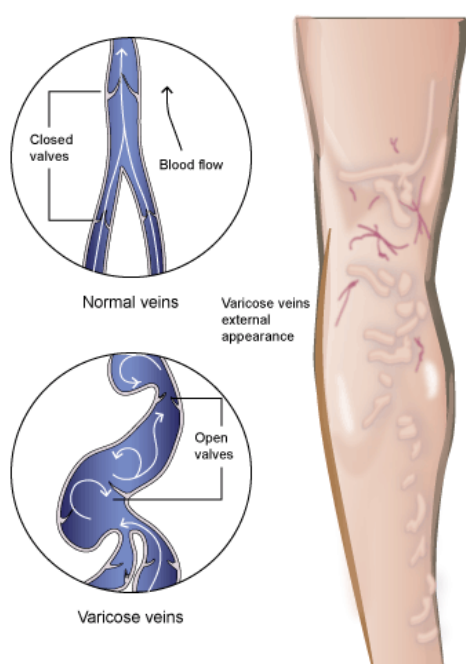
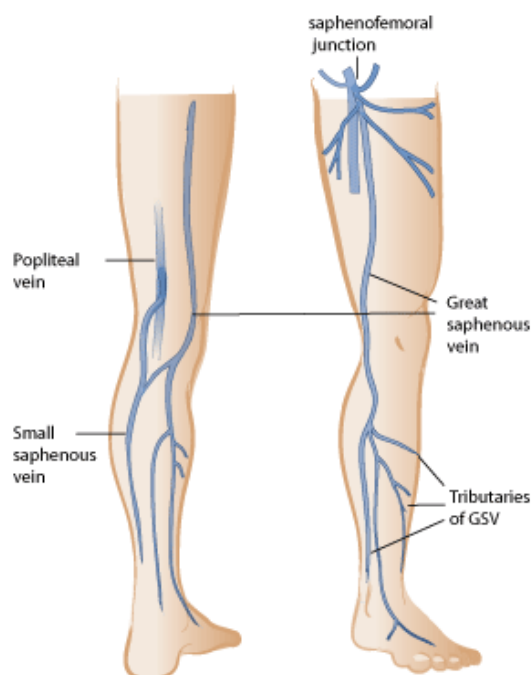


Figure 2. Great and Small Saphenous Veins



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 the vein when reflux is present. The goal of EVLA is to use laser energy to seal off the damaged portions of a vein 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 nanometers (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 are 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 may be 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. This therapy is also intended primarily for the treatment of varicose veins that result from GSV, SSV, or accessory vein reflux. 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.

The presence of thrombus in the vein segment to be treated is a contraindication for endovenous RFA (Medtronic, 2017).

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 liquid 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 sclerotherapy (FS) may be used for larger refluxing veins (Weiss et al., 2014; MFMER, 2017). FS may be 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 treatment 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. Varithena received FDA approval in 2013. Varithena is a 1% polidocanol endovenous microfoam (PEM) (also known as polidocanol injectable foam). It is a prescribed proprietary canister that generates a sterile, uniform, stable, low-nitrogen polidocanol 1% microfoam sclerosant intended for US-guided intravenous injection. Methods using liquid sclerosants to make foam sclerosants at the time of treatment by physicians have also been employed. This involves mechanically agitating a mixture of a liquid sclerosant and a gas (usually room air). The agitation is usually achieved by rapid, manual displacement of the mixture between 2 syringes joined by a straight connector (double-syringe system) or a 3-way valve (Tessari method). Physician-compounded foam sclerosants use a wide range of liquid to-gas ratios (from 1:1 to 1:8), resulting in foams generally containing 79% nitrogen and 21% oxygen, but of varying density, flow properties, and bubble size. Safety concerns have been raised regarding variability in bubble size and nitrogen concentration in physician-compounded foam sclerosants (Carugo et al., 2016).

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-inflammatories 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 Treatments for 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 (LNI) workers' compensation plan; and the HCA Medicaid (formerly Fee-for-Service) and the Managed Care (MCO) Medicaid 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 experiencing at least one of the CPT/HCPCS codes from Table I. Denied claims were excluded from the analysis.

Methods

Varicose vein treatments were calculated based on an individual experiencing a paid provider-patient face-to-face, on a specific date and including at least one of the CPT codes from Table I. Data evaluation included examining utilization by member; by treatment modality (Table I, Modality), and by total claims' cost incurred by a member on the date of their migraine/tension headache treatment (Total Claims).

Analyzing total claims for the date of service provided an enhanced view of the cost of a migraine/tension headache treatment (e.g., facility costs, labs, etc.). "Dollars" refers to paid dollars.

Table I. CPT Descriptions

36470	Injection of sclerosing solution; single vein: TYPE: Sclerosing injection
36471	Injection of sclerosing solution; multiple veins, same leg TYPE: Sclerosing injection
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated. TYPE: Radiofrequency Endovenous
36476	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure). TYPE: Radiofrequency Endovenous
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated. TYPE: Laser Endovenous Ablation
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure). TYPE: Laser Endovenous Ablation
37765	Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions. TYPE: Phlebectomy
37766	Stab phlebectomy of varicose veins, 1 extremity; more than 20 incisions. TYPE: Phlebectomy
37718	Ligation, division, and stripping, short saphenous vein. TYPE: Stripping
37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below. TYPE: Stripping
37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia. TYPE: Stripping

Table II. Definitions for Utilization and Cost Tables 3 - 10

Unique patients	Non-duplicated patient by year, reported by agency
Total treatments	Treatment defined as a single patient-provider face-to-face on a specific date.
Average treatment/patient	Total treatments/total unique patients
Dollars paid by total treatments	Paid dollars for all migraine and tension headaches treatments
Average dollars/patient	Total paid dollars for services received on the date of the treatment
Average dollars/treatment	Dollars paid on date of treatment/ Total treatments -- annual
Treatments/1,000 members	Count of total treatments divided by members greater than 17 years old.

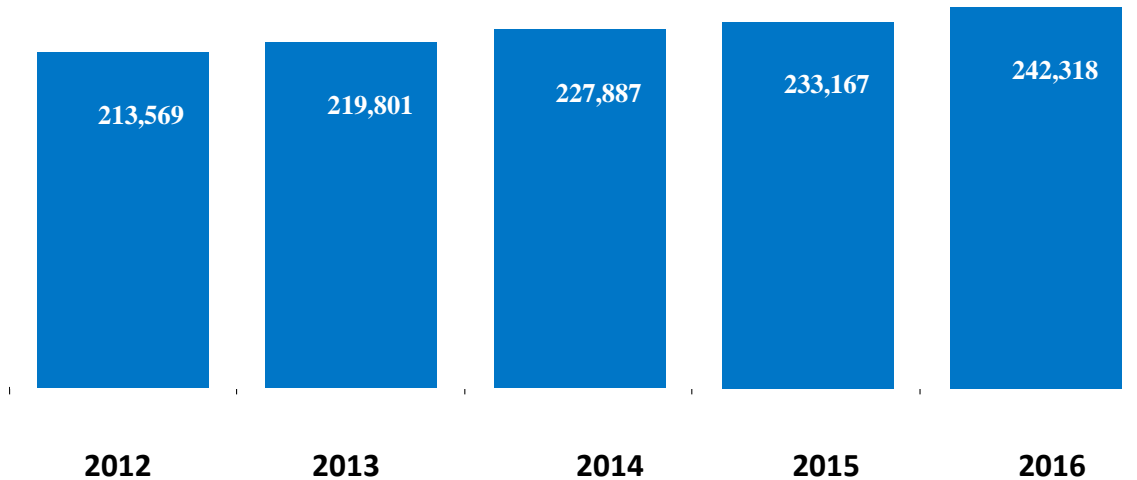
Demographics

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

PEBB Demographics 2012 – 2016

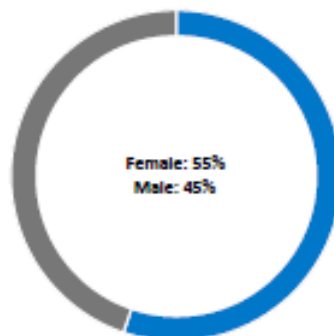
PEBB UMP and Medicaid/PEBB

PEBB population growth over time

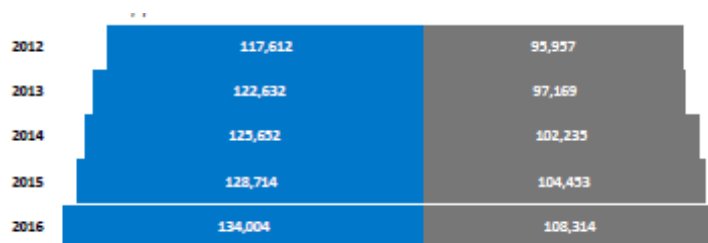
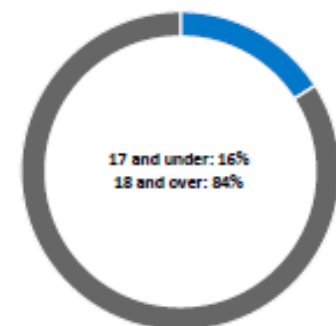


PEBB distribution by year: Gender and age cohorts with 5-year average

Five year average by Gender

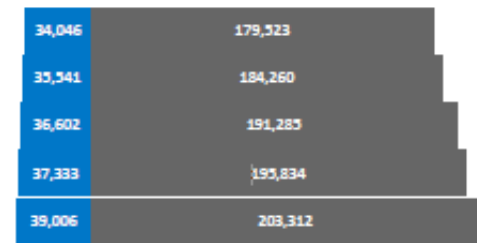


Five year average by age cohort



Female
Male

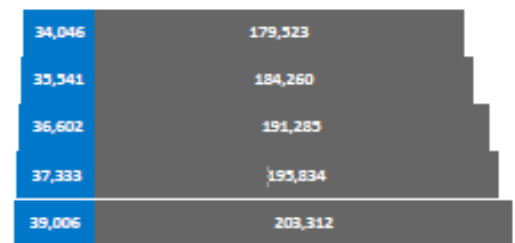
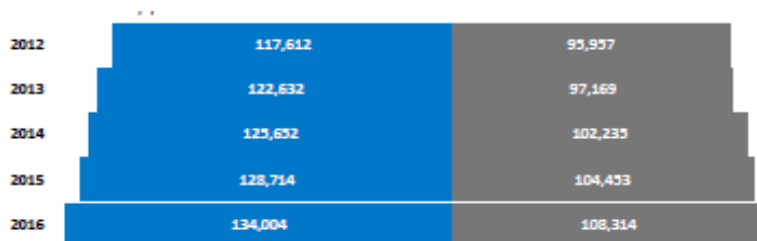
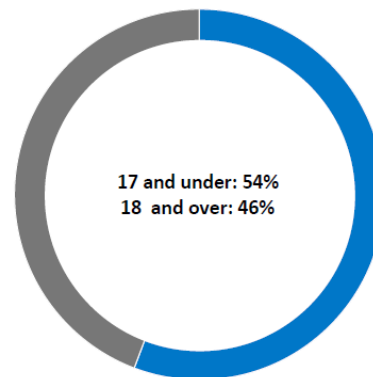
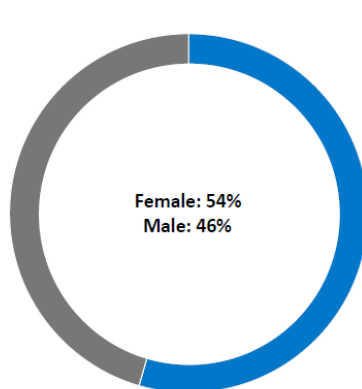
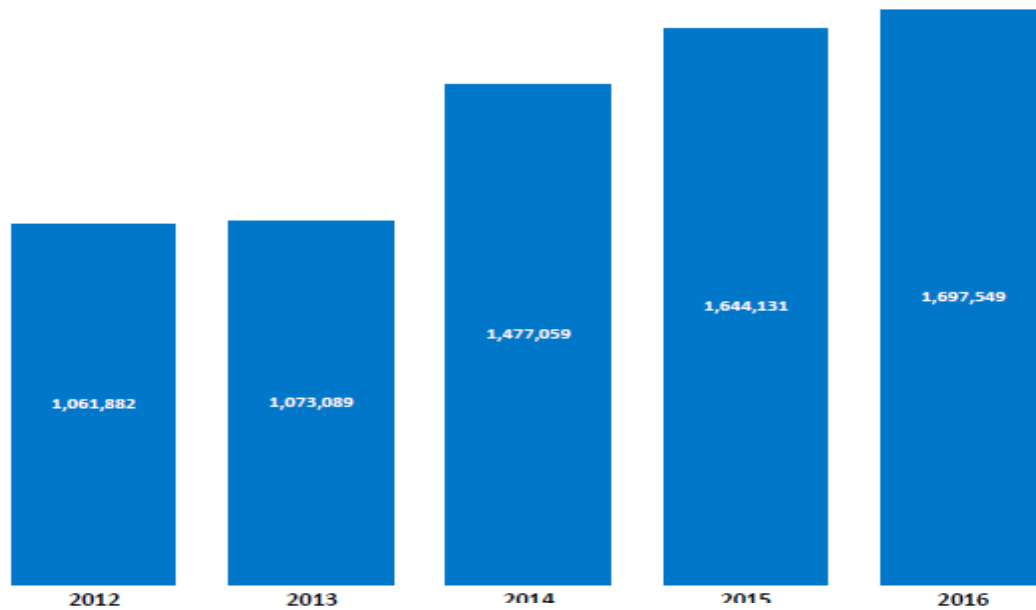
Distribution by gender



0-17
18+

Distribution by age

Medicaid Demographics 2012 – 2016 Managed and HCA



Female
Male

0-17
18+

2012 - 2016

PEBB/UMP, Medicare/PEBB, HCA Medicaid, MCO Medicaid, LNI

Varicose Vein Utilizations and Costs

Medicaid MCO	2012	2013	2014	2015	2016
Unique Patients	52	41	322	569	554
Total Treatments	96	80	626	1133	1140
Average Treatments/Patient	1.8	2.0	1.9	2.0	2.1
Dollars Paid by Total Treatment	\$128,340	\$143,757	\$644,554	\$871,035	\$825,727
Average Dollars/Patient	\$2,468	\$3,506	\$2,002	\$1,531	\$1,490
Average dollars/Treatment	\$1,337	\$1,797	\$1,030	\$769	\$724

Medicaid HCA [#]	2012	2013	2014	2015	2016
Unique Patients	35	9	7	15	14
Total Treatments	53	18	13	29	18
Average Treatments/Patient	1.5	2.0	1.9	1.9	1.3
Dollars Paid by Total Treatment	\$97,025	\$22,462	\$16,763	\$23,164	\$21,840
Average Dollars/Patient	\$2,772	\$2,496	\$2,395	\$1,544	\$1,560
Average dollars/Treatment	\$1,831	\$1,248	\$1,289	\$799	\$1,213

Combine: Medicaid MCO and HCA	2012	2013	2014	2015	2016
Treatments/1,000*	0.42	0.27	0.86	1.35	1.31

LNI	2012	2013	2014	2015	2016
Unique Patients	5	6	4	3	2
Total Treatments	19	29	11	6	3
Average Treatments/Patient	3.8	4.8	2.8	2.0	1.5
Dollars Paid by Total Treatment	\$25,481	\$27,017	\$13,809	\$6,581	\$4,150
Average Dollars/Patient	\$5,096	\$4,503	\$3,452	\$2,194	\$2,075
Average dollars/Treatment	\$1,341	\$932	\$1,255	\$1,097	\$1,383

Medicaid MCO	2012	2013	2014	2015	2016
Unique Patients	52	41	322	569	554
Total Treatments	96	80	626	1133	1140
Average Treatments/Patient	1.8	2.0	1.9	2.0	2.1
Dollars Paid by Total Treatment	\$128,340	\$143,757	\$644,554	\$871,035	\$825,727
Average Dollars/Patient	\$2,468	\$3,506	\$2,002	\$1,531	\$1,490
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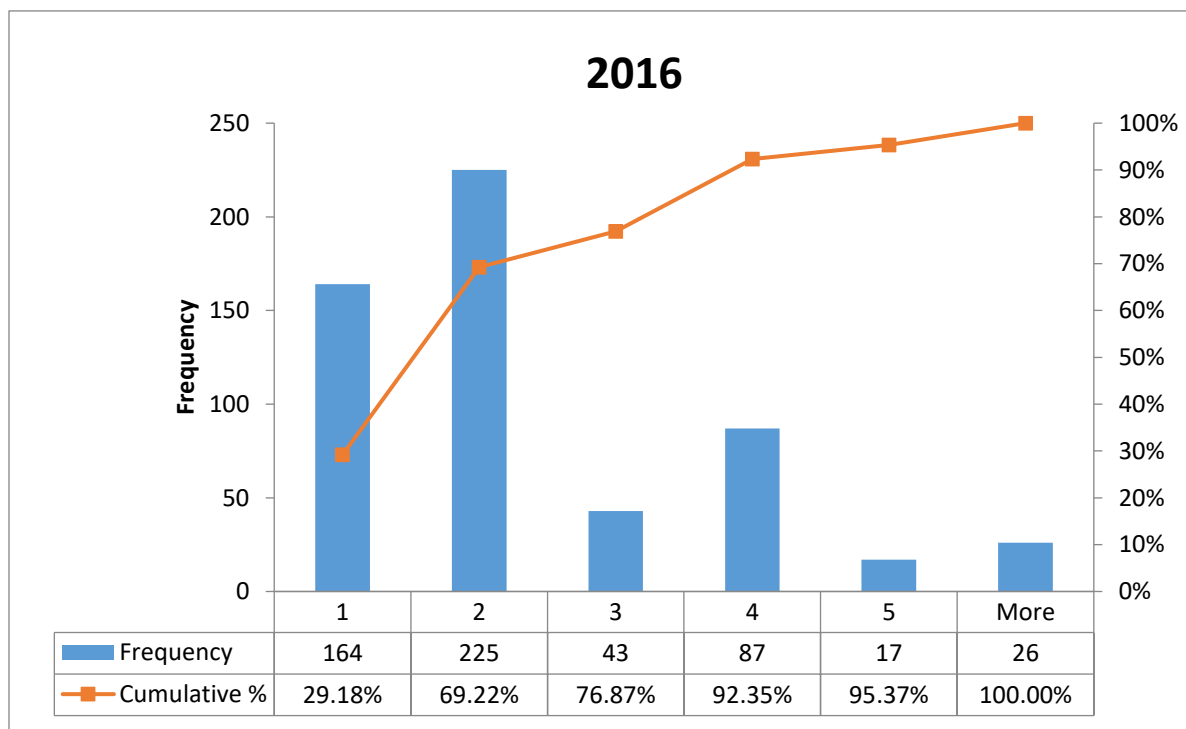
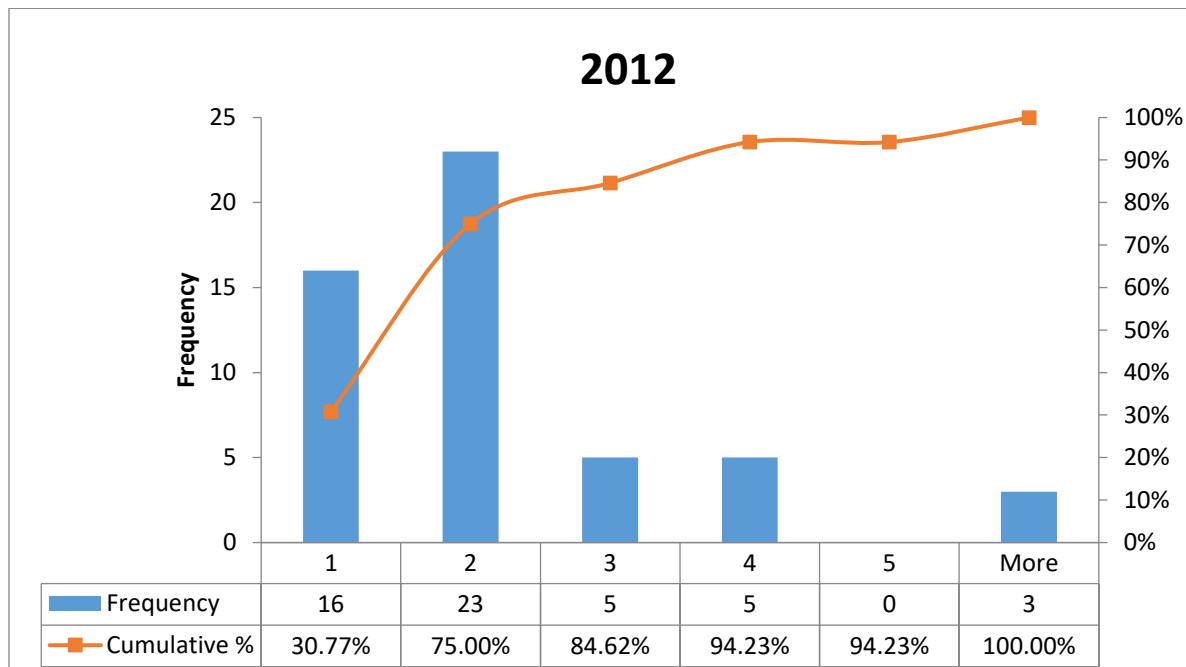
Medicaid HCA [#]	2012	2013	2014	2015	2016
Unique Patients	35	9	7	15	14
Total Treatments	53	18	13	29	18
Average Treatments/Patient	1.5	2.0	1.9	1.9	1.3
Dollars Paid by Total Treatment	\$97,025	\$22,462	\$16,763	\$23,164	\$21,840
Average Dollars/Patient	\$2,772	\$2,496	\$2,395	\$1,544	\$1,560
Average dollars/Treatment	\$1,831	\$1,248	\$1,289	\$799	\$1,213

