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Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)

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Technical Expert Panel

In designing the methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)

Structured Abstract

Objectives. For patients with lower extremity chronic venous disease (LECVD), the optimal diagnostic testing and treatment for symptom relief, preservation of limb function, and improvement in quality of life is not known. This systematic review included a narrative review of diagnostic testing modalities and assessed the comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) in patients with LECVD.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2000 to June 30, 2016.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects.

Results. A total of 111 studies contributed evidence, as follows:

Diagnosis of LECVD: A narrative review was conducted due to the scant literature and availability of only 10 observational studies evaluating the comparative effectiveness of diagnostic testing modalities in a heterogeneous population of patients with LECVD. In addition to the history and physical exam, multiple physiologic and imaging modalities (plethysmography, duplex ultrasound, intravascular ultrasonography, magnetic resonance venography, computed tomography venography, and invasive venography) are useful to confirm LECVD and/or localize the disease and guide therapy. There was insufficient evidence to support or refute the recommendations from current clinical guidelines that duplex ultrasound should be used as the firstline diagnostic test for patients being evaluated for LECVD or for those for whom invasive treatment is planned.

Treatment of lower extremity chronic venous insufficiency/incompetence/reflux: Ninety-three studies (87 randomized controlled trials, 6 observational) evaluated the comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention in patients with lower extremity chronic venous insufficiency/incompetence/reflux. There was no long-term difference in effectiveness between radiofrequency ablation (RFA) and high ligation plus stripping, but RFA was associated with less periprocedural pain, faster improvement in symptom scores and quality of life, and fewer adverse events.

Among patients undergoing endovenous interventions, RFA, endovenous laser ablation (EVLA), and sclerotherapy demonstrated improvement in quality-of-life scores and standardized symptom scores. When compared with patients treated with EVLA, those treated with foam sclerotherapy had significantly less periprocedural pain but lower rates of vein occlusion and higher rates of repeat intervention, and patients treated with RFA had significantly less periprocedural pain but

also less short-term improvement in Venous Clinical Severity Score. When compared with patients treated with placebo, those treated with foam sclerotherapy had statistically significant improvement in standardized symptom scores, occlusion rates, and quality of life. When compared with patients treated with placebo or no compression therapy, those treated with compression therapy had significant improvement in standardized symptom scores and quality of life.

Treatment of lower extremity chronic venous obstruction/thrombosis: Eight studies (3 randomized controlled trials, 5 observational) evaluated the comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention in patients with lower extremity chronic venous obstruction/thrombosis.

In patients with post-thrombotic syndrome, exercise training plus patient education and monthly phone follow-up resulted in improved quality of life but not improved symptom severity when compared with patient education and monthly phone follow-up. In patients with both May-Thurner Syndrome and superficial venous reflux who were treated with EVLA (with or without stent placement), there were fewer recurrent ulcerations, improvement in reflux severity and symptoms, and improvement in quality of life in long-term follow-up.

In patients with chronic proximal iliac vein obstruction, treatment with catheter-directed urokinase at the time of endovenous stenting resulted in similar effectiveness but catheter-directed urokinase had higher technical failure rates and bleeding risk when compared with endovenous stenting alone. Very few studies evaluated modifiers of effectiveness in the study population.

Conclusions. The available evidence for treatment of patients with LECVD is limited by heterogeneous studies that compared multiple treatment options, measured varied outcomes, and assessed disparate outcome timepoints. Very limited comparative effectiveness data have been generated to study new and existing diagnostic testing modalities for patients with LECVD. When compared with patients' baseline measures, endovenous interventions (e.g. EVLA, sclerotherapy, and RFA) and surgical ligation demonstrated improvement in quality-of-life scores and Venous Clinical Severity Score at various timepoints after treatment; however, there were no statistically significant differences in outcomes between treatment groups (e.g. endovenous vs. endovenous; endovenous vs. surgical). Several advances in care in endovenous interventional therapy have not yet been rigorously tested, and there are very few studies on conservative measures (e.g., lifestyle modification, compression therapy, exercise training) in the literature published since 2000. Additionally, the potential additive effects of many of these therapies are unknown. The presence of significant clinical heterogeneity of these results makes conclusions for clinical outcomes uncertain and provides an impetus for further research to improve the care of patients with LECVD.

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Introduction

Background

Lower extremity chronic venous disease (LECVD) is a heterogeneous term that encompasses a variety of conditions that are typically classified based on the CEAP classification, which defines LECVD based on Clinical, Etiologic, Anatomic, and Pathophysiologic parameters. This review focuses on treatment strategies for patients with LECVD, which is defined as patients who have had signs or symptoms of lower extremity (LE) venous disease for at least 3 months. Patients with LECVD can be asymptomatic or symptomatic, and they can exhibit a myriad of signs including varicose veins, telangiectasias, LE edema, skin changes, and/or ulceration. The etiology of LECVD includes venous dilation, venous reflux, (venous) valvular incompetence, mechanical compression (e.g., May-Thurner syndrome), and post-thrombotic syndrome. Because severity of disease and treatment are influenced by anatomic segment, LECVD is also categorized by anatomy (iliofemoral vs. infrainguinal veins) and type of veins (superficial veins, perforating veins, and deep veins). Finally, the pathophysiology of LECVD is designated typically as due to the presence of venous reflux, chronic unresolved thrombosis, and/or obstruction.

LECVD is common in the United States, where 25 million people have varicose veins, 2.5 million people have chronic venous insufficiency/incompetence, and the annual prevalence of venous thromboembolism (VTE, including both pulmonary embolism [PE] and deep vein thrombosis [DVT]) is approximately 1 million people.[1] While the majority of patients with LECVD are asymptomatic, serious complications can occur, including LE amputation, acute and chronic VTE, chronic thromboembolic pulmonary hypertension, and mortality.[2] A serious and common issue with LECVD is the formation of venous leg ulceration, affecting approximately 600,000 patients in the United States, and placing a burden on patients in terms of quality of life, pain, and social isolation. Furthermore, costs for the care of LECVD have increased substantially in the last few decades, with estimates in the United States of between $150 million and $1 billion per year.[3,4] Definitions of selected terms are provided in Table 1.

Table 1. Definitions of terms

Term	Definition
Venous obstruction	Defined as partial or complete blockage of venous flow in any venous segment; can result from internal blockage (e.g., thrombosis) or external compression of the vein
Venous reflux	Used to describe any retrograde venous flow in any venous segment; typically classified as (a) primary/idiopathic, (b) secondary (typically due to trauma, thrombosis, or mechanical/chemical/thermal etiologies), or (c) congenital
Venous thrombosis	Defined as the formation of a blood clot in any segment of the venous system; typically classified as deep or superficial
Chronic venous insufficiency/incompetence	Reserved for advanced venous disease, indicated by C3-C6 on the CEAP classification, and defined as morphological abnormalities of the venous system that lead to symptoms/signs (specifically, moderate-severe LE edema, skin changes, and/or venous ulcers)
Post-thrombotic syndrome	Describes chronic venous symptoms and/or signs that occur as a result of DVT and its sequelae

Abbreviations: CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; DVT=deep vein thrombosis; LE=lower extremity

Diagnosis

Adding complexity to a heterogeneous disorder, a multitude of diagnostic tests are currently used to diagnose acute and chronic venous disease.[5] A high index of suspicion and good clinical judgment often lead clinicians to diagnose acute and chronic venous disease using physical examination alone. After performing a thorough history and physical examination, venous duplex ultrasound (DUS); B-mode imaging and pulsed Doppler ultrasound with and without compression) is the most common diagnostic test performed. Other noninvasive tests (air plethysmography, computed tomography venography [CTV], magnetic resonance venography [MRV]) are also used to confirm the diagnosis and evaluate for anatomic or structural abnormalities. Contrast venography (also termed invasive venography, ascending or descending venography, and phlebography) and intravascular ultrasound (IVUS) are commonly utilized invasive tests, and their use is often reserved for patients undergoing endovascular or surgical management of LECVD.