Combine: Medicaid MCO and HCA	2012	2013	2014	2015	2016
Treatments/1,000*	0.42	0.27	0.86	1.35	1.31

Graphs 1 and 2
2012 and 2016

Medicaid MCO

Number of Treatments per Patient

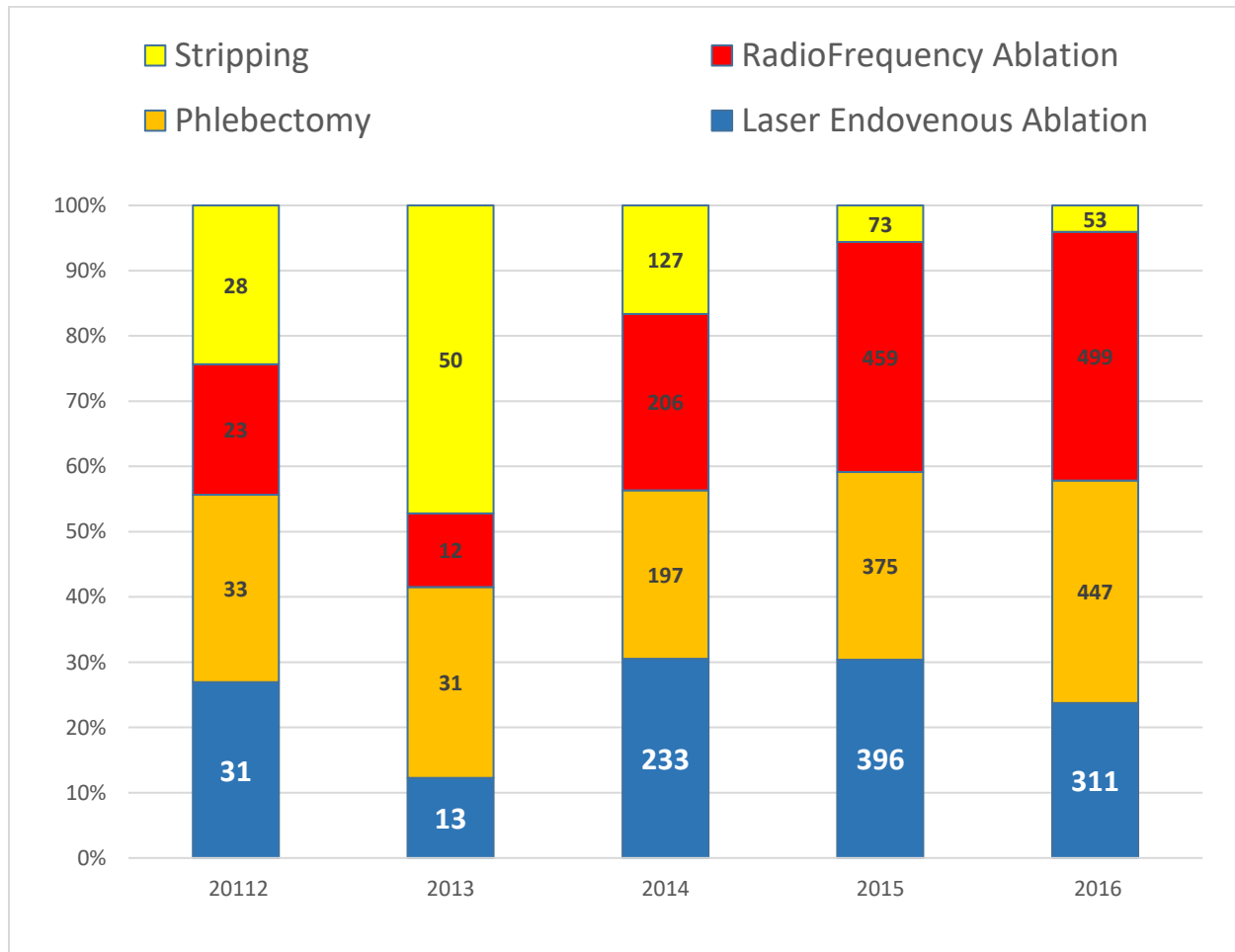


Graph 3
2012 - 2016

Medicaid MCO

Change in Distribution of Treatment Modalities Over Time

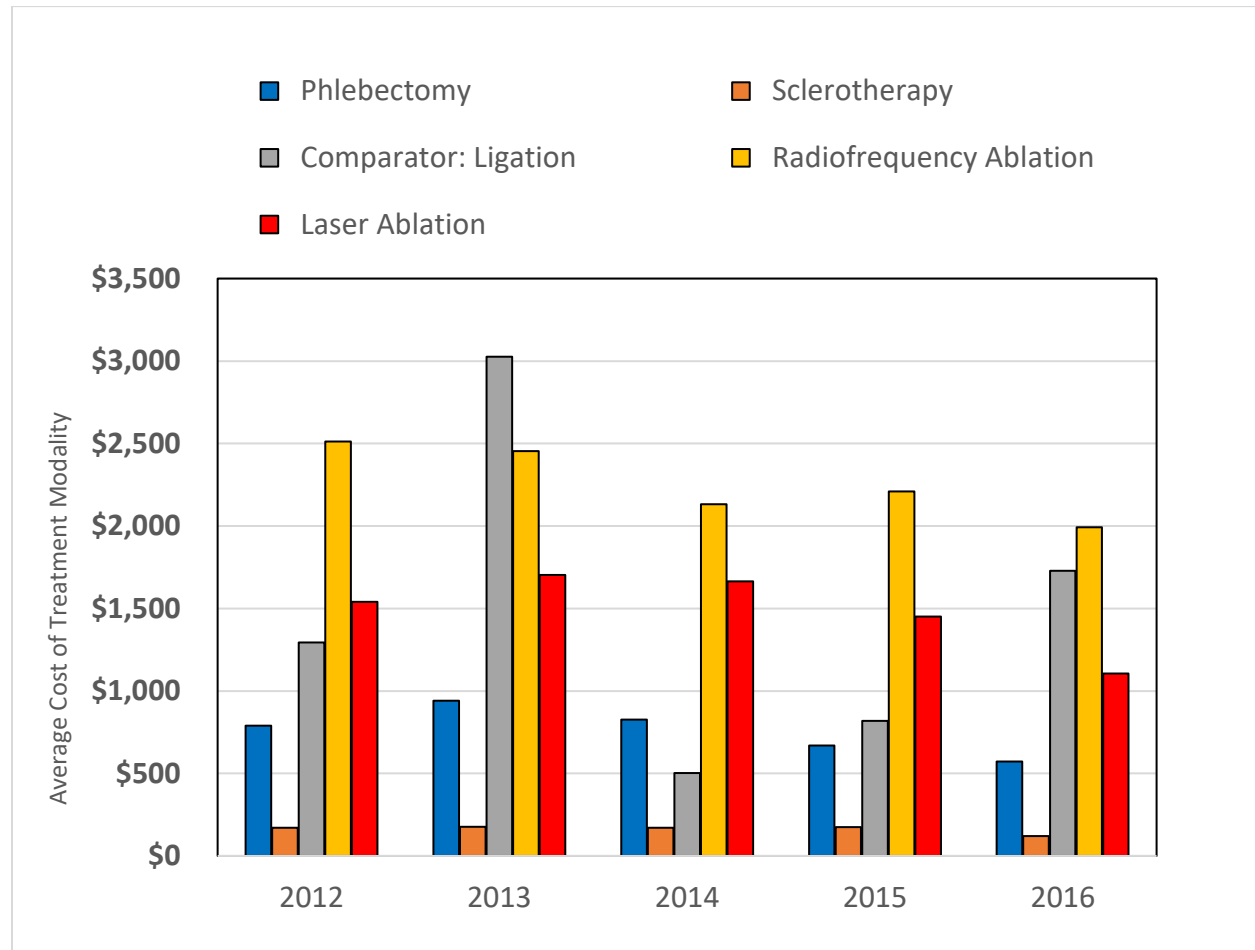
N = 1658



Graph 4
2012 - 2016
PEBB UMP

Average cost of varicose vein modalities by year

Note: Ligation Outliers in 2013; Outpatient with multiple modalities



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., 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 ($n \geq 500$), 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.

Initial searches of PubMed and the Centre for Reviews and Dissemination (CRD) electronic databases for relevant systematic reviews were conducted on September 6, 2016. 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. An update search of PubMed for systematic reviews was conducted on March 6, 2017. 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. A separate search was conducted for additional economic evaluations on February 1, 2017. In

preparing the final draft, searches of the PubMed and Embase databases were conducted on March 6, 2017, and March 9, 2017, to identify additional primary studies.

Practice Guidelines

In addition to guidelines found through the database and manual searches outlined above, the National Guidelines Clearinghouse and websites of professional organizations were also searched. 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 10**. The inclusion and exclusion criteria were derived in conjunction with the WA HTA program personnel based on feedback from the participating agencies.

Table 10. Inclusion/Exclusion Criteria

Key: CHIVA, French abbreviation for "Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire;" EVLA, endovascular laser ablation; pt(s), patient(s); QOL, quality of life; RCT(s), randomized controlled trial(s); RFA, endovascular radiofrequency ablation; VCSS, Venous Clinical Severity Score

Inclusion Criteria	Exclusion Criteria
Population: Adult pts being treated for varicose veins	Pts aged <18 yrs; pts being treated for complications from varicose veins or other forms of venous insufficiency (e.g., ulcer)
Intervention: EVLA, RFA, sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy)	Thermal ablation other than laser and RFA (e.g., steam ablation); CHIVA; cryostripping
Comparator: Vein ligation w/ or w/o stripping	Placebo/sham, other active comparators, or no comparison group
Outcomes: <u>Clinical outcomes</u> – 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) <u>Pt-centered outcomes</u> – Pt satisfaction/QOL; time to return to work or normal activity; pain <u>Safety</u> – 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 <u>Cost/cost-effectiveness outcomes</u>	

Inclusion Criteria	Exclusion 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.	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
Setting: Inpatient or outpatient	

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 794 citations for abstract and title review. After screening abstracts, 115 articles were selected for full-text review. A total of 23 publications were identified for data abstraction and assessment to answer the Key Questions. This includes 8 systematic reviews and 15 publications of primary data not already included in 1 or more of the systematic reviews. Eight of the 15 primary publications represent more recent data from studies that were included in the systematic reviews based on earlier publications.

See **Figure 3** for a summary of the literature search results.

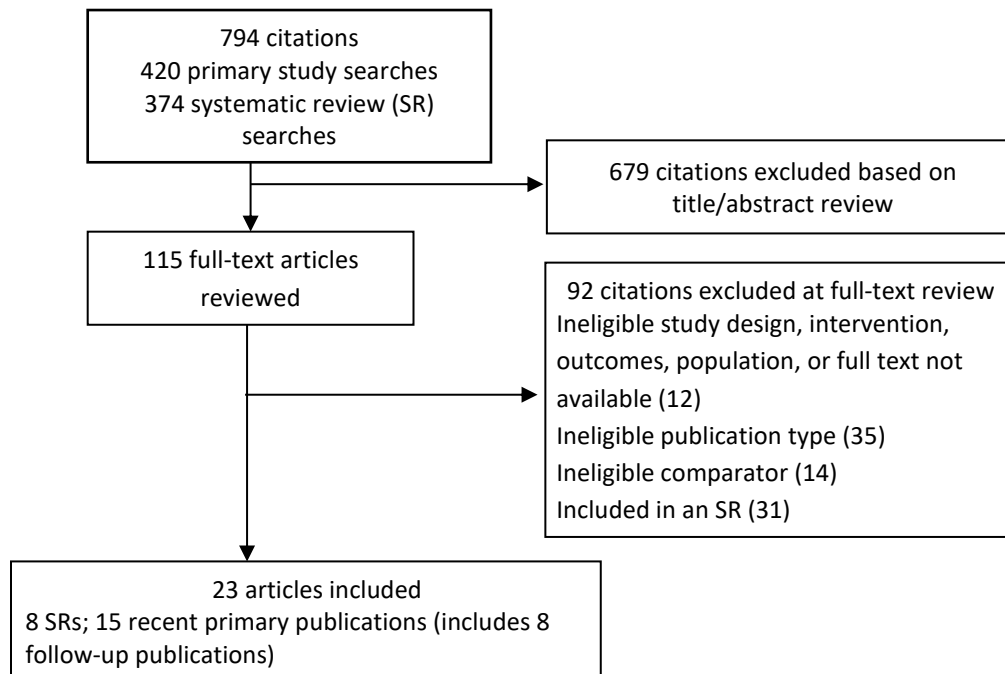
Included Studies

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.

Fifteen publications of primary data not already included in at least 1 of the systematic reviews were identified (Michaels et al., 2006; Eidson et al., 2011; Rasmussen et al., 2013b; Carruthers et al., 2014; Flessenkamper et al., 2014; Lin et al., 2014; Mozafar et al., 2014; Kalteis et al., 2015; O'Donnell et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016; Yin et al., 2017). Eight of these publications presented recent data from studies that contributed earlier data to 1 or more of the included systematic reviews (Rasmussen et al., 2013b; Flessenkamper et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016). Two U.S.-based cost studies were identified (Eidson et al., 2011; Lin et al., 2014).

Excluded Studies

See [Appendix IV](#) for a listing of the 92 studies that were excluded from analysis after full-text review.

Figure 3. Summary of Search Results

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 11** for a list of individual studies evaluated 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; however, 2 reviews included observational studies (Rathbun et al., 2012; Pan et al., 2014). Rathbun et al. (2012) included 104 studies; 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 liquid sclerotherapy or US-guided FS 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 included 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 11. 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; NR, not reported; pt, patient; RCT(s), randomized controlled trial(s); RFA, radiofrequency ablation; SR, systematic review; SSV, small saphenous vein; tx, treatment; tx'd, treated

Systematic Review Author, Year Total # Studies (Design) Patient Population Funding Source	# of Studies per Treatment vs Surgery Author, Year of Primary Studies
Carroll et al. (2013) n=34 (RCTs)* <i>Population:</i> Adults aged ≥16 yrs who are being tx'd for varicose veins <i>Funding:</i> NHS-NIHR HTA program (UK)	<ul style="list-style-type: none"> • <u>EVLA vs surgery (8 RCTs)</u>: 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 • <u>RFA vs surgery (6 RCTs)</u>: 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 • <u>FS vs surgery (10 RCTs)</u>: Bountouroglou et al., 2004; Liamis 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
Nesbitt et al. (2014) n=13 (RCTs) <i>Population:</i> Males and females of any age w/ varicose veins affecting the GSV system, confirmed on duplex ultrasound imaging,	<ul style="list-style-type: none"> • <u>EVLA vs surgery (8 RCTs)</u>: Beale et al., 2005; Rasmussen et al., 2007; Carradice et al., 2008; Darwood et al., 2008; Carradice et al., 2009; Flessenkaemper 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., 2013a

Systematic Review Author, Year Total # Studies (Design) Patient Population Funding Source	# of Studies per Treatment vs Surgery Author, Year of Primary Studies
<p>who were suitable for any of the tx options</p> <p><i>Funding source:</i> None</p>	<ul style="list-style-type: none"> • <u>RFA vs surgery (5 RCTs)</u>: 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 • <u>FS vs surgery (3 RCTs)</u>: 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
<p>Paravastu et al. (2016) n=3 (RCTs)</p> <p><i>Population:</i> Men and women aged ≥18 yrs who received tx for SSV varices</p> <p><i>Funding source:</i> None</p>	<ul style="list-style-type: none"> • <u>EVLA vs surgery</u>: Roopram et al., 2013 (VESPA trial); Samuel et al., 2013 (HELP2 trial) • <u>RFA vs surgery</u>: No studies identified for this comparison • <u>FS vs surgery</u>: Brittenden et al., 2014 (CLASS trial);
<p>Pan et al. (2014) n=13 (10 RCTs, 3 nonrandomized trials)</p> <p><i>Population:</i> Pts being tx'd for varicose veins</p> <p><i>Funding source:</i> NR</p>	<ul style="list-style-type: none"> • <u>EVLA vs surgery</u>: Medeiros et al., 2005; 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
<p>Rathbun et al. (2012) n=104* (20 RCTs, 82 observational studies, 2 not classified)</p> <p><i>Population:</i> Pts aged ≥19 yrs being tx'd for varicose veins, congenital venous malformations, or venous ulcers</p> <p><i>Funding source:</i> American College of Phlebology Foundation</p>	<ul style="list-style-type: none"> • FS vs surgery: A list of studies included in analyses of tx comparisons was not provided
<p>Rigby et al. (2009) n=9 (RCTs)</p>	<ul style="list-style-type: none"> • <u>Sclerotherapy vs surgery</u>: Hobbs et al., 1968; Chant et al., 1972; Hobbs et al., 1974; Doran et al., 1975; Jakobsen et al., 1979; Hobbs et al., 1984; Einarsson et al., 1993; Rutgers et al., 1994; Belcaro et al., 2000; Belcaro et al., 2003; deRoos et al., 2003