Adverse Effects of Diagnosis

The diagnosis of LECVD as the underlying cause of LE edema, skin changes, and/or ulceration often leads clinicians and patients down a pathway of invasive procedures in an attempt to correct the problem. Hence, a misdiagnosis of LECVD could lead to unnecessary invasive procedures for venous abnormalities or underdiagnosis of other treatable conditions that mimic LECVD, such as peripheral artery disease (PAD; e.g., critical limb ischemia), lymphedema, or congestive heart failure. Eliminating PAD as an underlying cause of symptoms (e.g., ulceration) is important because (a) untreated critical limb ischemia due to PAD often leads to LE amputation, and (b) compression therapy for LECVD is contraindicated in the presence of significant obstructive arterial disease.

Classification of LECVD

The most common classification scheme for LECVD is the CEAP classification, shown in Table 2.[6,7]

Table 2. Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification for chronic venous disease

Clinical (C)[a]	Etiologic (E)	Anatomic (A)	Pathophysiologic (P)
C_0 No visible sign of venous disease	E_c Congenital	A_s Superficial	P_r Reflux
C_1 Telangectasia or reticular veins	E_p Primary	A_d Deep	P_o Obstruction, chronic unresolved thrombosis
C_2 Varicose veins	E_s Secondary (e.g., post-thrombotic, trauma)	A_p Perforator	$P_{r,o}$ Reflux and obstruction
C_3 Edema	E_n No venous cause identified	A_n No venous location identified	P_n No venous pathophysiology identified
C_4 Changes in skin and subcutaneous tissue A Pigmentation or eczema B Lipodermatosclerosis or atrophie blanche	–	–	–
C_5 Healed ulcer	–	–	–
C_6 Active ulcer	–	–	–

[a]The descriptor A (asymptomatic) and S (symptomatic) is placed after the C (clinical classification).

Treatment Strategies

The treatment of LECVD varies tremendously and can be divided into noninvasive and invasive therapies. Noninvasive approaches include therapies that improve venous circulation and reduce LE edema (e.g., compression devices, medical therapy [e.g., diuretics], and exercise), therapies that prevent thromboembolic complications (e.g., anticoagulation), and therapies that specifically address skin changes and ulceration (e.g., wound care). When these more conservative measures fail, invasive therapies are often recommended and include endovascular intervention (e.g., ablation, angioplasty) and/or surgical management (e.g., venous ligation, venous excision). Table 3 lists and briefly describes all of the treatments considered in this review. While compression therapy is the mainstay of treatment for LECVD, the use of endovascular and surgical techniques has increased dramatically over the last decade. The wide variation in how patients are treated around the United States suggests that the present systematic review is warranted. This review formally evaluates the evidence supporting the harms and benefits of all the treatments listed in Table 3 and will allow more evidence-based and consistent care for patients. For this review, we considered all adult patients with LECVD (asymptomatic and symptomatic), all diagnostic tests, and all forms of treatment.

Table 3. Available treatments for LECVD

Name of Treatment	Description of Treatment
Noninvasive Interventions	
Exercise Training	Supervised or unsupervised (home) exercise training that aims to improve ankle range of motion and calf muscle pump function
Medical Therapy – Diuretics	Medications used to remove fluid from the body through the kidneys
Medical Therapy – Anticoagulants	Blood thinning medications used to prevent blood clot formation or treat in situ blood clots
Weight Reduction	Reduction in body weight with lifestyle modifications (e.g., diet, exercise) or bariatric surgery
Compression Therapy	The use of stockings, bandages, and/or pneumatic compression devices to improve venous function.
Skin/Wound Care	The delivery of active or interactive substances (e.g., growth factors, antibiotics) to the skin or wound of the LE
Endovenous Interventions	
Endovenous laser ablation (EVLA)	Removal or destruction of a vein or vein segment by means of laser
Mechanochemical ablation	Removal or destruction of a vein or vein segment by mechanochemical means
Radiofrequency ablation (RFA)	Removal or destruction of a vein or vein segment by means of radiofrequency energy
Cyanoacrylate embolization	Occlusion of a vein or vein segment by means of injection of cyanoacrylate (CA)
Sclerotherapy (liquid or foam)	Obliteration of a vein or vein segment by chemical introduction (liquid or foam)
Surgical Interventions	
High Ligation	Ligation and division typically of the great saphenous vein (GSV) at its junction with the common femoral vein, including ligation and division of GSV branches
Stripping	Removal of a long vein segment, usually segments of the GSV or the small saphenous vein (SSV)
Phlebectomy	Removal of a vein segment through a small skin incision
Cure Conservatrice et Hemodynamique de l'Insufficience Veineuse en Ambulatoire (CHIVA)	Conservative and ambulatory treatment of varicose veins that preserves the architecture of the venous structure through selective surgical ligation of venous structures
Cryostripping	A surgical procedure in which a rigid cryoprobe is inserted into the GSV, the GSV is frozen with liquid nitrous oxide, and the probe is then used to remove the GSV

Abbreviations: CA=cyanoacrylate; CHIVA=Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; EVLA=endovenous laser ablation; GSV=great saphenous vein; LE=lower extremity; LECVD=lower extremity chronic venous disease; RFA=radiofrequency ablation; SSV=small saphenous vein

After patients are diagnosed with LECVD and an initial treatment strategy is determined, symptoms are monitored clinically with subjective and objective measures as specified in the CEAP classification score and the Venous Clinical Severity Score (VCSS). More specifically, pretreatment and post-treatment vascular laboratory testing is compared, including venous refilling time (VRT) and/or ambulatory venous pressure (AVP). Patients with venous insufficiency/incompetence/reflux typically undergo air plethysmography and DUS. Patients undergoing treatment for chronic venous thrombosis/obstruction normally undergo measurements of venous flow via DUS or venography for assessment of patency and/or amount of reflux.

While symptoms and venous hemodynamics are important, outcomes such as ulcer healing, prevention of recurrences of LE ulcers, and need for LE amputation are often measured at intermediate-term (6-12 months) and long-term (>12 months) time points. Similarly, quality-of-life scores (e.g., Aberdeen Varicose Vein Questionnaire [AVVQ] and VCSS) and need for repeat intervention are also measured at similar time points.

Adverse Effects of Treatment

The adverse effects of treatments for patients with LECVD depend on the specific type of treatment utilized. Complications from invasive (endovenous and surgical) interventions include bleeding, infection, vessel dissection and perforation, venous thrombosis/thromboembolic events, and death. Adverse effects of noninvasive treatments include bleeding due to antithrombotic medications, exercise-related harms, and venous thrombosis/thromboembolic events. Adverse effects of undertreatment may include decreased patient quality of life, venous ulceration, failure to heal venous ulceration, superinfection and potentially amputation.

Scope and Key Questions

Scope of the Review

This systematic review focuses on the diagnosis and management of LECVD in outpatient and inpatient settings where care is coordinated by primary care physicians, vascular surgeons, vascular medicine specialists, cardiologists, and/or radiologists. All adult patients with LECVD are included in the analyses.