Systematic Review Author, Year Total # Studies (Design) Patient Population Funding Source	# of Studies per Treatment vs Surgery Author, Year of Primary Studies
<i>Population:</i> Pts being tx'd for cosmesis and/or symptomatic varicose veins <i>Funding source:</i> Sheffield Vascular Institute, UK; NHS R&D HTA Programme, UK; Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK; Chief Scientist Office, Scottish Government Health Directorates, Scottish Government, UK	
O'Donnell et al. (2016) n=7 (RCTs) <i>Population:</i> Pts tx'd w/ endovascular ablation (EVLA or RFA) for GSV incompetence <i>Funding source:</i> None	<ul style="list-style-type: none"> • EVLA vs surgery or cryostripping (4 studies): Disselhoff et al., 2008; Christenson et al., 2010; Rass et al., 2012; Rasmussen et al., 2013a; Rasumussen et al., 2013b • RFA vs surgery (3 studies): Lurie et al, 2005; Perala et al., 2005; Rasmussen et al., 2013b

*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

Eleven recent publications evaluating interventions of interest for this HTA, and not included in the systematic reviews described above, were identified for Key Question #1. Eight of these are follow-up publications related to previously published studies (Rasmussen et al., 2013b; Flessenkamper et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016), and 3 are publications unrelated to previously published studies (Michaels et al., 2006; Mozafar et al., 2014; Yin et al., 2017). Nine publications compare EVLA with surgery (Rasmussen et al., 2013b; Flessenkamper et al., 2014; Mozafar et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016), 5 publications compare sclerotherapy with surgery (Michaels et al., 2006; Rasmussen et al., 2013b; van der Velden et al., 2015; Cotton et al., 2016; Yin et al., 2017), and 1 publication compared RFA with surgery (Rasmussen et al., 2013b). 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=10) (Michaels et al., 2006; Rasmussen et al., 2013b; Flessenkamper et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016; Yin et al., 2017) to poor (n=1) (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: failure of procedure, technical recurrence, change in Venous Clinical Severity Score (VCSS), pain, symptomatic recurrence, QOL, and reintervention. 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 systematic reviews (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 of 467), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20 of 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]; $P<0.00001$; $I^2=51\%$) (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); $P=0.72$; $I^2=43\%$) (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 hazard ratio (HR) for EVLA compared with stripping was 0.84 (95% credible 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 (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 suggests no difference between EVLA and surgery (OR=0.72 [95% CI, 0.43-1.22]; $P=0.22$; $I^2=60\%$) 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]; $P=0.016$; $I^2=0\%$) (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]; $P=0.06$; $I^2=7\%$). The second analysis used 2-year follow up data from 5 studies and yielded RR=0.65 (95% CI, 0.37-1.12); $P=0.12$; $I^2=61\%$). 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]; $P=0.67$; $I^2=0\%$). 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); $P=0.63$; $I^2=62\%$ for clinical recurrence. The 2-year analysis yielded at RR=0.85 (95% CI, 0.64-1.11); $P=0.23$, $I^2=52\%$. 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% CrI, −0.94 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% CrI, −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 than 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, 1 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 the surgery group; 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 (RAND Corp.) (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 to 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]; $P=NR$). The investigators did not conduct a meta-analysis of data from the 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

Nine recent publications of studies comparing EVLA with surgery were identified (Rasmussen et al., 2013b; Flessenkamper et al., 2014; Mozafar et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; Flessenkamper et al., 2016; Gauw et al., 2016). Eight of these

represent recent publications of studies previously included in 1 or more of the systematic reviews discussed above (Rasmussen et al., 2013b; Flessenkamper et al., 2014; Kalteis et al., 2015; Rass et al., 2015; van der Velden et al., 2015; Cotton et al., 2016; 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). The recent follow-up 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; however, high attrition rates evident in some publications increase the uncertainty of conclusions based on these results.

In a 2013 publication, Rasmussen et al. (2013) present 3-year follow-up data for a study of 500 patients (580 legs) who received EVLA, RFA, FS, or surgery at 2 private surgical centers in Denmark. Data from an earlier publication from this study (Rasmussen et al., 2011) were included in the Carroll et al. (2013) and Nesbitt et al. (2014) systematic reviews, and the 3-year recurrence and retreatment data from this publication were included in analyses conducted by O'Donnell et al. (2016). Data on QOL and disease severity scores at 3 years were not previously included in the systematic reviews described above. At 3 years, overall 495 patients (573 legs) were analyzed. Analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for all the treatment groups; no between-group analysis was provided. Similarly, the Aberdeen Varicose Vein Severity Score (AVVSS) improved for all groups from 3 days to 3 years with no significant between-group differences. At baseline, the EVLA group mean (SD) AVVSS was 17.97 (9.0) and at 3 years it was 4.61 (5.8). In the surgery group, the mean (SD) scores were 19.3 (8.46) at baseline and 4.0 (4.87) at 3 years. There was no significant difference between groups at any time point with respect to the VCSS score; all groups showed statistically significant improvement from baseline. Specifically for the EVLA and surgery groups, the mean (SD) at baseline and 3 years were as follows: EVLA, 2.68 (2.25) at baseline and 0.34 (1.3) at 3 years; surgery 2.75 (1.62) at baseline and 0.3 (0.5) at 3 years. The authors conclude that EVLA and surgery are similar in the medium term with respect to VCSS and QOL.

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 midthigh 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. (2014 and 2016), published 2 follow-ups to a 2013 publication (Flessenkamper et al., 2013a). The 2013 publication reported results at 2 months; this publication was included in the Nesbitt et al. (2014) review. The 2014 and 2016 publications, respectively, report secondary outcome data for QOL at 2 months and clinical recurrence up to 6 years. The study involved comparisons between EVLA, high ligation/stripping (HL/S), and EVLA/high ligation (HL). Follow-up rates were: 76.4% (n=343) for questionnaire response at 2 months, and 74% at 2 years, 47% at 3 years, 39% at 4 years, 36% at 5 years, and 31% at 6 years for clinical recurrence. Analyses of patient responses to a survey using the Freiburg Life Quality Assessment-vein (FLQA-v) tool suggest no statistical difference between the treatment groups at 2 months in any of the categories measured. The categories included physical ailments, everyday life, social life, psychological wellbeing, therapy, satisfaction, and a global score. In the 2016 publication, 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 HL/S 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 Crossectomy 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 ± 2.87 in the EVLA group and 3.16 ± 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 ± 0.51 for EVLA and 1.39 ± 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 HL, 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 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 ($P=0.049$).

In a follow up publication from the CLASS trial, Cotton et al. (2016) present data on behavioral recovery, or return to activities, at 6 weeks. Other findings from the CLASS trial were included in the Paravastu et al. (2016) systematic review. Initially, 798 patients from 11 hospitals in the UK were randomized to either EVLA, UGFS, or surgery; at 6 weeks, 670 patients completed questionnaires, 655 of whom answered at least 1 question on the Behavioural Recovery After treatment for Varicose Veins (BRAVVO) questionnaire. Results suggest that for 13 of 15 behaviors, the EVLA group returned significantly faster than the surgery group. The surgery group resumed 1 activity faster than the EVLA group (taking a bath or shower), and there was no difference between groups for “wearing clothes that show the legs.”

An RCT by Mozafar et al. (2014) compared EVLA (n=30) with 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 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 the EVLA and RFA groups for comparison with pooled data from the surgery groups; results from this review are summarized above in the EVLA versus surgery section.

Failure of Procedure: 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 in each study group. The pooled percentage for the RFA patients was 4% (16 of 431), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20 of 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]; $P=0.88$; $I^2=70\%$).

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]; $P=0.47$; $I^2=39\%$). 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-analysis 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 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

One additional primary study publication comparing RFA with surgery not already included in 1 or more of the systematic reviews described above was identified for this Key Question. Rasmussen et al. (2013) published 3-year follow-up data from a study of 500 patients (580 legs) who received EVLA, RFA, FS, or surgery at 2 private surgical centers in Denmark. Data from an earlier publication from this study (Rasmussen et al., 2011) were included in the Carroll et al. (2013) and Nesbitt et al. (2014) systematic reviews, and 3-year data on recurrence and reoperation from this publication were analyzed by O'Donnell et al. (2016). At 3 years, overall 495 patients (573 legs) were analyzed. Disease severity and QOL outcomes were also reported in the Rasmussen et al. (2013b) publication but not synthesized in the systematic reviews described above. Analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for all the treatment groups; no between-group analysis was provided. Similarly, the AVVSS improved for all groups from 3 days to 3 years with no significant between-group differences. At baseline, the RFA group mean (SD) AVVSS was 18.74 (8.63) and at 3 years it was 4.43 (6.58). In the surgery group, the mean (SD) scores were 19.3 (8.46) at baseline and 4.0 (4.87) at 3 years. There was no significant difference between groups at any time point with respect to the VCSS score; all groups showed statistically significant improvement from baseline. Specifically for the RFA and surgery groups, the mean (SD) at baseline and 3 years were as follows: RFA 2.95 (2.06) at baseline and 0.44 (1.82) at 3 years; surgery 2.75 (1.62) at baseline and 0.3 (0.5) at 3 years. The authors conclude that RFA and surgery are similar in the medium term with respect to VCSS and QOL.

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 of 295), and the percentage for the conventional surgery (stripping and ligation) patients was 3% (20 of 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). Rigby et al. (2009) planned to conduct meta-analyses but found the studies too heterogeneous 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.

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]; $P=0.06$; $I^2=55\%$). 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]; $P=NR$).

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]; $P=NR$).

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. (2014) 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 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).

Additional Primary Studies: Sclerotherapy Versus Surgery

Five publications presenting information about sclerotherapy compared with surgery not already included in 1 or more of the systematic reviews described previously were identified for this Key Question (Michaels et al., 2006; Rasmussen et al., 2013b; van der Velden et al., 2015; Cotton et al.,

2016; Yin et al., 2017). Three of these are related to a previously published study (Rasmussen et al., 2013b; van der Velden et al., 2015; Cotton et al., 2016), and 2 are not related to a previously published study (Michaels et al., 2006; Yin et al., 2017).

Rasmussen et al. (2013) published 3-year follow-up data from a study of 500 patients (580 legs) who received EVLA, RFA, FS, or surgery at 2 private surgical centers in Denmark. Data from an earlier publication from this study (Rasmussen et al., 2011) were included in the Carroll et al. (2013) and Nesbitt et al. (2014) systematic reviews. At 3 years, overall 495 patients (573 legs) were analyzed. The *P* values presented in this publication represent a comparison across all 4 treatment groups; therefore, statistical significance between only 2 of the treatments was not reported. During 3 years of follow-up, 20 legs (Kaplan Meier estimate, 19.1%) in the UGFS group compared with 22 legs (20.2%) in the surgery group showed signs of varicose vein recurrence. In the UGFS group, 37 legs (Kaplan Meier estimate, 31.6%) were retreated during the 3-year follow-up compared with 18 legs (Kaplan Meier estimate, 15.5%) in the surgery group. Disease severity and QOL outcomes were also reported in this publication. Analysis of scores on the SF-36 showed statistically significant improvement from baseline to all time points for the mental component summary and physical component summary for all the treatment groups; no between-group analysis was provided. Similarly, the AVVSS improved for all groups from 3 days to 3 years with no significant between-group differences. At baseline, the UGFS group mean (SD) AVVSS was 18.38 (9.07) and at 3 years it was 4.76 (5.71). In the surgery group, the mean (SD) scores were 19.3 (8.46) at baseline and 4.0 (4.87) at 3 years. There was no significant difference between groups at any time point with respect to the VCSS score; all groups showed statistically significant improvement from baseline. Specifically for the UGFS and surgery groups, the mean (SD) at baseline and 3 years were as follows: UGFS 2.66 (1.45) at baseline and 0.15 (0.4) at 3 years; surgery 2.75 (1.62) at baseline and 0.3 (0.5) at 3 years. The authors conclude that UGFS and surgery are similar in the medium term with respect to clinical recurrence, VCSS, and QOL, but more patients in the UGFS group received retreatment ($P<0.0001$).

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 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).

In a follow-up publication from the CLASS trial, Cotton et al. (2016) present data on behavioral recovery, or return to activities, at 6 weeks. Other findings from the CLASS trial were included in the Paravastu et al. (2016) systematic review. Initially, 798 patients from 11 hospitals in the UK were randomized to either EVLA, UGFS, or surgery; at 6 weeks, 670 patients completed questionnaires, 655 of whom answered at least 1 question on the BRAVVO questionnaire. Results suggest that for 13 of 15 behaviors, the UGFS group returned significantly faster than the surgery group; there was no difference between groups for “taking a bath or shower” or “wearing clothes that show the legs”; median time to return to “activity behaviors” was 5 days for the UGFS group and 9 days for the surgery group.

The REACTIV trial included, among other comparisons, a comparison of liquid sclerotherapy with surgery. Results are presented in a 2006 HTA 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. QOL 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]). QOL 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 the EuroQOL 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).

A study comparing UGFS combined with HL of the GSV with GSV stripping plus multistab avulsion or transilluminated powered phlebectomy (TIPP) enrolled 177 patients with severe lower extremity varicosis (C4-C6). The primary outcome assessed in this study was cumulative reflux recurrence (any tortuous vein in the GSV area > 3 mm with reflux time > 0.5 seconds) at 12 months; secondary outcomes included complications, remission of symptoms, QOL, changes in hemodynamic parameters, patient satisfaction, and hospital costs. With respect to additional procedures because of technical failure, 29 patients in the UGFS group compared with 34 patients in the surgery group ($P=0.506$) experienced additional procedures. UGFS patients returned to normal activities faster than patients in the surgery

group; the average time to return to normal activities for each group was 5.4 days (range, 3-14) and 9.6 (range, 7-18); $P<0.001$. At 12 months, there was no difference between groups with respect to reflux recurrence (UGFS, 13.8%; surgery 13.5% [$P=0.995$]). While there was no difference between groups in change in disease severity scores at 6 months, the difference was statistically significant at 12 months. The median interquartile range (IQR) for the UGFS group was 2 (1), and it was 3 (2) for the surgery group ($P=0.006$). There was no difference between treatments with respect to change in AVVQ at 6 or 12 months or patient satisfaction at 12 months. Patient satisfaction was high in both groups (UGFS, 92.3%; surgery, 86.5%).

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 UGFS and liquid sclerotherapy in various doses and numbers of injections. Comparisons included open surgical procedures such as ligation or HL with or without stripping.

Six additional publications not already included in the systematic reviews described above were also identified for Key Question #2 (Carruthers et al., 2014; Mozafar et al., 2014; O'Donnell et al., 2015; Rass et al., 2015; Gauw et al., 2016; Yin et al., 2017). Two of these are follow-up publications related to studies already included in 1 or more systematic review (Rass et al., 2015; Gauw et al., 2016), and 4 are not related to previously published studies (Mozafar et al., 2014; Carruthers et al., 2014; O'Donnell et al., 2015; Yin et al., 2017). Details of included studies are presented in [Appendix V](#).

Study Quality

For those systematic reviews and individual studies that are included in Key Question #1 and Key Question #2, the quality assessment is described in the Key Question #1 section. The Dermody et al. (2013) review, and the Carruthers et al. (2014) and O'Donnell et al. (2015) publications were not

included in Key Question #1. Dermody et al. (2013) was rated as good quality based on the AMSTAR tool. The Carruthers et al. (2014) and O'Donnell et al. (2015) publications were rated as fair-quality large observational studies. Limitations of these studies include retrospective database analyses; 1 study did not adjust for baseline differences between groups (O'Donnell et al., 2015), and 1 study was limited to hospital-based procedures performed by vascular surgeons (Carruthers et al., 2014).

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 et al., 2016). 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 systematic reviews included data from some of the same primary studies. Table 11 includes lists of the individual studies included in each of the systematic reviews. 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.

Five additional publications not already included in the systematic reviews described above were also identified for this key question (O'Donnell et al., 2015; 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 3 are not related to previously published studies (Mozafar et al., 2014; Carruthers et al., 2014; O'Donnell et al., 2015). Two of these recent publications are observational studies (Carruthers et al., 2014; O'Donnell et al., 2015) 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 events were 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 and 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 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 collected from 2005 to 2011 and represent 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, sex, ethnicity, BMI, specialty of the treating surgeon, and venous ulceration did not significantly affect the odds of postoperative DVT. O'Donnell et al. (2015) analyzed diagnostic codes for adverse events from a large claims database (Truven Health). Patients included in the analysis ($n=131,887$) were treated with surgery, EVLA, RFA, sclerotherapy (liquid or foam), or multiple therapies from January 1, 2008 to June 30, 2012. The rate of diagnosed DVT within 30 days of EVLA was 701 of 22,980 (3.05%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins. The mortality rate among those diagnosed with DVT was 7 of 701 (1.0%) in the EVLA group and 6 of 277 (2.2%) in the surgery group. The rate of diagnosed PE within 30 days of EVLA was 58 of 22,980 (0.25%) and was 33 of 11,529 (0.29%) within 30 days of surgery. Mortality among those diagnosed with PE was 2 of 58 (3.4%) and 0 (0%) in the EVLA and surgery groups, respectively.

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" (Carroll et al., 2013, 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]; $I^2=0\%$) (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 results 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]; $P=0.0003$ $I^2=0\%$). Paravastu et al. (2016) found 2 studies that reported sural nerve injury. In 1 study, 8% (4 of 51) of EVLA patients compared with 27% (14 of 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 of 110) in the EVLA group and 31% (16 of 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 of 48] in the EVLA group, and 10% [5 of 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 of 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” (Carroll et al., 2013, 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]; $I^2=0\%$). 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 endovenous ablation (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, sex, ethnicity, 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” (Carroll et al., 2013, 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 results of the meta-analysis by Pan et al. (2014) for phlebitis did not reach statistical significance, but 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 of 52 events in the surgery group); pigmentation/skin bruising (1 study, 2 of 51 in EVLA arm, zero in the surgery arm); phlebitis (1 study, 3 of 51 in the EVLA arm, and 1 of 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 dyesthesia 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; the P value was not significant at any time point. Similarly, there was no difference between groups for depigmentation 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 dyesthesia (EVLA 3%, HL/S 2%) or hyperpigmentation (EVLA 0%, HL/S 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; $P=0.71$. O'Donnell et al. (2015) analyzed diagnostic codes for adverse events from a large claims database (Truven Health). Patients included in the analysis ($n=131,887$) were treated with surgery, EVLA, RFA, sclerotherapy (liquid or foam), or multiple therapies from January 1, 2008, to June 30, 2012. The rate of diagnosed DVT within 30 days of RFA was 954 of 21,637 (4.41%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins. The mortality rate among those with diagnosed DVT was 9 of 954 for the RFA-

treated patients and 6 of 277 (2.2%) among surgery patients. The rate of diagnosed PE within 30 days of RFA was 68 of 21,637 (0.31%) and was 33 of 11,529 (0.29%) within 30 days of surgery. Mortality among those diagnosed with PE was 1 of 68 (1.5%) and 0 (0%) in the RFA and surgery groups, respectively.

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. (2013) 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 they report 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. O’Donnell et al. (2015) analyzed diagnostic codes for adverse events from a large claims database (Truven Health). Patients included in the analysis ($n=131,887$) were treated with surgery, EVLA, RFA, sclerotherapy (liquid or foam), or multiple therapies from January 1, 2008, to June 30, 2012. The rate of diagnosed DVT within 30 days of sclerotherapy was 104 of 12,708 (0.82%) compared with 277 of 11,529 (2.40%) within 30 days of surgery for varicose veins. The mortality rate among those with diagnosed DVT was 0 (0%) for the sclerotherapy treated patients and 6 of 277 (2.2%) among surgery patients. The rate of diagnosed PE within 30 days of sclerotherapy was 19 of 12,708 (0.15%) and was 33 of 11,529 (0.29%) within 30 days of surgery. Mortality among those diagnosed with PE was 0 (0%) in both treatment groups. In the RCT conducted by Yin et al. (2017), 177 patients with severe lower extremity varicosis (C4-C6) were randomized to either UGFS combined with HL or to HL/S plus phlebectomy. No cases of PE were recorded in either group. One case of DVT was recorded in the UGFS group and there were 2 cases in the HL/S group.

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). Yin et al. (2017) reported paresthesia in 0 UGFS patients compared with 9 HL/S patients.

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). In a recent publication of results from an RCT conducted by Yin et al. (2017), there were 0 reported cases of incision/puncture site infections in the UGFS group, and 5 cases in the surgery group.

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]; $P=0.0001$). In the RCT conducted by Yin et al. (2017), the overall rate of minor complications was 27.7% in the UGFS group and 21.6% in the HL/S group ($P=0.406$). The overall rate of major complications was also not statistically significantly different between the groups (UGFS, 3.1% and HL/S, 2.7% [$P=0.897$]). In the UGFS group, there were 0 patients with hematoma compared with 5 patients in the surgery group. Patients with pain needing oral analgesics ($n=5$), saccular thrombophlebitis ($n=10$), and hyperpigmentation ($n=3$) were reported in the UGFS group but none of these events were reported in the surgery group.

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 systematic reviews 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, ethnicity, 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 systematic reviews 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 analyses 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 (Carroll et al., 2013) 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 EVLA 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, EVLA, 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, EVLA, phlebectomy, and surgery (Lin et al., 2014). 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 into 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 nights 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 L/S 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 HL/S 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.

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 (2011) and Management of venous leg ulcers: clinical practice guidelines (2014)

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 make 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:
 - HL 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).
 - HL 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 SSV incompetence with a GRADE of 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 of 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 UFS, and if UGFS 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).

European Society for Vascular Surgery (ESVS): Management of Chronic Venous Disease: Clinical Practice Guidelines (2015)

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, 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 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 noncomplicated 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, HL/S is recommended instead of HL only (recommendation 47, IA).
- Surgical stripping of the saphenous vein without HL 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, UGFS, 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 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, anterior accessory GSV [AAGSV], posterior accessory GSV [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 HL and invagination stripping to the level of the knee (2B), and recommend that when open surgery of the SSV is performed, it include HL 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).

American College of Phlebology (ACP): Guidelines – Treatment of refluxing accessory saphenous veins (2016)

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 UGFS 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.

American College of Radiology (ACR): ACR Appropriateness Criteria – Radiologic Management of Lower-Extremity Venous Insufficiency (2012)

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 SSV insufficiency resulting in intermittent pain and swelling without skin discoloration or ulceration. Rating 8 (usually appropriate) for endoluminal RF 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 RF 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 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 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 RF 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 DUS scanning, and all of the following criteria are met:
 - US-documented junctional reflux duration of 500 ms or greater in the saphenofemoral or saphenopopliteal vein to be treated.
 - Vein size is 4.5 mm or greater in diameter measured by US immediately below the SFJ or SPJ (not valve diameter at junction).
 - 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.

See Varicose Veins (Aetna Clinical Policy Bulletin No. [0050](#)).

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>). 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, including:

- 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, ERFA treatment and endovenous laser ablation (ELAS) (also known as endovenous laser treatment [EVL]), 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 into 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 saphenous veins (LSVs), SSVs, 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 LSVs, SSVs, 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 LSVs or SSVs may be considered medically necessary when all of the following are met:
 - All of the general criteria are met.
 - Minimum vein diameters where treatment is requested: LSV 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](#)).

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APPENDIXES

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. An update search of PubMed was conducted on March 6, 2017.

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 "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND (Review[ptyp] AND "2011/09/09"[PDat] : "2016/12/22"[PDat] AND English[lang])

Pubmed Systematic Review Search (3-6-17)

((varicose vein[All Fields] OR varicose veins[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND (Review[ptyp]) Sort by: Author Filters: Publication date from 2016/10/01 to 2017/03/06; English

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, targeted searches of PubMed, and reference lists of key publications were conducted on September 6, 2016, and March 6, 2017, for relevant primary data published subsequent to the review(s) selected for each indication. The initial search was limited to randomized controlled trials published in the English language from March 1, 2011, and the search date. Separate searches were conducted for additional economic evaluations and observational studies for Key Question #2 on February 1, 2017, and March 6, 2017.

PubMed searches

Search	Query
#10	Search #6 AND #7 Filters: Publication date from 2011/03/01 to 2016/09/16; English
#9	Search #6 AND #7 Filters: Publication date from 2011/03/01 to 2016/09/16
#8	Search #6 AND #7
#7	Search (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
#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	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	Query
#21	Search #19 NOT #20
#20	Search ("randomized controlled trial"[Publication Type]) OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])
#19	Search #18 AND #15

- #18 Search #16 AND #17
- #17 Search #13 OR #14
- #16 Search #5 OR #6 OR #7 OR #8 OR #11 OR #12
- #15 Search ("comparative study"[Publication Type]) OR "observational study"[Publication Type]
- #14 Search (venous insufficiency[MeSH Terms]) AND "therapy"[MeSH Subheading]
- #13 Search (varicose veins[MeSH Terms]) AND "therapy"[MeSH Subheading]
- #12 Search (vascular surgical procedures[MeSH Terms]) AND "mortality"[MeSH Subheading]
- #11 Search (vascular surgical procedures[MeSH Terms]) AND "complications"[MeSH Subheading]
- #8 Search (vascular surgical procedures[MeSH Terms]) AND "adverse effects"[MeSH Subheading]
- #7 Search (ablation techniques[MeSH Terms]) AND mortality[MeSH Subheading]
- #6 Search (ablation techniques[MeSH Terms]) AND "complications"[MeSH Subheading]
- #5 Search (ablation techniques[MeSH Terms]) AND "adverse effects"[MeSH Subheading]

Embase search

Search Query

- #8 'varicosis'/exp OR 'varicosis' AND ('laser surgery' OR 'endovenous laser ablation' OR 'catheter ablation' OR 'radiofrequency ablation' OR venacure OR 'pro v laser' OR cooltouch OR elves OR 'lumenis sharplan' OR medilas OR 'closure catheter' OR venefit OR ablation OR 'phlebectomy' OR 'sclerotherapy' OR 'endoscopic sclerotherapy' OR 'tetradecyl sulfate sodium' OR 'varithena' OR 'polidocanol' OR 'chemical ablation') AND 'randomized controlled trial'/de AND [1-3-2011]/sd NOT [6-3-2017]/sd
- #7 'varicosis'/exp OR 'varicosis' AND ('laser surgery' OR 'endovenous laser ablation' OR 'catheter ablation' OR 'radiofrequency ablation' OR venacure OR 'pro v laser' OR cooltouch OR elves OR 'lumenis sharplan' OR medilas OR 'closure catheter' OR venefit OR ablation OR 'phlebectomy' OR 'sclerotherapy' OR 'endoscopic sclerotherapy' OR 'tetradecyl sulfate sodium' OR 'varithena' OR 'polidocanol' OR 'chemical ablation') AND 'randomized controlled trial'/de
- #6 'varicosis'/exp OR 'varicosis' AND ('laser surgery' OR 'endovenous laser ablation' OR 'catheter ablation' OR 'radiofrequency ablation' OR venacure OR 'pro v laser' OR cooltouch OR elves OR 'lumenis sharplan' OR medilas OR 'closure catheter' OR venefit OR ablation OR 'phlebectomy' OR 'sclerotherapy' OR 'endoscopic sclerotherapy' OR 'tetradecyl sulfate sodium' OR 'varithena' OR 'polidocanol' OR 'chemical ablation')
- #5 'laser surgery' OR 'endovenous laser ablation' OR 'catheter ablation' OR 'radiofrequency ablation' OR venacure OR 'pro v laser' OR cooltouch OR elves OR 'lumenis sharplan' OR medilas OR 'closure catheter' OR venefit OR ablation OR 'phlebectomy' OR 'sclerotherapy' OR 'endoscopic sclerotherapy' OR 'tetradecyl sulfate sodium' OR 'varithena' OR 'polidocanol' OR 'chemical ablation'
- #4 'sclerotherapy' OR 'endoscopic sclerotherapy' OR 'tetradecyl sulfate sodium' OR 'varithena' OR 'polidocanol' OR 'chemical ablation'
- #3 'phlebectomy'
- #2 'laser surgery' OR 'endovenous laser ablation' OR 'catheter ablation' OR 'radiofrequency ablation' OR venacure OR 'pro v laser' OR cooltouch OR elves OR 'lumenis sharplan' OR medilas OR 'closure catheter' OR venefit OR ablation
- #1 'varicosis'/exp OR 'varicosis'

SEARCH FOR GUIDELINES

In addition to guidelines found through the database and manual searches outlined above, 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):

Step 1	<p><u>Systematic Review Appraisal</u></p> <p>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.</p>
Step 2	<p><u>Individual Study Appraisal</u></p> <ul style="list-style-type: none"> a. Initial rating according to study design <p><i>Good</i>: Randomized controlled trials</p> <p><i>Fair</i>: Nonrandomized trial (controlled, parallel-group, quasi-randomized)</p> <p><i>Poor</i>: 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)</p> <p><i>Very poor</i>: Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</p> c. Repeat for each study
Step 3	<p><u>Evaluation of Each Body of Evidence by Outcome, Key Question, or Indication</u></p> <ul style="list-style-type: none"> a. Initial quality designation according to best study design in a body of evidence b. Downgrade/upgrade c. Downgrade factors: Study weaknesses (Quality Checklists), lack of applicability, inconsistency of results, small quantity of data, publication bias (if adequate information is available) d. Possible upgrade factors: Strong association, dose-response effect, bias favoring no effect e. Assign final rating: High-Moderate-Low-Very Low f. Repeat for each outcome/question/application
Step 4	<p><u>Evaluation of Overall Evidence</u></p> <ul style="list-style-type: none"> a. Rank outcomes by clinical importance b. Consider overall quality of the evidence for each <i>critical</i> outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low
Step 5	<p><u>Evidence-Based Conclusion</u></p> <p>Overall quality of the evidence + balance of benefits and harms</p>

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.

Step 1	<u>Individual study appraisal:</u> <ol style="list-style-type: none"> Initial rating according to study design <i>Good:</i> Randomized controlled trials <i>Fair:</i> Nonrandomized trial (controlled, parallel-group, quasi-randomized) <i>Poor:</i> 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) <i>Very poor:</i> Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist Repeat for each study
Step 2	<u>Evaluation of each body of evidence by outcome, key question, or application:</u> <ol style="list-style-type: none"> Initial quality designation according to <i>best</i> study design in a body of evidence Downgrade/upgrade <i>Downgrade factors:</i> Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias <i>Possible upgrade factors:</i> Strong association, dose-response effect, bias favoring no effect Assign final rating: High-Moderate-Low-Very Low Repeat for each outcome/question/application
Step 3	<u>Evaluation of overall evidence:</u> <ol style="list-style-type: none"> Rank outcomes by clinical importance Consider overall quality of evidence for each <i>critical</i> outcome Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low
Step 4	<u>Evidence-based conclusion:</u> Overall quality of evidence + Balance of benefits and harms

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.

Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol*. 2013;66(2):140-150. PMID: [22863410](#).

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996;313(7052):275-283. PMID: [8704542](#).

Drummond M, Sculpher M. Common methodological flaws in economic evaluations. *Med Care*. 2005;43(7 Suppl):5-14. PMID: [16056003](#).

Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care*. 2005;21(2):240-245. PMID: [15921065](#).

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APPENDIX IV. Excluded Studies

The following 92 studies were excluded during full-text review.

Ineligible study design, intervention, outcomes, population, or full text not available (12)

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4. Burihan MC. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for great saphenous vein varices. *Sao Paulo Med J.* 2014;132(1):69.

5. Canadian Agency for Drugs and Technologies in Health. Endovascular thermal ablation technologies for treatment of varicose veins: A review of clinical effectiveness, safety, cost-effectiveness and guidelines – an update. CADTH Rapid Response Reports. 2014.
6. Canadian Agency for Drugs and Technology in Health. Foam sclerotherapy for treatment of varicose veins: A review of the clinical effectiveness, safety, cost-effectiveness, and guidelines. CADTH Rapid Response Reports. 2015.
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APPENDIX V. Evidence Tables

APPENDIX Va. Primary Studies

Key: AAGSV, anterior accessory GSV; AE, adverse event; avg, average; AVVSS, Aberdeen Varicose Vein Symptom Severity Score; BL, baseline; BMI, body mass index; BRAVVO, Behavioural Recovery After treatment for Varicose Veins; CIVIQ, Chronic Venous Insufficiency Quality-of-Life Questionnaire; CPT, Current Procedural Terminology; DVT, deep venous thrombosis; dx, diagnosis; EE, economic evaluation; ELVeS, Endo Laser Vein System; EQ-5D, EuroQoL; EVLA, endovenous laser ablation; FLQA-v, Freiburg Life Quality Assessment-vein; f/u, follow-up; grp(s), group(s); GSV, great saphenous vein; HL/S, high ligation and stripping; HR, hazard ratio; HVVSS, Homburg Varicose Vein Severity Score; hx, history; IQR, interquartile range; KM, Kaplan Meier; LS, liquid sclerotherapy; mm Hg, millimeter of mercury; nm, nanometer; NR, not reported; OR, operating room or odds ratio; postop, postoperative(ly); pt(s), patient(s); QALY, quality-adjusted life-years; (HR)QOL, (health related) quality of life; RCT, randomized controlled trial; RFA, radiofrequency ablation; SEPS, subfascial endoscopic perforator surgery; SF-36, SF-36 Health Survey (RAND Corp.); SFJ, saphenofemoral junction; S&L, stripping and ligation; SSV, small saphenous vein; STD or STS, sodium tetradecyl sulphate; sx, symptom(s); TIPP, transilluminated powered phlebectomy; tx, treatment (or therapy); tx'd, treated; UGFS, ultrasound-guided foam sclerotherapy; USD, U.S. dollars; VAS, visual analog scale; VCSS, Venous Clinical Severity Score

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
Michaels et al. (2006) Affiliation: Academic Vascular Unit, University of Sheffield, UK RCT <i>Time frame: January 2009 – January 2001</i> <i>F/u: 1 yr</i> <i>Funding source: National Health Technology Assessment Programme</i>	n=77 pts (52 at 1 yr) <i>Inclusion criteria:</i> Pts referred w/ a dx of varicose veins <i>Exclusion criteria:</i> Pts w/ deep venous insufficiency confirmed by duplex; allergy to sclerosant; diameter of varicose veins >2 cm; preexisting comorbidities that would preclude surgery; BMI >32 <i>Clinical hx/pt characteristics (LS grp; surgery grp):</i> Mean age (yrs): 47.0; 45.1 % men: 7.3%; 13.9% % smoker: 29.3%; 33.3% BMI (mean): 25.5; 26.3	Tx setting: 2 specialty vascular units Intervention: Sclerotherapy (liquid), 3% STD, then compression was applied using foam pads and a class II graduated compression stocking or bandage was applied all the way up the leg from the foot, after 2 wks further injections performed if necessary Control: Surgery, either outpatient or overnight hospital stay, long or short saphenous surgery depending on case, ligation and stripping, phlebectomies	<i>Clinical outcomes (Intervention grp; Control grp):</i> <u>Recurrence:</u> No difference at 1, 2, or 3 yrs <u>Symptomatic recurrence:</u> At 1 yr, no visible varicosities in 76% of surgery grp vs 39% of LS grp ($P<0.05$) <u>Pain:</u> VAS at 1 yr, mean (SD): LS, 0.77 (0.18); surgery, 0.83 (0.14); $P<0.05$ <u>QoL:</u> SF-36 1 yr: No difference SF-36 2 yrs: No difference EQ-5D 1 yr: LS, 0.80 (0.14); surgery, 0.85 (0.20); $P<0.05$ EQ-5D 2 yrs: No difference	<i>Limitations:</i> High attrition at 1 yr; nonblinded; underpowered <i>Study quality:</i> Fair <i>Conflicts of interest:</i> none

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
		done through small vertical stab incisions, compression applied at the end of surgery and left in place for a number of days (the 2 different clinics followed different postop procedures)	<p>Pt satisfaction (dissatisfied at 1 yr): LS, 4 of 28 (14.3%); surgery, 4 of 25 (16%); $P=NS$</p> <p><u>Complications:</u> Pain: LS, 1 (2.4%); surgery, NR Further LS required: LS, 1 (2.4); surgery, NR Wound problems: LS, 1 (2.4%); surgery, NR Phlebitis in first yr: LS, 2 (6.9%); surgery, NR Staining: LS, 15 (37%), surgery, 2 (6%) Allergy: LS, NR; surgery, 2 (5.6%) Urinary retention: LS, NR; surgery, 1 (2.8%) Tight bandage: LS, NR; surgery, 1 (2.8%) Wound infection: LS, NR; surgery, 1 (2.8%) Numbness: LS, NR; surgery, 7 (19%)</p>	
<p>Eidson et al. (2011) Scott & White Hospital, Texas A and M College of Medicine, Temple, TX</p> <p>Economic analysis (retrospective cohort)</p> <p><i>F/u:</i> 6 mos</p> <p><i>Time frame:</i> August 2002 – October 2007</p> <p><i>Funding source:</i> Non- industry</p>	<p>n=200 pts n=100 Open GSV/SSV stripping and ligations (S&L grp) n=100 RFA (RFA grp) Cost analysis based on 10 randomly selected records from each of 4 subgrps (RFA in tx room; RFA in OR; S&L inpatient; S&L outpatient)</p> <p><i>Inclusion criteria:</i> NR</p> <p><i>Exclusion criteria:</i> NR</p> <p><i>Clinical hx/pt characteristics (RFA grp; S&L grp):</i> Mean age (yrs): 57.7; 52.8 ($P=0.002$)</p>	<p>Tx setting: Community hospital, mixed inpatient and outpatient</p> <p>Intervention: RFA</p> <p>Control: Open GSV/SSV S&L</p> <p><i>Outcome measures:</i> Cost (avg of the actual direct costs)</p>	<p><i>Avg direct cost:</i> RFA grp (in tx room): \$906 RFA grp (in OR): \$2533 GSV S&L (inpatient): \$4241; excludes pts who had >1 nights hospital stay GSV S&L (outpatient): \$2622</p>	<p><i>Limitations:</i> Cost analysis is limited by statistically significant baseline differences b/t grps; small sample size; nonparallel grps</p> <p><i>Conflicts of interest:</i> One author was a proctor/consultant for VNUS Inc.</p>