Rationale and Context

There is substantial variation in how patients with LECVD are diagnosed and treated. In the past in the United States, general surgeons and vascular surgeons often diagnosed and treated patients with LECVD; now, however, primary care physicians, cardiologists, vascular medicine specialists, interventional radiologists, and others with and without formal training in venous care also diagnose and manage these patients. Other reasons for differences in diagnostic and treatment strategies exist and include: patient characteristics and preferences, reimbursement rates for diagnostic tests and treatment modalities, and the clinical care location of these diagnostic tests and invasive procedures (as this dictates reimbursement, specifically when physicians own the office-based clinics or ambulatory surgery centers where the procedures are performed). The evidence supporting the optimal diagnosis and treatment of peripheral venous disease is uncertain and a systematic review of the evidence base is timely both in terms of its potential impact on clinical care and on policy. As such, this systematic review was proposed as a large Technology Assessment by the Centers for Medicare and Medicaid Services (CMS). The main goal of this systematic review is to assess the clinical effectiveness and safety of each diagnostic testing modality and treatment modality for LECVD and identify whether specific patient or treatment characteristics are associated with improved outcomes.

Controversies around the treatment of LECVD include the following:

- In many instances, patients present with a combination of signs/symptoms (e.g., venous obstruction and thrombosis; venous obstruction and reflux) that lead to overlap in nomenclature and classification.
- Population inclusion and exclusion criteria have varied among studies, and stratification based on symptom status, presence of wounds, and other patient-specific factors is important.
- Measurement of outcomes has been variable in clinical studies of treatment strategies of patients with LECVD.
- There is a lack of data regarding the proportion of patients that progress from asymptomatic LECVD to symptomatic LECVD (especially leg pain and venous ulceration).
- There is a lack of data regarding the safety of treatment modalities in patients with LECVD.
- Improvements in both surgical and endovenous technologies have made direct comparison between “state-of-the-art” strategies more challenging.
- There is a lack of data regarding the use of disease-specific quality-of-life surveys and health outcomes in the care of LECVD.
- There is a lack of data focusing on LECVD in the Medicare and Medicaid population. How generalizable is existing evidence to this population of interest?

Key Questions (KQs)

KQ 1: Narrative review of the diagnostic methods and diagnostic criteria for all adult patients (symptomatic and asymptomatic) with LE varicose veins, LE chronic venous insufficiency/incompetence/reflux, and/or LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome).

KQ 2: Regarding treatments for all adult patients (symptomatic and asymptomatic) with LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux:

> 2a. What is the comparative effectiveness of exercise, medical therapy, weight reduction, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) on health outcomes?
>
> 2b. What diagnostic method(s) and criteria were used in each study?
>
> 2c. How does the comparative effectiveness of treatment vary by patient characteristics, including age, sex, risk factors, comorbidities, characteristics of disease, anatomic segment affected, and characteristics of the therapy (e.g., exercise intensity, type of mechanical compression)?
>
> 2d. What are the comparative safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by patient subgroup (age, sex, race, risk factors, comorbidities, anatomic segment, or disease severity)?

KQ 3: Regarding treatments for all adult patients (symptomatic and asymptomatic) with LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome):

> 3a. What is the comparative effectiveness of exercise, medical therapy, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) on health outcomes?
>
> 3b. What diagnostic method(s) and criteria were used in each study?
>
> 3c. How does the comparative effectiveness of treatment vary by patient characteristics, including age, sex, risk factors, comorbidities,

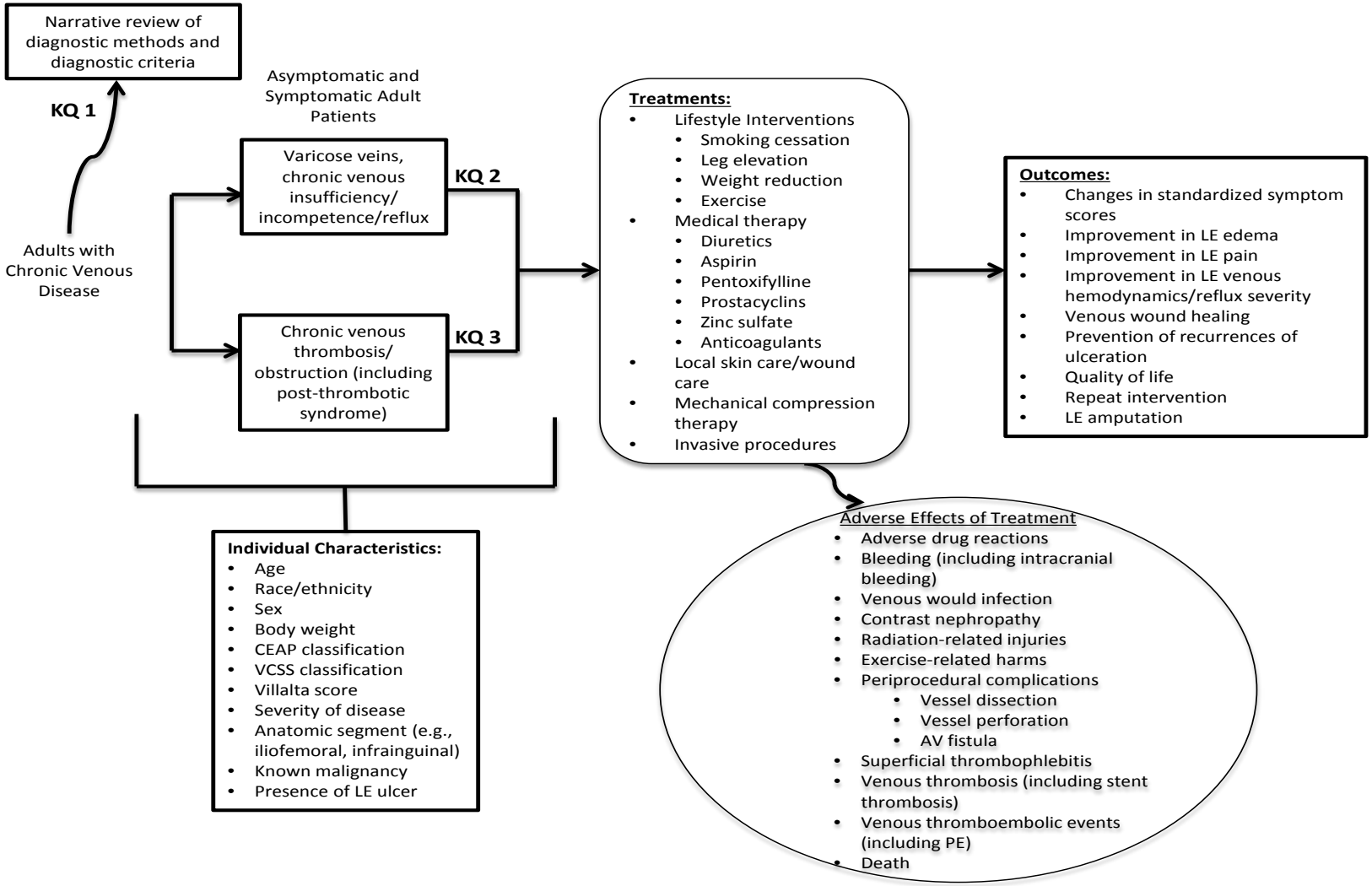
characteristics of disease, anatomic segment affected, and characteristics of the therapy (e.g., exercise intensity, type of mechanical compression)?

3d. What are the comparative safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by patient subgroup (age, sex, race, risk factors, comorbidities, anatomic segment, or disease severity)?

Analytic Framework

The analytic framework presented in Figure 1 illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. This figure shows how adults without known chronic venous disease may be diagnosed and treated, and how treatment is associated with a range of potential adverse effects and outcomes. Separate KQs were developed regarding the accuracy of various diagnostic strategies, and the effectiveness and risk of adverse events associated with pharmacologic, lifestyle, and invasive therapies.