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	% men: 14%; 34% ($P<0.05$) % smoker: NR CEAP 5/6: 26%; 18% ($P=NS$)			
Rasmussen et al. (2013) (f/u to Rasmussen et al., 2011) Danish Vein Centers and Surgical Center Roskilde, Naestved, Denmark RCT F/u: 3 yrs Time frame: February 2007 – July 2009 Funding source: Public Health Insurance Research Foundation of Denmark. RFA equipment provided by VNUS Medical Technologies.	n=500 pts (580 legs) <i>Inclusion criteria:</i> Pts w/ symptomatic varicose veins and GSV incompetence <i>Exclusion criteria:</i> Duplication of the saphenous trunk or an incompetent AAGSV, small saphenous or deep venous incompetence, previous DVT, arterial insufficiency, or a tortuous GSV rendering the vein unsuitable for endovenous tx <i>Clinical hx/pt characteristics (RFA grp; EVLA grp; UGFS grp; stripping grp):</i> Mean age (yrs): 51; 52; 51; 50 % men: 30%; 28%; 24%; 23% % smoker: NR CEAP 2-3 (% legs): 92%; 95%; 96%; 97% CEAP 4-6 (% legs): 8%; 5%; 4%; 3%	Tx setting: 2 private surgical centers Intervention: EVLA (ELVeS Ceralas D 980 or D 1470, bare fiber), RFA (ClosureFast), or UGFS (Aethoxysclerol 3%, 2 mL solution mixed w/ 8-mL air according to the method of Tessari) Control: PIN stripping (division and ligation of the GSV and division and ligation of all tributaries, GSV removed to just below the knee via a pin stripper) <i>Outcome measures (at 3 yrs):</i> Primary endpoint, closed or open GSV; secondary endpoints, recurrent varicose veins, frequency of reoperation, VCSS, QOL (AVVSS, SF-36)	<i>Clinical outcomes (RFA grp; EVLA grp; UGFS grp; stripping grp):</i> <u>Open and refluxing segments ≥ 10 cm in first 3 yrs, n (KM estimate):</u> 8 (7%); 8 (6.8%); 31 (26.4%); 8 (6.5%); $P<0.0001$ (P represents comparison across all tx grps, hypothesis that there are equal tx effects across all grps) <u>Legs w/ recurrent varicose veins, n (KM estimate):</u> 17 (14.9%); 24 (20%); 20 (19.1%); 22 (20.2%); $P=0.6596$ <u>Reoperation during 3 yrs f/u, n (KM estimate):</u> 12 (11.1%); 14 (12.5%); 37 (31.6%); 18 (15.5%); $P<0.0001$ VCSS, mean (SD) (at 3yrs): 0.44 (1.82); 0.34 (1.3); 0.15 (0.4); 0.3 (0.5); $P=NS$ AVVSS, mean (SD) (at 3 yrs): 4.43 (6.58); 4.61 (5.8); 4.76 (5.71); 4.0 (4.87); $P=NS$ SF-36: All grps showed statistically significant improvement from BL to all time points for the mental component summary and physical component summary; no between-grp analysis provided	<i>Limitations:</i> Nonblinded, differences in EVLA txs; differences in posttx care; moderate attrition <i>Study quality:</i> Fair <i>Conflicts of interest:</i> None
Carruthers et al. (2014) Boston Medical Center, Boston, MA	n=4364 pts	Intervention: Endovenous ablation (EVLA/RFA)	<i>Complications (Intervention grp; Control grp):</i>	<i>Limitations:</i> Retrospective database analysis; limited to hospital-based

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<p>Retrospective cohort study</p> <p><i>Time frame:</i> 2005-2011</p> <p><i>Funding source:</i> None</p>	<p><i>Inclusion criteria:</i> Pts treated for CVI in the American College of Surgeons National Surgical Quality Improvement Program data set (2005-2011)</p> <p><i>Exclusion criteria:</i> NR</p> <p><i>Clinical hx/pt characteristics (Intervention grp; Control grp):</i> Mean age (yrs): Overall, 52.4; EVLA/RFA, 53.3; surgery, 51.8 ($P<0.001$) % men: 33.6%</p>	<p>Control: Open surgery:</p> <p><i>Outcome measures:</i> Surgical site infection, DVT</p>	<p>50% decrease in the odds of DVT for pts undergoing open surgery compared w/ endovenous ablation (adjusted OR=0.52 [95% CI, 0.28-0.97]; $P=0.040$)</p> <p>Surgical site infection: Adjusted OR=2.56 [95% CI 1.19-5.50]; $P=0.016$ Those w/ venous ulcers (adjusted OR=2.55 [95% CI, 1.4-5.26]; $P=0.011$) and obese pts (adjusted OR=2.16 [95% CI, 1.10-4.24]; $P=0.025$)</p>	<p>procedures performed by vascular surgeons</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> None</p>
<p>Flessenkamper et al. (2014) Flessenkamper et al. (2016) (f/u to Flessenkamper et al., 2013) Center for Vascular Medicine, Helios Klinikum Emil von Behring, Berlin, Germany</p> <p>RCT</p> <p><i>F/u:</i> 2 mos and 6 yrs</p> <p><i>Timeframe:</i> May 2005 – July 2009</p> <p><i>Funding source:</i> German Society of Phlebology</p>	<p>n=449 pts randomized (343 completed FLQA-v at 2 mos; 139 [31%] assessed at 6 yrs)</p> <p><i>Inclusion criteria:</i> Pts w/ varicosity of the GSV; venous anatomy suitable for open and endoluminal tx; diameter of GSV 5 cm from SFJ had to be ≤ 16 mm</p> <p><i>Exclusion criteria:</i> Previous GSV surgery</p> <p><i>Clinical hx/pt characteristics:</i> % men: HL/S, 29.7%; EVLA/HL, 25%; EVLA, 31.7%</p>	<p>Intervention: EVLA/HL, inguinal crosssection followed by laser tx; EVLA (device from Biolitec, 980 nm, general anesthesia and local tumescent anesthesia</p> <p>Control: HL/S, junction ligature of the GSV, revision of the femoral vein up its dorsal circumference, followed by invagination stripping</p> <p>Miniphelebectomies were performed in all 3 grps</p> <p><i>Outcome measures:</i> Recurrence</p>	<p><i>Clinical outcomes (EVLA, EVLA/HL; HL/S):</i> Recurrence: No difference in time to clinical recurrence w/in 6-yr f/u (log rank test $P=0.5479$)</p> <p>FLQA-v Global Score, mean (SD): 1.7 (0.4) 95% CI, 1.6-1.7; 1.8 (0.5) 95% CI, 1.7-1.8; 1.7 (0.5) 95% CI, 1.6-1.8; $P=0.307$</p> <p>FLQA-v Physical Ailments, mean (SD): 1.6 (0.5) 95% CI, 1.5-1.7; 1.7 (0.6) 95% CI, 1.6-1.8; 1.6 (0.6) 95% CI, 1.5-1.7; $P=0.782$</p> <p>FLQA-v Everyday Life, mean (SD): 1.5 (0.6) 95% CI, 1.4-1.6; 1.5 (0.6) 95% CI, 1.4-1.6; 1.5 (0.6) 95% CI, 1.4-1.6; $P=0.706$</p> <p>FLQA-v Social Life, mean (SD): 1.2 (0.3) 95% CI, 1.1-1.2; 1.2 (0.4) 95% CI, 1.1-1.3; 1.2 (0.4) 95% CI, 1.1-1.3; $P=0.919$</p>	<p><i>Limitations:</i> Nonblinded, potentially underpowered; high overall attrition at 6 yrs; no adjustment for multiple testing for QOL analyses</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> None</p>

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			<p>FLQA-v Psychological Wellbeing, mean (SD): 2.3 (0.5) 95% CI, 2.2-2.4; 2.3 (0.6) 95% CI, 2.2-2.4; 2.2 (0.5) 95% CI, 2.1-2.3; $P=0.523$</p> <p>FLQA-v Therapy, mean (SD): 1.4 (0.5) 95% CI, 1.3-1.5; 1.5 (0.5) 95% CI, 1.4-1.6; 1.5 (0.6) 95% CI, 1.4-1.6; $P=0.418$</p> <p>FLQA-v Satisfaction, mean (SD): 2.1 (1.0) 95% CI, 1.9-2.3; 2.4 (1.1) 95% CI, 2.1-2.6; 2.2 (1.2) 95% CI, 2.0-2.5; $P=0.158$</p> <p><i>Complications (Intervention grp; Control grp):</i> NR at 6yrs</p>	
<p>Lin et al. (2014) Henry Ford Hospital, Detroit, MI</p> <p>Economic analysis (retrospective cohort)</p> <p><i>F/u:</i> NR</p> <p><i>Time frame:</i> January 1, 2010 – December 31, 2011</p> <p><i>Funding source:</i> NR</p>	<p>n=181 procedures in 2010; n=195 procedures in 2011</p> <p><i>Inclusion criteria:</i> Pts undergoing vein stripping, vein ablation procedures using EVLA or RFA, and miniphelebectomy of varicosities</p> <p><i>Exclusion criteria:</i> NR</p> <p><i>Clinical hx/pt characteristics (Intervention grp; Control grp):</i> Mean age (yrs): NR % men: NR % smoker: NR</p>	<p>Tx setting: Community hospital and a tertiary care hospital</p> <p>Intervention: RFA w/ VNUS ClosureFast (tertiary, office or community, OR); EVLA w/ 810 nm or 1470 nm laser fiber VenaCure EVLT system (tertiary, office); phlebectomy (tertiary, office or community, OR)</p> <p>Control: HL/S of GSV (tertiary, OR); HL/S (community, OR)</p> <p><i>Outcome measures:</i> Retrospective analysis of the professional and technical portions for the total charges, net revenue, total costs,</p>	<p><i>Costs per case (2010, USD):</i> RFA (tertiary, office): \$1074 RFA (community, OR): \$4884 EVLA (tertiary, office): \$1534 Phlebectomy (tertiary, office): \$3217 Phlebectomy (community, OR): \$5458 HL/S (tertiary, OR): \$12,788 HL/S (community, OR): \$4280</p> <p><i>Net profit or (loss) (2010, USD):</i> RFA (tertiary, office): \$845 RFA (community, OR): \$1123 EVLA (tertiary, office): \$835 Phlebectomy (tertiary, office): \$931 Phlebectomy (community, OR): \$1370 HL/S (tertiary, OR): \$3166 HL/S (community, OR): \$798</p> <p><i>Costs per case (2011, USD):</i> RFA (tertiary, office): \$1464 RFA (community, OR): \$6267</p>	<p><i>Limitations:</i> Perspective of a single healthcare system, costs reflect those associated only w/ each procedure and do not include other aspects of care</p> <p><i>Conflicts of interest:</i> None</p>

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		variable costs, and direct costs of procedures	EVLA (tertiary, office): \$1402 Phlebectomy (tertiary, office): \$2463 Phlebectomy (community, OR): \$5910 HL/S (tertiary, OR): \$6652 HL/S (community, OR): \$5626 <i>Net profit or (loss) (2011, USD):</i> RFA (tertiary, office): \$1011 RFA (community, OR): (\$496) EVLA (tertiary, office): \$711 Phlebectomy (tertiary, office): \$1217 Phlebectomy (community, OR): (\$362) HL/S (tertiary, OR): \$161 HL/S (community, OR): (\$585)	
Mozafar et al. (2014) Shohada-e Tajrish Medical Center, Tajrish Sq, Tehran, Iran RCT <i>F/u:</i> 18 mos <i>Time frame:</i> December 2010 – September 2012 <i>Funding source:</i> NR	n=65 pts <i>Inclusion criteria:</i> Age 18 to 65 yrs; insufficiency of GSV and the SFJ w/ reflux at least up to the knee; sx of GSV insufficiency or CVI <i>Exclusion criteria:</i> Pregnancy; active malignancy; arterial occlusive disease w/ 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 <i>Clinical hx/pt characteristics (EVLA grp; HL/S grp):</i> Mean age (yrs): 39.9; 39.26 ($P=0.88$) % men: 26.7%; 28.6%	Intervention: EVLA, local anesthesia, laser fiber was fixed, w/ a 980 nm diode laser in pulse mode, veins of pts w/ perforator insufficiency were surgically ligated through small incisions after EVLA Control: HL/S, SFJ access via groin incision, all branches of SFJ double ligated <i>Outcome measures:</i> Recurrence, AVVSS, pt satisfaction, complications	<i>Clinical outcomes (EVLA grp; HL/S grp):</i> <u>Recurrence:</u> 12 mos: 6.7% EVLA; 11.7% HL/S; $P=NR$ <u>Pain:</u> 1 wk: 16 (53.3%); 19 (54.3%); $P=0.939$ 3 mos: 1 (3.33%); 2 (5.7%); $P=NR$ 6 mos: 1 (3.33%); 2 (5.7%); $P=NR$ 12 mos: 1 (3.33%); 2 (5.7%); $P=NR$ 18 mos: 1 (3.33%); 2 (5.7%); $P=NR$ <u>Disease severity:</u> AVVSS: Lower in EVLA than HL/S at 12 mos ($P=0.019$) and 18 mos ($P=0.008$) <u>Pt satisfaction:</u> 6 mos: 28 (93.3%); 33 (94.3%); $P=0.999$ 12 mos: 28 (93.3%); 31 (88.6%); $P=0.678$ 18 mos: 28 (93.3%); 31 (88.6%); $P=0.678$ <u>Complications:</u> <u>DVT:</u> 0;0; $P=NR$	<i>Limitations:</i> Small sample size; nonblinded; randomization process not clearly described <i>Study quality:</i> Poor <i>Conflicts of interest:</i> NR

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
	C2: 14 (46.7%); 18 (51.4%) C3: 9 (30%); 10 (28.6%) C4: 6 (20%); 5 (14.3%) C5: 1 (3.3%); 2 (5.7%)		<u>Bruising:</u> 5 (16.7%); 12 (34.3%); $P=0.107$ <u>Dysesthesia:</u> 3 mos: 4 (13.3%); 6 (17.1%); $P=0.671$ 6 mos: 3 (10%); 4 (11.7%); $P=0.999$ 18 mos: 2 (6.7%); 3 (8.6%); $P=0.999$ <u>Dispigmentation:</u> 3 mos: 13 (43.3%); 8 (22.9%); $P=0.078$ 6 mos: 3 (10%); 4 (11.7%); $P=0.999$ 18 mos: 1 (3.33%); 4 (11.7%); $P=NR$ <u>Ulcer:</u> 3 mos: 1 (3.3%); 1 (2.86%) 6 mos: 1 (3.3%); 1 (2.86%) 18 mos: 1 (3.3%); 1 (2.86%)	
Kalteis et al. (2015) (5-yr f/u to Kalteis, 2008) BHS Hospital, Ried im Innkreis, Austria Study design: RCT F/u: 5-yrs Time frame: September 2004 – March 2006 Funding source: NR	n=100 pts randomized; 72 (75%) attended 5-yr f/u visit; EVLA/HL n=40 (83%), HL/S n=32 (68%) <i>Inclusion criteria:</i> Primary truncal varicosity of the GSV (CEAP-C Class 2-4) <i>Exclusion criteria:</i> Needing additional tx for an insufficient SSV or perforating vein <i>Clinical hx/pt characteristics</i> <i>(EVLA/HL grp; HL/S grp):</i> Mean age (yrs): 39.9; 39.26 ($P=0.88$) % men: 26.7%; 28.6% C2: 14 (46.7%); 18 (51.4%) C3: 9 (30%); 10 (28.6%) C4: 6 (20%); 5 (14.3%) C5: 1 (3.3%); 2 (5.7%)	Intervention: EVLA/HL, 810- nm diode laser, no tumescence Control: HL/S Stab avulsion of side tributaries completed the operation in both grps <i>Outcome measures:</i> QOL, patients' satisfaction	<i>Clinical outcomes (Intervention grp; Control grp):</i> <u>Recurrence:</u> No recurrence in 43% of HL+EVLA; 67% of HL/S; $P=0.049$ <u>Symptomatic recurrence:</u> Visible recurrence: HL+EVLA, 40%; HL/S, 40%; $P=NR$ <u>QOL:</u> CIVIQ-2: EVLA, 94; HL/S, 93; $P=NR$ Pt satisfaction: 87%, EVLA; 88%, HL/S rated good or very good; $P=NR$	<i>Limitations:</i> Nonblinded, moderate attrition; small sample size <i>Study quality:</i> Fair <i>Conflicts of interest:</i> None

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<p>O'Donnell et al. (2015) Cardiovascular Center, Tufts Medical Center, Boston, MA</p> <p>Retrospective database analysis</p> <p><i>F/u:</i> 30 days for AEs</p> <p><i>Time frame:</i> January 2007 – June 2012</p> <p><i>Funding source:</i> BTG International Ltd.</p>	<p>n=131,887 pts</p> <p>EVLA n=22,980 (17.4%); RFA n=21,637 (16.4%); sclerotherapy n=12,708 (9.6%); multiple tx n=63,033 (47.8%); surgery n=11,529 (8.7%)</p> <p><i>Inclusion criteria:</i> ≥1 ICD-9-CM diagnosis codes of 454 for varicose veins of lower extremities b/t 1/2008 to 6/2012; age ≥18 yrs; received invasive tx such as surgery, RFA, EVLA, or sclerotherapy; continuously eligible to receive medical and pharmacy services during 1-yr preindex period and 2-yr postindex period</p> <p><i>Exclusion criteria:</i> Received invasive procedure during preindex period; no evidence of invasive tx during assessment period; dx of varicose veins in any site other than lower extremities</p> <p><i>Clinical hx/pt characteristics (EVLA grp; RFA grp; sclerotherapy grp, multiple tx grp; surgery grp):</i> Mean (SD) age (yrs): 53.4 (13.0); 54.5 (13.2); 52.9 (12.7); 52.1 (12.0); 51.5 (12.3) % men: 27.8%; 29.3%; 8.5%; 25.6%; 25.6%</p>	<p>Intervention: EVLA, RFA, sclerotherapy, multiple txs (same day or deferred), grp assignment based on CPT code</p> <p>Control: Surgery, grp assignment based on CPT code</p> <p><i>Outcome measures:</i> AEs w/in 30 days of tx (DVT, PE), mortality</p>	<p><i>Complications (EVLA grp; RFA grp; sclerotherapy grp, multiple tx same day grp; multiple tx deferred grp; surgery grp):</i> <u>DVT:</u> 701/22,980 (3.05%); 954/21,637 (4.41%); 104/12,708 (0.82%); 1110/32,311 (3.44%); 795/30,722 (2.59%); 277/11,529 (2.40%)</p> <p><u>PE:</u> 58/22,980 (0.25%); 68/21,637 (0.31%); 19/12,708 (0.15%); 73/32,311 (0.23%); 75/30,722 (0.24%); 33/11,529 (0.29%)</p> <p><u>Mortality among pts w/ DVT:</u> 7/701 (1.0%); 9/954 (0.9%); 0 (0%); 9/1110 (0.8%); 4/795 (0.5%); 6/277 (2.2%)</p> <p><u>Mortality among pts w/ PE:</u> 2/58 (3.4%); 1/68 (1.5%); 0 (0%); 3/73 (4.1%); 2/75 (2.7%); 0 (0%)</p>	<p><i>Limitations:</i> Retrospective database analysis; no adjustment for baseline differences between grps</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> Authors are consultants and/or employees of ≥1 of the following companies: BTG International Ltd., Tactile Medical, Covidien, Xcenda</p>