Figure 1. Analytic framework



Abbreviations: AV=arteriovenous; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; KQ=key question; LE=lower extremity; PE=pulmonary embolism; VCSS=Venous Clinical Severity Score

Organization of This Report

The remainder of the report details our methodology and presents the results of our literature synthesis, with summary tables and strength of evidence grading for major comparisons and outcomes. In the discussion section, we offer our conclusions, summarized findings, and other information that may be relevant to translating this work for clinical practice and future research.

Appendices provide further details on our methods and the studies we assessed, as follows:

- Appendix A. Exact Search Strings
- Appendix B. Data Abstraction Elements
- Appendix C. List of Included Studies
- Appendix D. List of Excluded Studies
- Appendix E. Key to Included Primary and Companion Articles
- Appendix F. Characteristics of Included Studies

A list of abbreviations and acronyms is provided at the end of the report.

Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality's (AHRQ's) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[8] (hereafter referred to as the *Methods Guide*) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[9] See the review protocol (http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/lecvd_protocol.pdf) for full details.

Protocol Development

The topic of this report and the key questions (KQs) arose through nomination by the Centers for Medicare and Medicaid Services (CMS). The EPC drafted the protocol and the protocol was reviewed by AHRQ, CMS, and the technical expert panel (TEP). The TEP was recruited to provide high-level content and methodological expertise throughout the development of the review. The TEP represented clinician/researchers and scientific experts in areas of cardiovascular/endovascular medicine, interventional cardiology, radiology, vascular surgery, and thrombosis; payers; and Federal agencies. The finalized protocol is posted on the AHRQ website.[10] The PROSPERO registration is CRD42016035669.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews, limiting the search to articles published from January 1, 2000, to June 30, 2016. The timeframe of 2000 forward represents contemporary treatment strategies in the field and corresponds to timings where significant changes in the availability of endovascular techniques occurred within the peripheral vascular treatment community. An experienced search librarian guided all searches.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.[11-51] The reference lists for identified pivotal articles were manually hand-searched and cross-referenced against our database, and additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic bibliographical database (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias in recent studies, we searched ClinicalTrials.gov to identify completed but unpublished studies (we also explored the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques). Other gray literature databases searched were the National Guidelines Clearinghouse and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal. Both registry sources (ClinicalTrials.gov and the WHO ICTRP) and the results from the National Guidelines Clearinghouse were used to identify relevant articles from completed studies. Search dates and search terms used for all of the above sources are provided in Appendix A. Additional gray literature was solicited through the AHRQ Effective Health Care (EHC) website and a notice posted in the Federal Register.

Inclusion and Exclusion Criteria

We specified our inclusion and exclusion criteria based on the PICOTS (populations, interventions, comparators, outcomes, timing, settings) identified for each question. Table 4 summarizes the inclusion and exclusion criteria used in the review.

Table 4. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	KQ 1: Adults (over age 18) with the diagnosis of LE varicose veins, LE chronic venous /insufficiency/incompetence/reflux, and/or LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome) KQ 2: Asymptomatic or symptomatic adults (over age 18) with the diagnosis of LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux KQ 3: Asymptomatic or symptomatic adults (over age 18) with the diagnosis of LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome) Subgroups of interest for KQs 2-3: • Age • Race/ethnicity • Sex • Body weight • CEAP classification • VCSS classification • Villalta score • Severity of disease • Anatomic segment affected (e.g., iliofemoral, infrainguinal) • Known malignancy • Presence of LE ulcer	Individuals younger than 18 years of age. Studies including both adults and patients under 18 were excluded unless data for the adult population was reported separately. Individuals with acute venous disease (including acute DVT). Studies with mixed populations of both acute and chronic disease were excluded unless data for the patients with chronic disease was reported separately. Pregnant women
Interventions	KQ 1: Any standard chronic venous disease diagnostic strategy, including: air plethysmography, LE DUS (with and without compression), invasive venography, MRV, computed tomographic venography, D-dimer testing KQ 2: Lifestyle interventions (e.g., smoking cessation, leg elevation, weight reduction, exercise), medical therapy, local skin care/wound care, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) • Medical therapies: diuretics, aspirin, pentoxifylline, prostacyclins, zinc sulfate • Invasive surgical/endovascular procedures: sclerotherapy (liquid, foam, glue), RFA, thermal ablation, chemical ablation, ambulatory phlebectomy, transilluminated powered phlebectomy, venous ligation, venous excision KQ 3: Lifestyle interventions (e.g., smoking cessation, leg elevation, weight reduction, exercise), medical therapy, local	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	skin care/wound care, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) • Medical therapies: anticoagulants including warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran; diuretics • Invasive surgical/endovascular procedures: endovenous angioplasty/stenting, ultrasound accelerated thrombolysis for chronic DVT (EkoSonic® endovascular system), surgical thromboembolectomy	
Comparators	KQ 1: Specific diagnostic modalities listed above were compared with one another KQs 2-3: Specific treatments were compared to other included treatments as described above or to no treatment (placebo or usual care)	Same treatment comparisons that vary by characteristics such as dose, timing, manufacturer, compression level, or energy level. Comparisons between interventions for local skin care/ wound care.
Outcomes	KQ 1: • Accuracy of diagnostic strategy, as measured by: o Sensitivity o Specificity o Positive predictive value o Negative predictive value o Inter-rater reliability o Internal consistency o Test-retest reliability o False positives o False negatives o Positive likelihood ratio o Negative likelihood ratio KQs 2-3: • Changes on standardized symptom scores (Villalta score, CEAP classification, and VCSS score) • Qualitative reduction in LE edema • Qualitative reduction in LE pain • Improvement in LE venous hemodynamics/reflux severity as measured by air plethysmography, DUS, or invasive venography • Venous wound healing • Recurrent ulceration • Patient-reported quality of life (including AVVQ) • Repeat intervention • LE amputation • Adverse effects of treatment, including: o Adverse drug reactions o Bleeding (including intracranial bleeding) o Venous wound infection o Contrast nephropathy o Radiation-related injuries	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	○ Exercise-related harms ○ Periprocedural complications (vessel dissection, vessel perforation, and AV fistula) ○ Superficial thrombophlebitis ○ Venous thrombosis/occlusion (including stent thrombosis), ○ Venous thromboembolic events (including PE) • Death	
Timing	Studies with all durations of follow-up were included in the review, incorporating short-term (≤30 days), intermediate-term (31 days to 6 months), and long-term (>6 months) events	
Settings	All clinical settings, including inpatient and outpatient (KQ 1 only)	
Study design	• Original data • RCTs, prospective and retrospective observational studies with comparator • RCTs: sample size ≥20 subjects • Observational studies: sample size ≥20 subjects for KQs 1 and 3; for KQ 2, sample size ≥500 subjects relevant to the KQ 2 population	Editorials, nonsystematic reviews, letters, case series, case reports, abstract only, articles that have been retracted or withdrawn
Publications	• English language only • Published on or after January 1, 2000 • Relevant systematic reviews, meta-analyses, or methods articles (used for background only)[a]	Non-English language articles[b]

[a] Systematic reviews and meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional citations to consider in the review.
[b]Non-English language articles were excluded due to: (1) the high volume of literature available in English language publications, (2) the focus of our review on applicability to populations in the United States, and (3) the scope of our KQs.
Abbreviations: AV=arteriovenous; AVVQ=Aberdeen Varicose Vein Questionnaire; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; DUS=duplex ultrasound; DVT=deep vein thrombosis; KQ(s)=key question(s); LE=lower extremity; MRV=magnetic resonance venography; PE=pulmonary embolism; PICOTS=populations, interventions, comparators, outcomes, timing, settings; RCTs=randomized controlled trials; RFA=radiofrequency ablation; VCSS=Venous Clinical Severity Score

Study Selection

For citations retrieved from PubMed, Embase, and the Cochrane Database of Systematic Reviews, two reviewers independently screened each title and abstract for potential relevance to the research questions using prespecified inclusion/exclusion criteria described in Table 4. Citations included by either reviewer underwent full-text screening.

At the full-text screening stage, two reviewers independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reconciled the difference through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction. We did not contact study authors for additional data. All screening results were tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

Appendix C provides a list of all articles included for data abstraction. Appendix D provides a list of articles excluded at the full-text screening stage, with reasons for exclusion.

Data Extraction

The investigative team created abstraction forms that were programmed using the DistillerSR software. The abstraction forms were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Based on their clinical and methodological expertise, a pair of researchers were assigned to abstract data from each of the eligible articles. One researcher abstracted the data and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached. We linked related studies to avoid duplication of patient cohorts.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). Particular attention was given to describing the details of the treatment (e.g., timing of therapy relative to venous thrombosis event, pharmacotherapy dosing, duration of pharmacotherapy, anatomic segment of interventional therapies), patient characteristics (e.g., symptom status via CEAP and Villalta scores, presence or absence of LE venous wounds, history of malignancy, age), and study design (e.g., randomized controlled trial [RCT] versus observational) that could be related to outcomes. Comparators were described carefully because treatment standards may have changed during the period covered by the review. The safety outcomes were framed to help identify adverse events, including those from drug therapies (such as bleeding), LE venous wound infections, and those resulting from procedural complications (including access site complications wound infections).

Quality Assessment of Individual Studies

We assessed methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias tool for RCTs,[52] and the Newcastle-Ottawa Scale for observational studies.[53] Briefly, we rated each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. Table 5 describes the overall study quality assessment ratings. Individual study quality ratings are provided in Appendix F.

Table 5. Definitions of overall quality ratings

Rating	Definition
Good (low risk of bias)	These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
Fair (moderate risk of bias)	These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The grading was outcome-specific such that a given study that analyzed its primary outcome well but did an incomplete analysis of a secondary outcome could be assigned a different quality grade for each of the two outcomes. Studies of different designs were graded within the context of their respective designs. Thus, RCTs were graded as good, fair, or poor, and observational studies were separately graded as good, fair, or poor (Appendix B).

For studies relevant to KQ 1, we also applied the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool for assessment of diagnostic accuracy studies.[54,55] Table 6 describes the overall study quality assessment ratings used for this evidence.

Table 6. Definitions of overall quality ratings based on QUADAS-2 assessments

Rating	Definition
Low risk of bias	No major features that risk biased results. RCTs are considered a high-quality study design, but studies that include consecutive patients representative of the intended sample for whom diagnostic uncertainty exists may also meet this standard. A "low risk" study avoids the multiple biases to which medical test studies are subject (e.g., use of an inadequate reference standard, verification bias), and key study features are clearly described, including the comparison groups, outcomes measurements, and characteristics of patients who failed to have actual state (diagnosis or prognosis) verified.
Medium risk of bias	Susceptible to some bias, but flaws not sufficient to invalidate the results. The study does not meet all the criteria required for a rating of low risk, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk of bias	Significant flaws imply biases of various types that may invalidate the results. The study has significant biases determined a priori to be major or "fatal" (i.e., likely to make the results either uninterpretable or invalid).

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies-2; RCTs=randomized controlled trials

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We ordered our findings by treatment comparison and then within these comparisons by outcome with long-term final outcomes emphasized.

We reviewed and highlighted studies using a hierarchy-of-evidence approach. The best evidence available was the focus of our synthesis for each key question. If high quality evidence was not available, we described any lower quality evidence we were able to identify, but we underscored the issues that made it lower quality and the uncertainties in our findings. We assessed and stated whether the inclusion of lower quality studies would change any of our conclusions and performed sensitivity analyses excluding this evidence where appropriate.

We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility was dependent on the volume of relevant literature (we required 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, and completeness of the reporting of results. If the above criteria were met and a meta-analysis was appropriate, we used random-effects models to synthesize the available evidence quantitatively. We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may have been limited. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals. We anticipated that intervention effects may be

heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation would be associated with the intervention effects. If there were sufficient studies, we performed subgroup analyses and/or meta-regression analyses to examine these hypotheses. We performed quantitative and qualitative syntheses separately by study type and discussed their consistency qualitatively.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) for each outcome assessed; thus, the SOE for two separate outcomes in a given study may be graded differently. The SOE was assessed using the approach described in AHRQ's *Methods Guide*.[8,56,57] In brief, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias, as described in detail above. Additional domains used when appropriate (most relevant to observational studies) were coherence, dose-response association, impact of plausible residual confounders, and strength of association (magnitude of effect). When the body of evidence for a particular outcome included both RCTs and observational studies, we graded each study type separately using design-specific criteria. In considering the overall strength of the entire body of evidence, we considered the extent to which the observational evidence was consistent with RCT data, particularly with regard to direction and magnitude of effect. Because of the risk of unmeasured confounding, observational studies generally would not contribute to estimates of the magnitude of effect, and judgment about the precision of the effect, when RCT data were available. If there were other issues (such as differences in when and where RCTs were performed compared to observational studies, and how these differences might affect applicability), this would generally lead to increased uncertainty about the magnitude and precision of any treatment effect.[58] These domains were considered qualitatively, and a summary rating of high, moderate, or low SOE was assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the definitions given in Table 7.

Table 7. Definition of SOE ratings

Rating	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Applicability

We assessed applicability across our KQs using the method described in AHRQ's *Methods Guide*.[8,59] In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes were different across studies that recruit different populations (e.g., age groups, risk factors, comorbidities, characteristics of disease, U.S. vs. non-U.S. settings) or used different methods to implement the interventions of interest; that is, important characteristics were those that affected baseline (control group) rates of events, intervention group rates of events, or both. We used a checklist applied to each abstracted study to guide the assessment of applicability (Appendix B). For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. We then used these data across KQs to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, the possibility of treatment intervention learning curves, and clinical relevance and timing of the outcome measures. We summarize issues of applicability qualitatively.

Peer Review and Public Commentary

Experts in the fields of cardiology, radiology, thrombosis, vascular medicine, vascular surgery, and public health were invited to provide external peer review of the draft report. AHRQ, CMS, and members of the TEP were also given the opportunity to provide comments. In addition, the draft report was posted on the AHRQ website for public comment from July 8, 2016, to August 3, 2016. We have addressed all reviewer comments, revising the text as appropriate, and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the EHC website. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

Results

Introduction

In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by key question (KQ). Under each of the three KQs, we begin by listing the key points of the findings, followed by a brief description of included studies and a detailed synthesis of the evidence. Within KQ 2 and KQ 3, the detailed syntheses are organized first by treatment comparison and then by outcome. We conducted quantitative syntheses where possible, as described in the Methods chapter.