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<p>Rass et al. (2015) RELACS trial (f/u to Rass et al., 2012)</p> <p>Affiliation: Saarland University Hospital, Homburg, Germany</p> <p>RCT</p> <p>F/u: 5 yrs</p> <p>Time frame: September 2004 – March 2007</p> <p>Funding source: none</p>	<p>n=400 pts randomized; per-protocol population n=346; (n=281 at 5 yrs)</p> <p><i>Inclusion criteria:</i> GSV incompetence w/ saphenofemoral and GSV reflux at least to the knee; primary symptomatic varicose veins, CEAP ≥2; age 18-65 yrs; ASA I-II</p> <p><i>Exclusion criteria:</i> Previous surgery in groin area (except herniotomy); anterior or posterior accessory saphenous vein incompetence in same limb; SSV incompetence requiring tx in the same limb; acute DVT or post-thrombotic syndrome; known thrombophilia; arterial occlusive disease; active malignancy; poor compliance or inability to understand study procedures; pregnant or breastfeeding</p> <p><i>Clinical hx/pt characteristics (EVLA grp; HL/S grp):</i> Mean age (yrs): 48; 50; $P=0.946$ % male: 33%; 30%; $P=0.563$ C2: 53 (29%); 47 (29%); $P=NR$ C3: 95 (52%); 76 (47%); $P=NR$ C4: 36 (20%); 35 (22%); $P=0.747$ C5: 1 (1%); 2 (1%); $P=NR$ C6: 0; 1 (1%); $P=NR$</p>	<p>Tx setting: 2 clinics (a university dermatology department and a private vein clinic) in Germany</p> <p>Intervention: EVLA w/ 810 nm diode laser (MedArt), bare fibers and Seldinger's technique delivered in a continuous pull back fashion</p> <p>Control: HL/S, transection of all groin tributaries to the second branching level, flush ligation of the SFJ, followed by stripping of the GSV to just below knee</p> <p>Incompetent perforators and varicose veins were ligated or removed by multiple stab avulsions in the same session in both grps</p> <p><i>Outcome measures:</i> Clinical recurrence, duplex recurrence in the groin, tx-related side effects, clinical and functional outcome HVVSS, disease specific QOL (CIVIQ-2), pts' satisfaction, cosmetic outcome, and recovery</p>	<p><i>Clinical outcomes (Intervention grp; Control grp):</i> <i>Recurrence:</i> 45% EVLA; 54% HL/S ($P=0.152$)</p> <p><i>Disease severity:</i> HVVSS: EVLA, 3.00 ± 2.87; HL/S, 3.16 ± 3.48; $P=0.789$</p> <p><i>QOL:</i> CIVIQ-2 scores: No difference Pt satisfaction: EVLA, 1.28 ± 0.51; HL/S, 1.39 ± 0.58; $P=0.078$</p> <p><i>Reintervention:</i> 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%; $P=0.028$ SSV surgery – EVLA, 1%; HL/S, 4%; $P=0.620$</p>	<p><i>Limitations:</i> Nonblinded; potentially underpowered; high attrition at 5 yrs; different procedures done at different clinics</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> One author received honoraria for lecturing and travel reimbursement by Covidien</p>

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
<p>van der Velden et al. (2015) MAGNA trial (follow-up to Biemans, 2013) Erasmus University Medical Center, Rotterdam, the Netherlands</p> <p>Study design: RCT</p> <p>F/u: 5 yrs</p> <p>Time frame: January 2007 – December 2009</p> <p>Funding source: NR</p>	<p>n=223 pts, 240 legs (193 [86.2%] of 224 legs evaluated at 5 yrs); pts w/ both legs randomized were not included in analyses for HRQoL outcomes</p> <p><i>Inclusion criteria:</i> Symptomatic pts w/ SFJ reflux and a refluxing GSV above the knee w/ a diameter of at least 5 mm (measured mid-thigh)</p> <p><i>Exclusion criteria:</i> 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 anesthetics or sclerosing agents, immobility, arterial disease (ankle : brachial pressure index <0.6), age <18 yrs and inability to provide written informed consent</p> <p><i>Clinical hx/pt characteristics (Intervention grp; Control grp):</i> Mean age (yrs): EVLA, 50.2; surgery, 52.5; UGFS 56.4 F:M ratio: EVLA, 49:21; surgery, 45:20; 44:20 UGFS % smoker: NR</p>	<p>Intervention: EVLA, 940 nm diode, nare tipped fiber, continuous pullback, tributaries removed by phlebectomies concomitantly or in a subsequent session, local tumescent anesthesia; UGFS, Tessari method w/ 1 mL of 3% polidocanol and 3 mL air, volume of injected foam determined by length and diameter of the vein (max of 10 mL per session), tributaries not tx'd systematically at time of UGFS, if needed UGFS of GSV was repeated b/t 3 mos and 1 yr after initial tx</p> <p>Control: Surgery, HL of SFJ followed by invagination stripping of the above-knee GSV and phlebectomies of varicose tributaries, w/ spinal or general anesthesia</p> <p><i>Outcome measures:</i> Obliteration or absence of the tx'd 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</p>	<p><i>Clinical outcomes:</i> 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 KM estimates of obliteration or absence of the GSV data provided in the publication)</p> <p>10 of 69 (14.5%) in the surgery grp and 59 of 77 (77%) in the UGFS grp ($P<0.001$)</p> <p>QoL (EVLA n=62; UGFS n=59; surgery n=52): NS differences between EVLA and surgery w/ respect to changes in CIVIQ Venous QoL scores or EQ-5D scores; $P=NR$ for surgery vs UGFS.</p> <p>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 tx'd w/ EVLA (OR=1.3 [95% CI, 1.1-1.5]).</p> <p>No difference in the distribution of class C between legs in the surgery grp (OR=1.4 [95% CI, 1.2-1.6]) and those tx'd w/ UGFS (OR=1.3 [95% CI, 1.1-1.5]).</p> <p>Reintervention and additional tx given ≥ 1 times (% limbs at 5yrs): Surgery, 10%; EVLA, 10%; UGFS, 32% (log rank test, $P<0.001$)</p> <p><i>Complications:</i> NR at 5yrs</p>	<p><i>Limitations:</i> Nonblinded; statistically significant differences in age between EVLA and other 2 grps at baseline; moderate attrition over 5 yrs</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> None</p>

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
		SFJ, progression of venous disease and number of reinterventions or additional txs		
<p>Cotton et al. (2016) (publication from the CLASS trial, f/u to Brittenden et al., 2014 and Brittenden et al., 2015) University of Aberdeen, Foresterhill, Aberdeen, UK</p> <p>RCT</p> <p>F/u: 6 wks</p> <p>Time frame: November 2008 – October 2012</p> <p>Funding source: National Institute for Health Research Health Technology Assessment Programme (project No. 06/45/02)</p>	<p>n=798 pts (670 completed 6-wk questionnaires; 655 completed at least on question on BRAVVO)</p> <p><i>Inclusion criteria:</i> Age ≥18 yrs; primary or unilateral symptomatic varicose veins (CEAP 2 or above); GSV or SSV; reflux exceeding 1 sec on duplex ultrasonography</p> <p><i>Exclusion criteria:</i> Current DVT; acute superficial vein thrombosis; GSV or SSV diameter <3 mm or >15 mm; tortuous veins unsuitable for EVLA or stripping; contraindications to UGFS or anesthesia</p> <p><i>Clinical hx/pt characteristics (EVLA grp; UGFS grp; surgery grp):</i> Mean age (yrs): 49.7; 49; 49.2 F:M ratio: 120:90; 162:124; 163:126 BMI, mean (kg/m²): 27.0; 27.1; 27.7 CEAP2, n (%): 113 (54.1); 169 (59.1); 147 (51.2) CEAP3, n (%): 28 (13.4); 35 (12.2); 39 (13.6) CEAP4, n (%): 56 (26.8); 74 (25.9); 90 (31.4) CEAP5/6, n (%): 12 (5.7); 8 (2.8); 11 (3.8)</p>	<p>Tx setting: 11 hospitals in the UK</p> <p>Intervention: EVLA, local anesthesia, pts offered UGFS after 6-wk f/u if required except at 1 clinic that performed concurrent phlebectomies; UGFS, Tessari technique using 0.5 mL STS to 1.5 mL air, 3% for GSV/SSV truncal veins and 1% for varicosities, max 12 mL foam injected per session</p> <p>Control: Surgery, proximal GSV/SSV L&S (all GSV) and concurrent phlebectomies performed under general or regional anesthetic as a day-case procedure</p> <p>Compression stockings applied after all txs</p> <p><i>Outcome measures:</i> Time to return to activities (BRAVVO questionnaire)</p>	<p><i>Pt-centered outcomes:</i> <u>Behavioral recovery</u> UGFS vs surgery: for 13 of 15 behaviors, the UGFS grp returned significantly faster than the surgery grp; there was no difference b/t grps for “taking a bath or shower” or “wearing clothes that show the legs”; median time to return to “activity behaviors”: UGFS, 5 days; surgery, 9 days. <u>Behavioral recovery</u> EVLA vs surgery: for 13 of 15 behaviors, the EVLA grp returned significantly faster than the surgery grp; the surgery grp resumed 1 activity faster than the EVLA grp (taking a bath or shower); there was no difference b/t grps for “wearing clothes that show the legs”</p>	<p><i>Limitations:</i> Nonblinded; only 8 of 11 centers offered EVLA; 17% of participants did not complete questionnaire</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> None</p>

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
Gauw et al. (2016) (5-yr f/u to Pronk, 2010) Centrum Oosterwal, the Netherlands RCT F/u: 5 yrs Time frame: NR Funding source: None	n = randomized 130 legs (121 at 5 yrs) <i>Inclusion criteria:</i> Length of the incompetent GSV of ≥ 15 cm measured from the SFJ downward, w/ a diameter >3 mm <1.5 cm <i>Exclusion criteria:</i> Having a previous surgical tx or an intrafascial GSV length of <15 cm, pregnancy, and immobility <i>Clinical hx/pt characteristics (Intervention grp; Control grp):</i> Mean age (yrs): EVLA, 49 (11.0); SFL/S, 50 (10.5) % men: EVLA, 26%; SFL/S, 22% BMI, mean (SD): 25 (3.3); 24.5 (3.7) C2: 29 (47%); 26 (38%) C3: 36 (53%); 29 (47%) C4: 5 (7%); 4 (6%) C5: 1 (1%); 0 (0%)	Tx setting: Single center, outpatient specialty clinic Intervention: EVLA, bare fiber 980 nm diode (Biolitec), continuous wave energy, tumescent anesthesia Control: SFL/S, groin incision, HL and division of GSV flush at SFJ, tributaries divided and ligated, followed by inversion stripping of the GSV, tumescent anesthesia <i>Outcome measures:</i> Recurrence at 10 yrs (publication reports 5-yr data), EQ-5D questionnaire, relief of venous sx, postop complications, CEAP stage, and pt satisfaction, long-term posttreatment complications such as paresthesia and hyperpigmentation	<i>Clinical outcomes (EVLA grp; SFL/S grp):</i> <u>Recurrence:</u> EVLA, 49%; SFL/S, 23%; log-rank test $P=0.02$ <u>Reintervention:</u> Did not receive reintervention: EVLA, 70%; saphenofemoral ligation, 80%; log-rank test $P=0.20$ <i>Complications (EVLA grp; SFL/S grp):</i> <u>Nerve damage:</u> Persistence of pretibial neurosensory deficit for 5 yrs in 1 pt (1/66 [2%]) who received saphenofemoral L/S and no occurrences of this in the EVLA grp	<i>Limitations:</i> Nonblinded; potentially underpowered (enrollment ceased after 1-yr interim analysis) <i>Study quality:</i> Fair <i>Conflicts of interest:</i> None
Yin et al. (2017) Department of Vascular Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China RCT F/u: 1 yr	n=177 pts (139 analyzed) <i>Inclusion criteria:</i> Primary GSV insufficiency, CEAP C4-C6 and EpAsPr (primary, superficial, and having reflux) <i>Exclusion criteria:</i> Previous intervention on the varicose veins by any technique; ventricular or	Tx setting: Hospital Intervention: UGFS and ligation, spinal anesthesia, SFJ exposed and ligated via 2-3 cm groin incision, foam created via Tessari method using sclerosant to air ratio of 1:4, 1% polidocanol, additional foam injections if	<i>Clinical outcomes (UGFS/L grp; HL/S+phlebectomy grp):</i> <u>Additional procedures b/c of technical failure, n:</u> 29; 34; $P=0.506$ <u>Time to return to normal activities, days (range):</u> 5.4 (3-14); 9.6 (7-18); $P<0.001$ Reflux recurrence rate at 12 mos, (%): 13.8%; 13.5%; $P=0.995$ Change in VCSS at 6 mos, median (IQR): 4 (4); 4 (3); $P=0.869$	<i>Limitations:</i> Nonblinded, moderate attrition, advanced disease among pt population <i>Study quality:</i> Fair <i>Conflicts of interest:</i> NR

Authors/Study Design	Study Population	Treatment	Results	Quality/Comments
<p><i>Time frame:</i> January 2012 – December 2014</p> <p><i>Funding source:</i> NR</p>	<p>atrial septal defect; previous DVT; pregnancy, malignancy, severe cardiac, pulmonary, or renal disease; immobility or noncompliance w/ compressive tx; primary deep vein insufficiency; contraindication to FS</p> <p><i>Clinical hx/pt characteristics (UGFS/L grp; HL/S+phlebectomy grp):</i> Mean age (yrs): 53.2; 54.8 % male: 36.6%; 38.9% CEAP4, n (%): 48 (58.5); 51 (53.7) CEAP5, n (%): 24 (29.3); 33 (34.7) CEAP6, n (%): 10 (12.2); 11 (11.6) Mean (range) GSV diameter, mm: 8.7 (4.0-15.6); 8.0 (4.5-14.5)</p>	<p>residual patent tributaries detected</p> <p>Control: HL/S+phlebectomy, SFJ exposed and ligated via 2-3 cm groin incision, GSV trunk stripped to below the knee, dilated distal GSV trunk and varicose tributaries in the calf removed by standard multistab avulsion or TIPP</p> <p>Enlarged perforators >2 mm ablated by SEPS in both grps</p> <p><i>Outcome measures:</i> Reflux recurrence (any tortuous vein in the GSV area >3 mm w/ reflux >0.5 secs) at 12 mos; complications, remission of sx, QOL, changes in hemodynamic parameters, pt satisfaction, costs, avg operating and recovery times</p>	<p>Change in VCSS at 12 mos, median (IQR): 2 (1); 3 (2); $P=0.006$ Change in AVVQ at 6 mos, median (IQR): 10 (8); 11 (9.5); $P=0.647$ Change in AVVQ at 12 mos, median (IQR): 7 (6.5); 8 (9); $P=0.413$ Pt satisfaction, %: 92.3%; 86.5%; $P=0.270$</p> <p><i>Complications (UGFS/L grp; HL/S+phlebectomy grp):</i> <u>Overall minor complication rate (%)</u>: 27.7%; 21.6 %; $P=0.406$ Hematoma, n: 0; 5 Incision/puncture site infection, n: 0; 2 Paresthesia, n: 0; 9 Pain needing oral analgesics, n: 5; 0 Saccular thrombophlebitis, n: 10; 0 Hyperpigmentation, n: 3; 0 Overall major complication rate (%): 3.1%; 2.7%; $P=0.897$ PE, n: 0; 0 DVT, n: 1; 2 Visual disturbance, n: 0; 0 Respiratory embarrassment, n: 1; 0 Headache/cough/dizziness, n: 0; 0</p> <p><i>Hospital costs:</i> \$1575; \$853; $P<0.001$</p>	

APPENDIX Vb. Systematic Reviews

Key: AVVQ, Aberdeen Varicose Veins Questionnaire; BMI, body mass index; CADTH, Canadian Agency for Drugs and Technologies in Health; COI, conflict of interest; CRD, Centre for Reviews and Dissemination; CrI, credible interval; DVT, deep vein thrombosis; EQ-5D, EuroQol; 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; MD, mean difference; mmHg, millimeter of mercury; NA, not available; NHS, National Health Service; NIHR, National Institute for Health Research; nm, nanometer; 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, radiofrequency ablation; RFA-CF, ClosureFAST catheter; RFA-CP, ClosurePLUS catheter; RoB, risk of bias; RR, risk ratio; SR, systematic review; SSV, short saphenous vein; SVT, superficial venous thrombosis or thrombophlebitis; tx, treatment (or therapy); tx'd, treated; UGFS, ultrasound-guided foam sclerotherapy; UK, United Kingdom; VAS, visual analog score; VCSS, Venous Clinical Severity Score