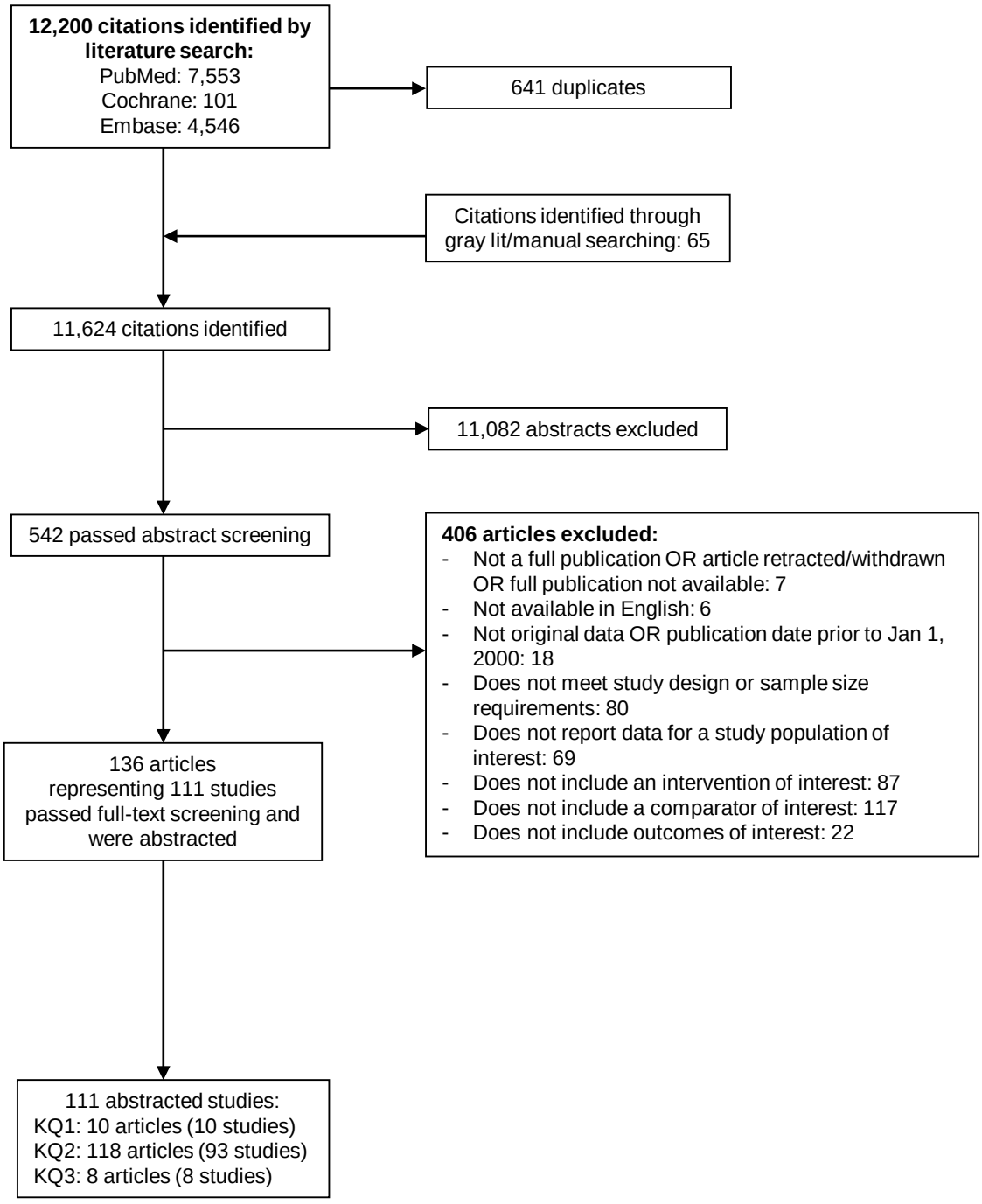
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and the Cochrane Database of Systematic Reviews yielded 11,559 unique citations. Manual searching of gray literature databases and bibliographies of key articles or referral by investigators identified 65 additional citations, for a total of 11,624 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 542 full-text articles were retrieved and screened. Of these, 406 were excluded at the full-text screening stage, leaving 136 articles for data abstraction. These 136 articles described 111 unique studies. The relationship of studies to the review questions is as follows: 10 studies relevant to KQ 1, 93 studies relevant to KQ 2, 8 studies relevant to KQ 3.

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a "study key" table listing the primary and companion publications for the 111 included studies.

Figure 2. Literature flow diagram



Description of Included Studies

Overall, we included 111 studies described in 136 publications: 10 studies were relevant to KQ 1, 93 studies to KQ 2, and 8 studies to KQ 3. Studies were conducted wholly or partly in continental Europe or the United Kingdom (UK; 73 studies – 65%), the United States or Canada (19 studies – 17%), the Middle East (3 studies – 3%), Asia (8 studies – 7%), Africa (1 study – <1%), Latin America (4 studies – 4%), Australia/New Zealand (2 studies – 2%), and both in the United States and the UK/Europe (2 studies – 2%). Further details on the studies included for each KQ are provided in the relevant results sections, below, and in Appendix F.

We searched the ClinicalTrials.gov study registry as a mechanism for ascertaining publication bias by identifying studies that have been completed but are as yet unpublished. We acknowledge that this is not an exhaustive strategy, as several other registries also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the widely used, U.S.-based ClinicalTrials.gov registry provided the most relevant information to the populations and interventions of interest in this review. Our search yielded 285 records of completed trials for screening. Manual review identified 19 of those records as potentially relevant to this review. Of those 19 records, we were not able to identify publications for 4 studies that had expected completion dates 3 years or more prior to our search. All 4 were considered potentially relevant to KQ 2. Planned enrollment among these studies ranged from 40 to 98 individuals, for a total combined sample size of 248 patients. No results from these studies were posted to ClinicalTrials.gov.

Comparisons assessed in the 4 studies were: use of graduated compression stockings versus no use (a pilot feasibility study enrolling patients already randomized to the PeriOperative ISchemic Evaluation-2 Trial),[60] a structured physical therapy program versus control for management of chronic venous insufficiency/incompetence,[61] crossectomy and avulsion versus foam sclerotherapy for treatment of isolated varicosis of the anterior accessory great saphenous vein,[62] and use of a topical antisense compound versus control for treatment of venous leg ulcers.[63] We did identify a conference abstract[64] for the study assessing the topical compound, but were not able to find a corresponding peer-reviewed publication. These 4 studies if completed would add 248 patients to our analysis. The included studies in KQ 2 represent evidence from 110,744 patients. We do not believe that these 4 “missing” trials are likely to have had a meaningful impact on our review’s results. Because of the relatively low proportion of unpublished studies identified through our ClinicalTrials.gov registry analysis, we do not believe these findings indicate significant publication bias in the evidence base that would impact our overall conclusions.

Key Question 1. Narrative Review of Diagnostic Methods and Criteria for Adult Patients with Lower Extremity Chronic Venous Disease (LECVD)

KQ 1 reviews the diagnostic methods and diagnostic criteria for all adult patients, symptomatic and asymptomatic, with lower extremity (LE) varicose veins, LE chronic venous insufficiency/incompetence/reflux, and/or LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome).

Description of Included Studies

We identified 10 studies published since Jan 1, 2000 that examined diagnostic methods for all adult patients with LECVD.[65-74] All 10 were observational studies, representing a total of 769 patients. Three of the studies were conducted in the United States,[66,69,72] five in the UK/Europe,[65,68,70,73,74] one in Asia,[67] and one in Latin America.[71] Seven studies reported conducting the studies at a single center,[66,67,69,71-74] and three studies did not report the number of study sites or this number was unclear.[65,68,70] Seven studies did not report the funding source or the funding source was unclear.[65,66,69-73] One study reported funding from an industry source,[68] and two studies reported funding from a non-government, non-industry source.[67,74] Seven studies were conducted in a specialty practice,[66,67,69,71-74] while the remaining three studies did not report a specific setting or the setting was unclear. Both the Newcastle-Ottawa Scale and Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) were used for quality assessment of these studies. Eight studies were rated as fair quality with a medium risk of bias,[65-69,71-73] one study was rated as good quality with a low risk of bias[74] and the remaining study was rated as poor quality with a high risk of bias.[70].

Characteristics of the included studies are summarized in Table 1 in Appendix F. The following comparisons were assessed in the included studies and are detailed in the descriptive analysis that follows:

- Magnetic resonance venography (MRV) versus invasive venography and intravascular ultrasound (IVUS) – one study[69]
- 3-dimensional computed tomography venography (CTV) versus DUS– one study[67]
- Ascending and descending phlebography versus DUS– two studies[66,68]
- Ambulatory strain gauge plethysmography versus DUS – one study[68]
- DUS versus surgical evaluation/confirmation – three studies[65,70,71]
- Ascending phlebography versus surgical evaluation/confirmation – two studies[65,70]
- DUS versus venography + IVUS – two studies[72,74]
- Air Plethysmography versus Doppler ultrasound + MRV versus Doppler ultrasound + CTV versus DUS – one study[73]

Key Points

- There are very few comparative studies of diagnostic testing methods for LECVD in the recent literature, with the majority of the comparative studies of diagnostic testing methods for LECVD published prior to 2000 (and therefore not included in this review).
- There was extreme heterogeneity of patients, comparisons, and outcomes reported in the included diagnostic studies.

- Evidence was insufficient for any specific diagnostic test method for any of the outcomes studied.

Detailed Synthesis

When considering characteristics of diagnostic tests that may be used in patients with LECVD, the following concepts are applicable:

- Performance of the diagnostic test
  - The inclusion/exclusion criteria of studies
  - The presence of a gold standard
  - The comparisons included in the study of diagnostic tests
  - The outcomes measured, including sensitivity and specificity
  - Other measures including reliability, validity, responsiveness
- Whether the diagnostic test influenced the choice of treatment for LECVD
- Whether the severity of disease influenced the type of diagnostic test
- Whether the treatment of LECVD influenced the type of diagnostic test

A summary of each individual study included in this KQ is summarized in Table 1 in Appendix F. The studies evaluating diagnostic methods in patients with LECVD were, in general, heterogeneous, fair quality, and had small sample sizes. The patients in the studies included asymptomatic and symptomatic patients, patients with LE varicose veins, LE chronic venous insufficiency/incompetence/reflux, LE venous ulceration, and LE chronic venous obstruction/thrombosis. Finally, the outcomes assessed varied across studies based on the location of the disease (e.g., greater saphenous vein [GSV], popliteal vein, site of prior venous ligation). Due to these factors, no meta-analyses were performed on this group of studies. The sections that follow include descriptive analyses of diagnostic methods and criteria for patients with LECVD.

General Concepts and Methods of Diagnosis for LECVD

The clinical presentation of patients and severity of disease often dictate whether diagnostic testing is performed, and if performed, which tests are chosen. In patients with mild and moderate symptoms, including LE varicose veins and LE edema, diagnostic testing is not required and often not performed. In patients with severe clinical manifestations, such as more significant LE edema, LE ulceration, and LE skin changes, the clinical signs are often sufficient to guide clinicians to establish a diagnosis of LECVD. In all patients with signs of LECVD, further diagnostic testing may still be performed to confirm the diagnosis, grade the severity, and determine the location and etiology of disease. Additionally, diagnostic testing may identify patients with LECVD that may benefit from specific treatment strategies such as endovenous procedures and surgical treatment.

The clinical practice guidelines established by the Society of Vascular Surgery (SVS), American Venous Forum (AVF), and American College of Phlebology describe the appropriate use of diagnostic tests in patients with LECVD.[75,76] The recommendations made in these guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (www.gradeworkinggroup.org). SVS/AVF also have established guidelines for venous ulcers.[77] Similarly, the United Kingdom's (UK's) National Institute for Health and Care Excellence (NICE) has published a clinical guideline on varicose veins.[78]

History and Clinical Examination

The medical history is an important component of the initial evaluation of all patients with suspected LECVD. Specifically, the chronicity of symptoms and signs, prior history of deep vein thrombosis (DVT) or superficial thrombophlebitis, family history of LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux, and pregnancy history in women are critical parts of this medical history. For those patients with a prior history of DVT, further questioning about the whether the DVT was provoked or unprovoked, and then type and duration of treatment is warranted. In patients with LE ulceration, questioning about diagnostic testing to evaluate alternative causes of ulceration (e.g., peripheral artery disease [PAD], diabetes mellitus, trauma) is also important.

Clinical examinations of patients being evaluated for LECVD should include comprehensive physical examinations (cardiovascular and abdominal examinations) and focused examinations of the LE. The clinician should focus the LE evaluation on the venous system, but he/she should ensure that alternative diseases such as PAD and skin infection are excluded. Inspection and palpation of the lower extremities are the essential parts of the clinical examination. Details such as varicose vein(s) location and size, the presence and location of telangiectasia(s), the presence and severity of LE edema (pitting or nonpitting), the characterization of skin changes (e.g., induration, pigment changes, dermatitis, lipodermatosclerosis), and the presence, size, and location of LE ulceration should be recorded. The goal of the history and clinical examination is to classify CEAP of LECVD (as detailed in the Introduction of this report).

Ambulatory Plethysmography (Air, Strain Gauge, and Photo Plethysmography)

Plethysmography is a useful noninvasive test to evaluate LE chronic venous insufficiency/incompetence/reflux and LE chronic venous obstruction. Air plethysmography uses a transducer, pressure sensor, and electrical circuit to measure the venous limb volume with different patient maneuvers (e.g., supine, standing, ankle flexion). Measurements such as venous volume, venous refilling time (VRT), venous filling index, maximum venous outflow (MVO) and ejection volume are recorded and can be compared over time and before/after treatment. Strain gauge plethysmography uses limb circumference changes to estimate venous volume changes after inflation and rapid deflation of a thigh occlusion cuff or tourniquet. VRT and MVO are often calculated using strain gauge plethysmography.

VRT is defined as the time in seconds required for the lower leg to be filled with blood after the calf muscle has emptied the veins as thoroughly as possible. VRT is measured in a seated position, and a normal VRT is considered to be >120 seconds (as all venous filling occurs via arterial inflow to the lower leg). In patients with venous insufficiency/incompetence/reflux, VRT occurs more rapidly and is often dependent on the severity of incompetence/reflux (i.e., asymptomatic or mild reflux: 40-120 seconds; significant reflux: 20-40 seconds; severe reflux: <20 seconds).

MVO testing is useful to determine whether venous obstruction exists in the LE, and can be measured using air plethysmography or strain gauge plethysmography. To perform the test, a tourniquet is applied to the upper thigh to occlude flow for approximately 2 minutes and then is suddenly released. A 1-second outflow fraction is then determined by air plethysmography, and it is a percentage of the venous volume ejected in 1 second.

Photoplethysmography uses infrared light to indirectly measure venous limb volume changes. A cutaneous light sensor continuously records the signal intensity in superficial

capillary networks at baseline, with plantar flexion/extension exercises, and with a tourniquet applied above or below the knee. VRT is the most common measurement recorded, and increased capillary filling with exercise is indicative of chronic venous insufficiency/incompetence/reflux. Once this diagnosis has been established, placement of a tourniquet and subsequent release of the tourniquet is useful to determine the site of incompetence/reflux by observing whether the venous system returns to the baseline pressure (failure to return to baseline is indicative of incompetence/reflux).