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
<p>Carroll et al. (2013)</p> <p><i>Aim:</i> To evaluate the clinical effectiveness, safety, and cost-effectiveness of the minimally invasive techniques of FS, EVLA, and RFA compared w/ other techniques, including traditional surgical techniques, LS, and conservative management, in the management of varicose veins</p> <p>EVLA vs surgery studies: Carradice et al., 2011a and Carradice et al.,</p>	<p><i># included studies:</i> Total: 34 RCTs (54 papers); EVLA vs surgery 8 RCTs; RFA vs surgery 6 RCTs; FS vs surgery 10 RCTs</p> <p><i>Search dates:</i> Inception to July 2011</p> <p><i>Data sources:</i> MEDLINE; Embase; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library; Biological Abstracts; Science Citation Index; Social Sciences Citation Index; Conference Proceedings Citation Index-Science; UK Clinical</p>	<p><i>Study design:</i> RCTs</p> <p><i>Sample size:</i> 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</p> <p>EVLA vs surgery: Total: 1221 Range: 20-276</p> <p>RFA vs surgery: Total: 642 Range: 16-249</p> <p>FS vs surgery:</p>	<p>Initial failure of the procedure and retx (w/in 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</p>	<p><i>Effectiveness and pt-centered outcomes:</i></p> <p><u>Failure of procedure (12 studies):</u> EVLA: 5/467 (1%) RFA: 16/431 (4%) FS: 2/295 (7%) Stripping: 20/681 (3%) P=NR</p> <p><u>Return to work or normal activity (12 studies):</u> 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</p>	<p><i>Authors' conclusions:</i> 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.</p> <p><i>Limitations:</i> Analyses used aggregate data and not adjusted for observations that were not independent (i.e., different limbs w/in the same pt); the results of individual studies and</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
2011b (n=276) Christenson et al., 2010 (n=200) Darwood et al., 2008 (114) De Medeiros et al., 2005 (n=20) Kalteis et al., 2008 (n=95) Rasmussen et al., 2007; Rasmussen et al., 2009; Rasmussen et al., 2010 (n=137) Rasmussen et al., 2011 (249) Pronk, et al., 2010 (n=130) RFA vs surgery: ElKaffas et al., 2011 (n=180) Hinchliffe et al., 2006 (n=16) Rasmussen et al., 2011 and Lawaetz et al., 2010 (n=249) Rautio et al., 2002 and Perala et al., 2005 (n=28) Lurie et al., 2003 (n=81) Subramonia et al., 2010 and Balakrishnan et al., 2008 (n=88) FS vs surgery: Abela et al., 2008 (n=90)	Research Network; Current Controlled Trials; and ClinicalTrials.gov <i>Inclusion criteria:</i> RCTs assessing EVLA, RFA, FS compared w/ other techniques in terms of recurrence of varicose veins, retx and clinical symptoms, as measured by the VCSS, pain and QOL <i>Eligible comparators:</i> Traditional surgical techniques, LS, and conservative management <i>Exclusion criteria:</i> Non-RCT study designs; trials comparing different forms of the same intervention; RCTs of comparison interventions; RCT of co-interventions <i>Quality assessment:</i> Quality assessment criteria adapted from a published checklist for surgical interventions; the authors note that blinding	Total: 1351 Range: 56-425 <i>Interventions:</i> EVLA, RFA, FS, FS+ligation <i>Comparator:</i> Traditional surgery <i>F/u:</i> Network MAs were done using 6 mos, 1 yr, and 2 yr f/u data when available <i>Study quality:</i> 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)	The following outcomes were subjected to formal network MA: Technical recurrence, VCSS, and pain score Economic outcomes in terms of cost-effectiveness, cost-utility or cost-benefit	Carroll et al. (2013) RFA: No difference in 1 study; results favored RFA in 3 studies FS: No difference in 1 study; results favored FS in 1 study (2 studies not relevant to this HTA) <i>Results of network MA:</i> <u>Technical recurrence (23 studies) HR (95% CrI [probability HR >1]):</u> 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] RFA 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] FS vs surgery: 6 mos: 1.12 (0.53-2.27) [0.659]; 2 yrs: 0.92 (0.43-1.60) [0.359] <u>VCSS at 1 yr (6 studies, includes 2 studies</u>	the review are affected by uncertainty on account of the relatively high RoB present across the individual studies; cost evaluations were limited by the data used in the models. <i>Quality of review:</i> Good <i>Conflicts of interest:</i> The authors do not have any COI

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
<p>Bountouroglou et al., 2004 and Bountouroglou et al., 2006 (n=58) Figuereido et al., 2010 (n=56) Jia et al., 2010 (n=60) Kalodiki et al., 2008 and Kalodiki et al., 2011 (n=82) Liamis et al., 2005 (n=60) Rasmussen et al., 2011 and Lawaetz et al., 2010 (n=248) Shadid et al., 2010 (n=425) Wright et al., 2006 (n=272)</p> <p>(studies of other comparisons are not listed)</p> <p><i>Funding source:</i> NIHR HTA program (UK)</p>	<p>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.</p>			<p><u>comparing EVLA w/ RFA), median (95% CrI [probability of MD >0]):</u> EVLA vs surgery: 0.10 (-0.94 to 0.73) [0.324] RFA vs surgery: 0.15 (-0.50 to 0.95) [0.739] FS vs surgery: -1.63 (-2.90 to -0.42) [0.015]</p> <p><u>Pain (w/in 7-14 days of tx) (9 studies, includes 3 studies comparing EVLA w/ RFA), median (95% CrI [probability of MD >0]):</u> EVLA vs surgery: 0.10 (-0.49 to 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]</p> <p><i>Harms:</i> <u>DVT and PE (11 studies):</u> EVLA: 1 DVT RFA: 1 PE FS: 13 DVT; 2 PE Surgery: 1 DVT P=NR</p> <p>Bruising and skin discoloration, hematoma, paresthesia, infection and phlebitis were reported</p>	

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>most frequently by trials. Other complications reported by >1 studies were nerve injury and skin changes. For all adverse events, the number of events was very small and statistically significant differences were not often reported.</p> <p><i>Economic outcomes:</i> From review of 4 economic studies, the authors conclude that economic analyses of endovenous txs in comparison w/ 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.</p>	
<p>Dermody et al. (2013)</p> <p><i>Aim:</i> Analyze the current literature for short-term complications of EVLA</p>	<p><i># included studies:</i> 17 (7 EVLA vs L&S; 5 RFA vs L&S; 4 RFA vs EVLA; 1 comparing EVLA/RFA/L&S)</p>	<p><i>Study design:</i> RCTs</p> <p><i>Sample size:</i> 2349</p> <p><i>Interventions:</i> EVLA</p>	Harms	<p><i>Harms (short term [<1 yr]), results from MA:</i></p> <p><u>Wound infection, OR (95% CI):</u></p>	<p><i>Authors' conclusions:</i> The majority of complications for endovenous thermal ablation and L&S</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
<p>compared w/ L&S</p> <p>Almeida et al., 2009; Carradice et al., 2011; Christenson et al., 2010; 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</p> <p><i>Funding source:</i> None reported</p>	<p><i>Search dates:</i> January 2008 – January 8, 2013</p> <p><i>Data sources:</i> MEDLINE, the Cochrane Central Trials Registry, and individual journals</p> <p><i>Inclusion criteria:</i> RCTs comparing RFA and/or EVLA and/or L&S to treat GSV incompetence</p> <p><i>Eligible comparators:</i> L&S</p> <p><i>Exclusion criteria:</i> FS studies, and studies of re-do GSV surgery, and studies of the addition of high GSV ligation to an EVLA procedure</p> <p><i>Quality assessment:</i> A list of 6 criteria (combination of Jadad scale and author's own criteria)</p>	<p>(wavelength ranged from 810-1470 nm across studies), RFA (6 studies used RFA-CP, and 4 used RFA-CF [NOTE: RFA-CP studies not included in MA.])</p> <p><i>Comparator:</i> L&S</p> <p><i>F/u:</i> <1 yr</p> <p><i>Study quality:</i> 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 >20% attrition; 25% of trials did not specify protocol for examining pts for complications; all studies lack sufficient descriptions of complications; most events were unblinded, subjective assessments; RCTs underpowered to analyze most complications</p>		<p>RFA vs L&S (1 study): 0.96 (0.06-15.4)</p> <p>EVLA vs L&S (7 studies, 9 comparisons; $I^2=0\%$): 0.24 (0.10-0.58)</p> <p><u>Paresthesia, OR (95% CI):</u> RFA v. L&S (1 study): 1.15 (0.35-3.85) EVLA vs L&S (7 studies, 9 comparisons; $I^2=0\%$): 0.53 (0.34-0.82)</p> <p><u>Thrombophlebitis, OR (95% CI):</u> RFA vs L&S (1 study): 2.29 (0.86-6.1) EVLA vs L&S (6 studies, 8 comparisons [$I^2=51\%$]): 1.83 (1.13-2.95)</p> <p><i>Harms, pooled incidences, % limbs (95% CI) (P is significance compared w/ L&S):</i></p> <p><u>DVT:</u> 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&S (12 studies): 0.7 (0.2-1.3)</p>	<p>procedures to treat GSV incompetence are benign and self-limited. L&S has a higher rate of wound infection vs EVLA. EVLA has a higher rate of thrombophlebitis than L&S. EVLA has a lower rate of paresthesia than RFA and L&S. The rate of venous thromboembolic events is low in the RCT literature.</p> <p><i>Limitations:</i> 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.</p> <p><i>Quality of review:</i> Good</p> <p><i>Conflicts of interest:</i></p>

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				<p><u>Infection:</u> EVLA (12 studies): 0.7 (0.3-1.3); $P=0.006$ RFA-CF (4 studies): 1.0 (0.3-2.0); $P=0.71$ L&S (12 studies): 2.1 (1.3-3.1)</p> <p><u>Paresthesia:</u> EVLA (12 studies): 3.3 (2.4-4.5); $P<0.001$ RFA-CF (4 studies): 7.8 (5.8-10.1); $P=0.43$ L&S (15 studies): 6.7 (5.3-8.3)</p> <p><u>SVT:</u> 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&S (12 studies): 2.9 (1.9-4.0)</p> <p><u>Bruising:</u> EVLA (8 studies): 34.5 (31.2-38.0); $P=0.55$ RFA-CF (1 study): 3.1 (0.12-9.9); $P<0.001$ L&S (8 studies): 36.1 (32.6-39.6)</p> <p><u>Hematoma:</u> EVLA (6 studies): 2.1 (1.1-</p>	None reported

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				<p>3.5); $P < 0.001$ RFA-CF (2 studies): 0.2 (0-1.3); $P < 0.001$ L&S (11 studies): 13.5 (11.1-16.1)</p> <p><u>Skin burn:</u> 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 L&S (none):</p>	
<p>Nesbitt et al. (2014)</p> <p><i>Aim:</i> To determine whether endovenous ablation (RFA and EVLA) and FS have any advantages or disadvantages compared w/ open surgical saphenofemoral L&S of GSV varices</p> <p>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.,</p>	<p><i># included studies:</i> 8 studies added w/ update for a total of 13 studies (FS 3 studies [n=870]; EVLA 8 studies [n=1760]; RFA 5 studies [n=642])</p> <p><i>Search dates:</i> Update search done January 2014</p> <p><i>Data sources:</i> Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Registry, and reference</p>	<p><i>Study design:</i> RCTs</p> <p><i>Sample size:</i> 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.)</p> <p><i>Intervention:</i> FS, RFA, EVLA (810-470 nm)</p> <p><i>Comparator:</i></p> <p><i>F/u:</i> 3 mos in all studies;</p>	<p>Primary outcomes: Recurrence; recanalization; neovascularization; technical failure and reintervention; QOL; postoperative complications</p> <p>Secondary outcomes: Length of the procedure or operative time; duration of hospital stay; procedural costs</p> <p>Other outcomes: Time to return to work or normal activities; type of anesthetic required; post-procedure pain</p>	<p><i>Primary outcomes:</i> (Only results for outcomes eligible for this HTA are shown.)</p> <p><u>Recurrence, OR (95% CI):</u> UGFS vs surgery (3 studies reported clinician noted recurrence, $I^2=55\%$): 1.74 (0.97-3.12) $P=0.06$ 1 study reported symptomatic recurrence, 1.28 (0.66-2.49) EVLA vs surgery (7 studies reported clinician noted recurrence, $I^2=60\%$): 0.72 (0.43-1.22) $P=0.22$ 3 studies reported symptomatic recurrence</p>	<p><i>Authors’ conclusions:</i> 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.</p> <p><i>Limitations:</i> The authors note that, “Despite an apparent congruity in the outcome measures of the studies there was a serious lack of</p>

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<p>2011 HELP-1 (Carradice et al., 2008, 2009, 2011a, 2011b, 2012) 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</p> <p><i>Funding source:</i> None</p>	<p>lists from relevant studies and reviews</p> <p><i>Inclusion criteria:</i> RCTs evaluating UGFS of the GSV, RFA and EVLT GSV ablation</p> <p><i>Eligible comparators:</i> Open GSV HL/S</p> <p><i>Exclusion criteria:</i> Studies that included pts who had undergone tx of both GSVs and SSVs and did not provide any subanalyses of these grps were excluded</p> <p><i>Quality assessment:</i> Cochrane Collaboration's tool for assessing RoB</p>	<p>1-2 yrs in most studies</p> <p><i>Study quality:</i> All studies deemed to have low risk 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.</p>		<p>($I^2=0\%$): 0.87 (0.47-1.62) $P=0.67$ RFA vs surgery (4 studies reported clinician noted recurrence, $I^2=39\%$): 0.82 (0.49-1.39); $P=0.47$ 1 study reported symptomatic recurrence: 2.00 (0.30-13.26); $P=NR$</p> <p><u>Technical failure of procedure, OR (95% CI):</u> 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); $P=0.88$</p> <p><u>QOL:</u> 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, w/ worsening</p>	<p>compatible data, including differences in the outcome definitions, metrics and f/u time points, w/ 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 w/ bilateral varicose veins and presentation of data by numbers of limbs introduced a potential confounding bias.</p> <p><i>Quality of review:</i> Good</p> <p><i>Conflicts of interest:</i> 2 of the authors co-edited a textbook on vascular surgery; no other COI reported</p>

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				<p>w/in the first few days or wks followed by an overall improvement over the f/u period, w/ no difference between the grps.</p> <p>RFA vs surgery: General improvements over the length of the f/u for both tx grps, w/ most studies reporting no overall differences between the grps.</p> <p><u>Complications:</u> 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.</p> <p>EVLA vs surgery: Early and late complications were distributed between the grps and w/ very few major adverse</p>	

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>events. RFA vs surgery: Higher rates of hematoma and wound problems in the surgical grp compared w/ RFA; and the increased rate of hematoma and saphenous vein injury in the surgical grp were still evident in later complications. Overall, number of complications were low, especially for major complications.</p> <p><i>Secondary outcomes:</i></p> <p><u>Procedural costs:</u> 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.</p> <p><i>Other outcomes:</i></p> <p><u>Time to return to work or normal activities:</u> No MA was conducted. FS vs surgery: Reported</p>	

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>in 1 study, showed less recovery time for FS than surgery.</p> <p>EVLA vs surgery: Reported in 6 studies, most showed less recovery time for EVLA than surgery.</p> <p>RFA vs surgery: 5 studies reported less recovery time for RFA grp than surgery grp.</p> <p><u>Postprocedural pain:</u> No MA conducted.</p> <p>FS vs surgery: Reported in 2 studies, 1 study showed no large change in pain for either grp, 1 study reported less pain during procedure for FS than surgery.</p> <p>EVLA vs surgery: No overall conclusion; 2 robust studies found increased pain in EVLA grp.</p> <p>RFA vs surgery: Studies generally reported less pain in RFA grp than surgery grp.</p>	
Paravastu et al. (2016)	<i># included studies:</i> 3 (EVLA 3 [n=311]; UGFS 1	<i>Study design:</i> RCTs	<i>Primary outcomes:</i> Recanalization or	<i>Primary outcomes:</i>	<i>Authors' conclusions:</i> Low- to moderate-

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
<p><i>Aim:</i> To compare the effectiveness of EVLA, RFA, and UGFS vs conventional surgery in the tx of SSV varices</p> <p>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)</p> <p><i>Funding source:</i> None</p>	<p>[n=42])</p> <p><i>Search dates:</i> NR</p> <p><i>Data sources:</i> Specialised Register, Cochrane Register of Studies, World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Registry, reference lists of relevant articles and reviews,</p> <p><i>Inclusion criteria:</i> RCTs</p> <p><i>Eligible comparators:</i> Conventional surgery</p> <p><i>Exclusion criteria:</i> Population not SSV, not RCT</p> <p><i>Quality assessment:</i> Cochrane's RoB tool</p>	<p><i>Sample size:</i> EVLA vs surgery 311; UGFS vs surgery 42</p> <p><i>Intervention:</i> EVLA, UGFS</p> <p><i>Comparator:</i> Surgery</p> <p><i>F/u:</i> 6 wks – 2 yrs</p> <p><i>Study quality:</i> 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.</p>	<p>persistence of reflux at 6 wks; recurrence of reflux at 1 yr; clinical evidence of recurrence; reintervention</p> <p><i>Secondary outcomes:</i> QOL; postoperative pain; complications; healing of ulcers</p>	<p><u>Recanalization or persistence of reflux at 6 wks (tx failure), OR (95% CI):</u> EVLA vs surgery (3 studies, $I^2=51\%$): 0.07 (0.02-0.22); $P<0.00001$</p> <p><u>Recurrence of reflux at 1 yr (determined by recanalization on US), OR (95% CI):</u> 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); $P=NR$</p> <p><u>Clinical recurrence (presence of visible varicose veins), OR (95% CI):</u> EVLA vs surgery (1 study): 0.54 (0.17-1.75) $P=NR$ FS vs surgery: No analysis)</p> <p><u>Reintervention due to technical failure:</u> EVLA vs surgery (1</p>	<p>quality evidence exists to suggest that recanalization or persistence of reflux at 6 wks and recurrence of reflux at 1 yr are less frequent when EVLA is performed, compared w/ conventional open surgery. For the UGFS vs conventional surgery comparison, we assessed the quality of evidence as low; consequently, the effectiveness of UGFS compared w/ conventional surgery in the tx of SSV varices is uncertain.</p> <p><i>Limitations:</i> 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.</p> <p><i>Quality of review:</i> Good</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>study): No MA; 4 pts in EVLA grp and 3 pts in surgery grp received further tx FS vs surgery: Results not available</p> <p><i>Secondary outcomes:</i></p> <p><u>QOL (AVVQ), MD (95% CI):</u> EVLA vs surgery (2 studies, $I^2=0\%$, 6 wks f/u): 0.15 (-1.65-1.95) $P=0.87$ EVLA vs surgery (1 study, 1-yr f/u): 1.08 (-3.39-1.23) FS vs surgery: No results</p> <p><u>QOL (EQ-5D questionnaire):</u> EVLA vs surgery (2 studies): No MA; both studies reported no difference between grps FS vs surgery: No results</p> <p>QOL (36-Item SF-36 Health Survey): EVLA vs surgery (1 study): No MA, both grps achieved higher scores over time in 5 of 8</p>	<p><i>Conflicts of interest:</i> 1 author is a director of a specialist vascular services provider and has received sponsorship to attend training for ClariVein and VenaSeal devices. No COI reported for other authors.</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>categories, EVLA grp improved in general health domain from 1 wk-6 wks, score was 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</p> <p><u>Postoperative pain (VAS scores):</u> 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</p>	

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				<p><u>Postoperative complications:</u> EVLA vs surgery (2 studies): No MA, both studies reported few 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. FS vs surgery: No results</p> <p><u>Return to work:</u> EVLA vs surgery (2 studies): No MA, both studies reported that the EVLA grp returned to work faster than the surgery grp FS vs surgery: No results</p>	
<p>O'Donnell et al. (2016)</p> <p><i>Aim:</i> To define the overall incidence of REVAS as well as both the sites of reflux and the causes of REVAS</p>	<p><i># included studies:</i> 7 studies (8 comparisons: 3 RFA vs L&S; 4 EVLA vs L&S; 1 EVLA vs cryostripping)</p> <p><i>Search dates:</i> January 1,</p>	<p><i>Study design:</i> RCTs</p> <p><i>Sample size:</i> >1500 limbs</p> <p><i>Intervention:</i> EVLA (810 nm-910 nm), RFA (Closure PLUS catheter)</p>	<p><i>Outcomes:</i> Recurrence (duplex and clinical); site of recurrence; cause of recurrence; tx of REVAS</p>	<p><i>Clinical outcomes:</i></p> <p><u>Duplex recurrence, pooled percentage (95% CI):</u> EVLA (4 studies): 12.5 (8.9-16.5)</p>	<p><i>Authors' conclusions:</i> No difference in the overall incidence of REVAS between EVLA and L&S, and REVAS appeared progressive over time.</p>

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<p>through an systematic review and MA of RCTs for endovascular ablation</p> <p>Christenson et al., 2010 (n=200, limbs) Disselhoff 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=374, pts) Rasmussen et al., 2013b (n=121, pts) Rass et al., 2012 (n=346)</p> <p><i>Funding source:</i> None</p>	<p>2000-July 1, 2014</p> <p><i>Data sources:</i> MEDLINE, Embase, Cochrane, and Clinical Trials Registry</p> <p><i>Inclusion criteria:</i> RCTs evaluating endovenous ablation (EVLA or RFA) of GSV incompetence</p> <p><i>Eligible comparators:</i> L&S or an alternative form of stripping, such as cryostripping</p> <p><i>Exclusion criteria:</i> 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</p> <p><i>Quality assessment:</i> A list of 6 criteria (combination of Jadad scale and authors' own criteria)</p>	<p>or ClosureFast catheter)</p> <p><i>Comparator:</i> 7 L&S, 1 cryostripping</p> <p><i>F/u:</i> 2 yrs</p> <p><i>Study quality:</i> NR</p>		<p>RFA (3 studies): 12.4 (7.3-18.6) L&S (5 studies): 7.2 (4.4-10.6); $P=0.32$</p> <p><u>Clinical recurrence pooled percentage (95% CI):</u> 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); $P=0.98$</p> <p><u>Reoperation, pooled percentage (95% CI):</u> 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); $P=0.74$</p>	<p><i>Limitations:</i> Authors describe quality assessment; however, a discussion of individual study and body of evidence quality is missing.</p> <p><i>Quality of review:</i> Good</p> <p><i>Conflicts of interest:</i> 1 author previously served as a consultant for Covidien, Tactile Medical, and BTG International. No other COI reported</p>

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<p>Rigby et al. (2009)</p> <p><i>Aim:</i> To identify whether the use of surgery or sclerotherapy should be recommended for the management of primary varicose veins</p> <p>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</p> <p><i>Funding source:</i> Sheffield Vascular Institute, UK; NHS R&D HTA Programme, UK; Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK; Chief Scientist Office, Scottish Government Health Directorates, the Scottish Government, UK</p>	<p><i># included studies:</i> 9 RCTS (14 publications) (6 compared sclerotherapy w/ general anesthetic surgery; 1 compared sclerotherapy w/ ambulatory phlebectomy; 1 compared endovascular sclerotherapy w/ general anesthetic surgery or local anesthetic surgery and sclerotherapy; 1 compared general anesthetic surgery w/ local anesthetic surgery and sclerotherapy)</p> <p><i>Search dates:</i> Database inception through June 2004</p> <p><i>Data sources:</i> 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</p>	<p><i>Study design:</i> RCTs</p> <p><i>Sample size:</i> 3313</p> <p><i>Intervention:</i> Sclerotherapy (liquid or foam) alone or in combination w/ other tx (e.g., L&S+sclerotherapy)</p> <p><i>Comparator:</i> Surgery (e.g., ligation, ambulatory phlebectomy)</p> <p><i>F/u:</i> 2-5 yrs</p> <p><i>Study quality:</i> 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</p>	<p><i>Outcomes:</i> Initial tx success; early complications; long-term complications; economic analyses (cost-effectiveness)</p>	<p><i>Effectiveness outcomes:</i></p> <p><u>Tx success or failure:</u> At 1 yr, 3 studies stated 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.</p> <p><i>Harms:</i></p> <p><u>Complication rates:</u> 2 studies reported no statistically significant differences between interventions and 1 study did not provide data on complications</p> <p><u>PE:</u></p>	<p><i>Authors' conclusions:</i> This review found that sclerotherapy was better than surgery in 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.</p> <p><i>Limitations:</i> No MA possible due to nature of data available; comparisons between txs were not always clear in the summary of complication rates.</p> <p><i>Quality of review:</i></p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
	<p>manual searches of relevant journals</p> <p><i>Inclusion criteria:</i> RCTs of pts being tx'd for cosmesis and/or symptomatic primary varicose veins (e.g., ache, itch, etc.)</p> <p><i>Eligible comparators:</i> Any surgical tx for primary varicose veins</p> <p><i>Exclusion criteria:</i> Trials including pts undergoing tx for complications of varicose veins, venous ulceration, and chronic venous insufficiency or pts undergoing tx for recurrent varicose veins</p> <p><i>Quality assessment:</i> Jadad</p>	<p>was also variable. Internal validity was a problem w/ many of the studies, mainly due to a lack of reporting adequate methods of randomization and concealment of allocation.</p>		<p>Ranged from 0.48%-1.25% in 1 study</p> <p><u>DVT:</u> 1 occurrence in 1 study (grp not specified)</p> <p><u>Wound infection:</u> Ranged from 6%-7.25% in 1 study</p> <p><u>Nerve injury:</u> 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</p> <p><u>Overall:</u> The overall complication rate for sclerotherapy in 1 study was 6.6%, but went as high as 22% for phlebitis</p> <p><u>Costs:</u> Costs were analyzed in some studies but the methodology was not adequately stated in 1 study and the figures were outdated in 1</p>	<p>Good</p> <p><i>Conflicts of interest:</i> 2 authors were undertaking a study of the txs of varicose veins, funded by the NHS Health Technology Assessment Programme</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				study. Sclerotherapy was cheaper in terms of cost to the hospital and to the pt, measured in terms of money and days off work.	
<p>Rathbun et al. (2012)</p> <p><i>Aim:</i> To systematically and comprehensively evaluate the literature to provide accurate estimates of safety and efficacy outcomes for this procedure</p> <p>(104 studies included in the review; list of primary studies omitted from this table)</p> <p><i>Funding source:</i> American College of Phlebology Foundation</p>	<p><i># included studies:</i> 104</p> <p><i>Search dates:</i> Searches completed in 2010, dates varied depending on database</p> <p><i>Data sources:</i> 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 National Health Service</p>	<p><i>Study design:</i> 20 RCTs, 82 observational studies, 2 not classified</p> <p><i>Sample size:</i> Range 1-1200, median 60, avg 153</p> <p><i>Intervention:</i> Endovenous FS; dose and tx type varied; FS used as adjuvant tx to either EVLA, surgery, or LS in 16 studies; 17 grps of pts tx'd w/ LS</p> <p><i>Comparator:</i> EVLA (5 grps), surgery (12 grps), some included studies did not include comparators</p> <p><i>F/u:</i> Range 1 day-37 yrs, mean 52.5 wks</p> <p><i>Study quality:</i> Low overall</p>		<p><i>Effectiveness outcomes:</i></p> <p><u>Anatomical closure, RR (95% CI):</u> Surgery vs FS (6 studies, $I^2=NR$: 0.92 (0.86-0.97); $P=0.0036$</p> <p><u>Residual saphenofemoral incompetence, RR (95% CI):</u> FS vs surgery (4 studies, $I^2=NR$: 0.92 (0.56-1.51); $P=0.73$)</p> <p><i>Harms, RR (95% CI):</i> <u>DVT:</u> 1.45 (0.47-4.53); $P=0.52$</p> <p><u>Superficial thrombophlebitis:</u> 16.85 (2.27-124.74), $P=0.0057$</p> <p><u>Skin pigmentation:</u> FS vs surgery: No difference</p>	<p><i>Authors' conclusions:</i> Endovenous FS was found to be effective w/ 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 w/ a low-risk profile that is no greater than other varicose vein txs.</p> <p><i>Limitations:</i> Large number of observational and noncomparative studies; few comparisons between</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
	<p>Economic Evaluation Database using OVID, and manual searches</p> <p><i>Inclusion criteria:</i> Studies w/ pts age >19 yrs 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</p> <p><i>Eligible comparators:</i></p> <p><i>Exclusion criteria:</i> Studies that did not report original findings, such as review articles or editorials</p> <p><i>Quality assessment:</i> Method used NR</p>			<p><u>Paresthesia:</u> FS vs surgery: No difference</p> <p><u>Ecchymosis:</u> FS vs surgery: 0.44 (0.25-0.64); $P=0.0001$</p> <p><u>Pain:</u> FS vs surgery (1 study): 0.32 (0.17-0.62); $P=0.0006$</p>	<p>txs for outcomes of interest; list of included and excluded studies not provided.</p> <p><i>Quality of review:</i> Good</p> <p><i>Conflicts of interest:</i> NR</p>
<p>Pan et al. (2014)</p> <p>Aim: To evaluate the efficiency and safety of EVLA for primary lower</p>	<p><i># included studies:</i> 13</p> <p><i>Search dates:</i> May 2012</p> <p><i>Data Sources:</i> MEDLINE,</p>	<p><i>Study design:</i> Prospective nonrandomized studies and RCTs</p>	<p><i>Outcomes:</i> Technical success; duplex-detected recurrence at 1- and 2-yr f/u; clinical recurrence and</p>	<p><i>Clinical outcomes:</i> <u>Technical success:</u> Meta-analyses based on data for number of limbs w/ technical failure</p>	<p><i>Authors' conclusions:</i> EVLA is a safe and effective alternative for tx of varicose veins.</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
<p>extremity varicosities compared w/ HL/S Medeiros et al., 2005; 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</p> <p><i>Funding Source:</i> NR</p>	<p>PubMed, Cochrane Library</p> <p><i>Inclusion criteria:</i> Prospective clinical studies comparing EVLA and HL/S for tx of varicose veins; all f/u periods were allowed; all wavelengths and energy parameters</p> <p><i>Eligible comparators:</i> HL/S</p> <p><i>Exclusion criteria:</i> Retrospective studies, investigations on EVLA alone, studies comparing EVLA w/ other endovenous therapies other than HL/S and studies in languages other than English</p> <p><i>Quality assessment:</i> Sackett's classification scheme</p>	<p><i>Sample size:</i> 2245 limbs (EVLA n=1128; HL/S n=1117)</p> <p><i>Intervention:</i> EVLA</p> <p><i>Comparator:</i> HL/S</p> <p><i>F/u:</i> Ranged from 3 mos – 5 yrs</p> <p><i>Study quality:</i> Ranged from Sackett's classification I-II (3 were classified as II and 10 were classified as I)</p>	<p>1- and 2-yr f/u; common complications (phlebitis, bleeding, hematoma, petechial, wound infection, or paresthesia)</p>	<p><u>Initial technical success (9 studies):</u> RR, 1.11 (95% CI, 0.62-1.97); $P=0.72$ Initial technical success rates were 97.3% (EVLA) and 97.6% (HL/S).</p> <p><u>Technical success at 1 yr (6 studies):</u> RR, 2.52 (95% CI, 1.20-5.28); $P=0.01$; favors HL/S The procedural failure rates after EVLA and HL/S at 1 yr were 2.6% and 2.1%, respectively.</p> <p><u>Technical success at 2 yrs (5 studies):</u> RR 2.79 (95% CI, 1.24-6.27); $P=0.01$; favors HL/S</p> <p><u>Duplex recurrence at 1 yr (6 studies):</u> RR, 0.65 (95% CI, 0.41-1.02); $P=0.06$</p> <p><u>Duplex recurrence at 2 yrs (5 studies):</u> RR, 0.65 (95% CI, 0.37-1.12); $P=0.12$</p> <p><u>Clinical recurrence at 1</u></p>	<p><i>Limitations:</i> Unclear whether duplicate study selection and abstraction was conducted, did not provide list of excluded studies.</p> <p><i>Quality of review:</i> Good</p> <p><i>Conflicts of interest:</i> NR</p>

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>yr (6 studies): RR 0.83 (0.39-1.77), $P=0.63$</p> <p><u>Clinical recurrence at 2 yrs (5 studies):</u> RR, 0.85 (95% CI, 0.64-1.11); $P=0.23$</p> <p><u>Long term recurrence:</u> 1 study (Disselhoff 2011) found no statistical difference between the 5-yr recurrence rates of 62% and 51% for EVLA and HL/S, respectively.</p> <p><u>Time to return to work or normal activity:</u> 1 study reported longer time to return to work in EVLA grp than HL/S grp ($P=0.054$); other studies showed shorter recovery times for the EVLA grp, 2 of which reported statistically significant differences.</p> <p><u>Pain:</u> 3 studies (Rasmussen 2009; Carradice 2011; Vuylsteke 2006) found postoperative pain higher in HL/S grp than</p>	

Systematic Review (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Outcomes	Results	Conclusions/ Limitations
				<p>EVLA grp; 4 studies (Rass 2012; Rasmussen 2011; Darwood 2008; Christenson 2010) showed no difference; 1 study (Pronk 2010) found significantly more pain in EVLA grp than HL/S grp</p> <p><i>Complications</i></p> <p><u>Phlebitis (8 studies)</u>: RR 1.54 (95% CI, 0.97-2.44); $P=0.06$</p> <p><u>Hematoma (6 studies)</u>: RR, 0.30 (95% CI, 0.15-0.57); $P=0.0003$; favors EVLA</p> <p><u>Bruise (6 studies)</u>: RR, 0.74 (95% CI, 0.33-1.66); $P=0.47$</p> <p><u>Infection (7 studies)</u>: RR, 0.28 (95% CI, 0.11-0.70); $P=0.006$; favors EVLA</p> <p><u>Paresthesia (9 studies)</u>: RR, 0.59 (95% CI, 0.45-0.79); $P=0.0003$; favors EVLA</p>	

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

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
<p>Society for Vascular Surgery and the American Venous Forum (Gloviczki et al., 2011)</p> <p><i>The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum</i></p>	<ul style="list-style-type: none"> • Open venous surgery: <ul style="list-style-type: none"> ○ 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: 	<p>5.8 - Good</p> <p><i>Limitations:</i> No mention of external review of guidelines or a procedure for updating</p>

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
	<ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ Liquid sclerotherapy 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: <ul style="list-style-type: none"> ○ 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). 	
<p>Society for Vascular Surgery and the American Venous Forum (O'Donnell et al., 2014)</p> <p><i>Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum</i></p>	<p><i>Recommendations specific to operative/endovascular management</i></p> <p><u>Guideline 6.1: Superficial Venous Reflux and Active Venous Leg Ulcer – Ulcer Healing:</u> 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]</p> <p><u>Guideline 6.2: Superficial Venous Reflux and Active Venous Leg Ulcer – Prevent Recurrence:</u> 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]</p> <p><u>Guideline 6.3: Superficial Venous Reflux and Healed Venous Leg Ulcer:</u> In a patient with a healed venous leg ulcer (C5) and</p>	<p>6.2 – Good</p> <p><i>Limitations:</i> Criteria for selecting evidence is not clearly described; need to update mentioned, but the method for updating was not identified</p>

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
	<p>incompetent superficial veins that have axial reflux directed to 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]</p> <p><u>Guideline 6.4: Superficial Venous Reflux With Skin Changes at Risk for Venous Leg Ulcer (C4b):</u> 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]</p> <p><u>Guideline 6.5: Combined Superficial and Perforator Venous Reflux With or Without Deep Venous Reflux and Active Venous Leg Ulcer:</u> 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]</p> <p><u>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):</u> 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]</p> <p><u>Guideline 6.7: Pathologic Perforator Venous Reflux in the Absence of Superficial Venous Disease, With or Without Deep</u></p>	

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
	<p><u>Venous Reflux, and a Healed or Active Venous Ulcer:</u> In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >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]</p> <p><u>Guideline 6.8: Treatment Alternatives for Pathologic Perforator Veins:</u> 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 (RF or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin. [GRADE – 1; LEVEL OF EVIDENCE – C]</p> <p><u>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:</u> 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]</p> <p><u>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:</u> 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]</p> <p>Guidelines 6.11 – 6.17 do not mention the interventions of interest for this HTA.</p>	
National Institute for Health and Care Excellence (NICE)	<p><i>Major recommendations for treatment for people with confirmed varicose veins and truncal reflux:</i></p> <ul style="list-style-type: none"> • Offer endothermal ablation (RFA or EVLA) • If endothermal ablation is unsuitable, offer USGFS. 	<p>6.4 – Good</p> <p><i>Limitations:</i> Process for external review not described</p>

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
<p>(National Clinical Guideline Centre, 2013)</p> <p><i>Diagnosis and management of varicose veins in the legs: NICE guideline</i></p>	<ul style="list-style-type: none"> • 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. <p><i>Management during pregnancy:</i></p> <ul style="list-style-type: none"> • 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. <p>Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy.</p>	
<p>European Society for Vascular Surgery (Wittens et al., 2015)</p> <p><i>Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)</i></p>	<ul style="list-style-type: none"> • 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) 	<p>5.6 – Good</p> <p><i>Limitations:</i> Methods for formulating recommendations included considering expert opinion, the process for external review was not described, and process for updating was not described</p>

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
	<ul style="list-style-type: none"> • 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 quality of life (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, UGFS, or phlebectomies should be considered for the treatment of recurrent varicose veins (recommendation 63, IIaB). • 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). 	
American College of Phlebology (Gibson et al., 2016) <i>American College of Phlebology Guidelines - Treatment of refluxing accessory saphenous veins</i>	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).	4.3 – Fair <i>Limitations:</i> Criteria for selecting evidence not described, limited discussion of the strength and limitations of the evidence, methods for formulating recommendations not well described, external review and process for

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
		updating were not described
American College of Phlebology (Rathbun et al., 2014) <i>Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP/SVM/AVF/SIR quality improvement guidelines</i>	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.	5 – Fair <i>Limitations:</i> 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

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
<p>American College of Phlebology (ACP, 2014)</p> <p><i>Treatment of Superficial Venous Disease of the Lower Leg</i></p>	<ul style="list-style-type: none"> • 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, anterior accessory GSV, posterior accessory GSV) 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 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) 	<p>3.2 – Poor</p> <p><i>Limitations:</i> Limitations evident in all Rigor of Development domain items</p>
<p>American College of Radiology (Rochon et al., 2012)</p>	<p>Ratings in different scenarios described within the guidelines for the populations and interventions selected for this HTA are shown below.</p>	<p>3.9 – Fair</p> <p><i>Limitations:</i> Criteria for selecting evidence not described, process for external review not</p>

Sponsor (Year), Title	Relevant Recommendations	Quality*/Main Limitations
<p>ACR <i>Appropriateness Criteria: radiologic management of lower-extremity venous insufficiency</i></p>	<ul style="list-style-type: none"> • Variant 2: Left SSV insufficiency resulting in intermittent pain and swelling without skin discoloration or ulceration. Rating 8 (usually appropriate) for endoluminal RF 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 RF 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 RF 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 RF therapy; Rating 5 (may be appropriate) for surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy. • 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 RF therapy; Rating 4 (may be appropriate) for repeat surgical vein stripping; Rating 4 (may be appropriate) for injection sclerotherapy. 	<p>described, procedure for updating not described, and competing interests of authors not recorded or addressed</p>

*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).