In one included study,[73] ambulatory plethysmography was compared to DUS alone, DUS + MRV, and DUS + CTV. Sensitivity ranged between 35 percent and 64 percent, and specificity ranged between 47 percent and 88 percent; however, the gold standard was unclear for this study. Another included studies evaluated ambulatory plethysmography as compared to triplex ultrasound,[68] and the sensitivity of ambulatory strain-gauge plethysmography was very low (4 percent in femoral and saphenous veins; 5 percent in popliteal veins), while specificity was 100 percent in both venous systems. In the SVS/AVF consensus guidelines, the selective use of ambulatory plethysmography for diagnosis of simple varicose veins (CEAP class C_2) is GRADE 2C, while its use in patients with advanced LECVD (CEAP class C_3-C_6) is GRADE 1B.[75]

Duplex Ultrasound

DUS is a common, direct method of evaluation of patients with evidence of LECVD, and it is generally accepted as the gold standard for noninvasive diagnosis of LECVD. DUS is useful to evaluate the presence of anatomic/congenital abnormalities, venous obstruction, and/or valvular incompetence/reflux. Equipment with power/color Doppler and pulse-wave Doppler capabilities is routinely utilized to document the direction of venous flow, the presence of venous obstruction, and venous turbulence. DUS also remains the most common method of evaluation for acute DVT, and these changes are often distinguished from findings of LECVD. DUS should be performed by experienced technicians and/or physicians and interpreted by licensed physicians who have significant experience with LECVD.

When DUS is performed to evaluate LECVD, patients should be in the upright position and examination should be performed from the inguinal ligament down to the foot. Complete examinations include interrogation of all deep veins (common femoral, femoral, deep femoral, popliteal, sural, peroneal, gastrocnemial, anterior tibial, and posterior tibial veins) and all superficial veins (GSV, small saphenous [SSV], accessory saphenous, and perforating veins). Four components of DUS are commonly reported: visualization, compressibility, flow (which includes a measure of venous reflux), and augmentation.[75] Comprehensive examinations include transverse and longitudinal imaging to assess patency of each venous segment with compression.

In patients with LE varicose veins, the diameter of the saphenous vein at the mid-thigh and knee is often measured by DUS. When considering additional treatment of LE varicose veins (e.g., endovenous ablation), DUS should be performed prior to this additional treatment to identify all LE varicose veins and all sources of superficial venous filling (e.g., tributaries and incompetent perforating veins) as these often contribute to recurrence of LE varicose veins and LE chronic venous insufficiency/incompetence/reflux.[75,78]

Unlike plethysmography, DUS is capable of measuring and localizing valvular incompetence and venous reflux in individual veins (e.g., GSV). DUS assesses the competence of each vein and the saphenovenous junction after augmentation of flow by cuff compression of the calf and rapid release of the cuff while observing for retrograde flow. The most common measurement of reflux as measured by DUS after Valsalva maneuver and/or cuff compression/release of the calf

is reflux time. An international consensus recommends a cutoff value of 500 milliseconds for diagnosis of saphenous, tibial, deep femoral, and perforating vein reflux, and 1 second for diagnosis of femoral and popliteal vein reflux. A longer duration of reflux (i.e., greater reflux time) is suggestive of more severe disease.[75]

The characteristics of DUS that are useful for chronic venous obstruction/thrombosis include compressibility and flow patterns. To evaluate for proximal obstruction, direct visualization of common femoral and iliac veins for intrinsic or extrinsic abnormalities is possible in many patients. Interrogation of ipsilateral and contralateral common femoral vein waveforms is also important; in patients with unilateral obstruction, continuous flow is observed in the ipsilateral, occluded limb, while normal flow with right atrial pulsations and/or respiratory variation is observed in the contralateral, normal limb. For patients with suspected post-thrombotic syndrome, DUS should be performed of the entire deep venous system to evaluate for areas of vein narrowing, occlusion, or collateralization.[79]

Nine of the included studies evaluated the use of DUS with another imaging modality in the diagnosis of LECVD.[65-68,70-74] In two of the studies,[67,68] DUS was used as the gold standard, and the gold standard was unclear in one study,[73] while it was compared to another imaging modality or surgical evaluation in the remaining seven studies.[65,66,69-72,74] There was significant heterogeneity in the populations studied and clinical indication for diagnostic testing, and limited conclusions can be drawn from these studies. The SVS/AVF consensus guidelines recommend the use of DUS as a ubiquitous imaging test for the diagnosis of patients with suspected LECVD (GRADE 1A).

Magnetic Resonance Venography (MRV)

The use of MRV involves contrast-enhanced and noncontrast-enhanced pulse sequences, and has similar characteristics to routinely used magnetic resonance imaging (MRI) tests. MRV has been limited to specific indications due to its expense and time-consuming nature. MRV has been found to be useful for obese patients and patients with LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux who have suspected pelvic, caval, and/or iliac vein obstruction or compression when DUS is inconclusive (GRADE 1B). One of the included studies[69] evaluated MRV versus another diagnostic modality (invasive venography and IVUS) in the diagnosis of LE chronic venous obstruction. MRV was 100 percent sensitive for the diagnosis of proximal venous obstruction, but specificity was only 22.8 percent and the false-positive rate was 41.5 percent.

Computed Tomography Venography (CTV)

The use of CTV has also been limited to specific indications due to its expense, requirement for iodinated contrast, and radiation exposure. When compared with MRV, CTV has similar indications (i.e., obese patients and patients with suspected proximal obstruction), excellent spatial resolution, and is safe for patients with MRI incompatible devices such as pacemakers and defibrillators (GRADE 1B). One of the included studies[67] evaluated CTV versus another diagnostic modality (DUS) in the diagnosis of LECVD. The sensitivity of CTV for the diagnosis of GSV insufficiency was 98.2 percent and SSV insufficiency was 53.3 percent, while the specificity for GSV insufficiency was 83.3 percent and for SSV insufficiency was 94.9 percent.

Invasive Phlebography or Venography

Ascending or descending phlebography or venography has long been considered the gold standard for invasive diagnosis of LECVD. Ascending phlebography is performed by injection of iodinated contrast into a vein in the dorsum of the foot and visualization of this contrast traveling up the deep venous system of the limb. Ascending phlebography is most useful to detect patency of the deep veins of the limb, but has been largely replaced by DUS and other noninvasive diagnostic methods. Descending phlebography is performed by injection of iodinated contrast into a proximal vein of the leg during a Valsalva maneuver and visualization of this contrast traveling back into the common femoral vein and saphenofemoral junction. Descending phlebography is most useful to detect valvular incompetence and venous reflux in the femoral veins, but it has been largely replaced by DUS and is mostly used when noninvasive imaging techniques are inconclusive.[1] Direct venous pressure measurements can be performed during ascending and/or descending phlebography to evaluate for venous reflux and/or chronic venous obstruction, however there is no consensus regarding how pressure measurement results should guide treatment decisions such as surgical reconstruction or endovenous intervention.

Contrast phlebography or venography is often employed during endovenous intervention procedures such as angioplasty or stenting. Adjunctive techniques such as IVUS are commonly utilized to (a) confirm the diagnosis of proximal venous obstruction and (b) optimize treatment including choice of balloon/stent diameter and evaluation of stent expansion and apposition. An observational assessment of routine IVUS use at the time of contrast phlebography is currently underway and results are expected in late 2016.[80]

Seven of the included studies evaluated the use of invasive phlebography or venography with another imaging modality in the diagnosis of LECVD.[65,66,68-70,72,74] In four of these studies,[66,69,72,74] invasive phlebography or venography was used as the gold standard, while it was compared to another imaging modality or surgical evaluation in the remaining three studies.[65,68,70] There was significant heterogeneity in the populations studied and clinical indication for diagnostic testing, and limited conclusions can be drawn from these studies. The SVS/AVF consensus guidelines recommend the use of invasive venography or phlebography in patients who are undergoing invasive treatment of LECVD (GRADE 1B). Adjunctive use of IVUS during invasive venography is also recommended in patients with suspected proximal chronic venous obstruction or post-thrombotic syndrome (GRADE 1B).

Conclusions

In many cases, the diagnosis of LECVD is made after a detailed medical history and clinical examination. In addition to the history and physical, multiple physiologic and imaging modalities (plethysmography, DUS, MRV, CTV, invasive venography or phlebography) are useful to confirm LECVD and/or localize the disease and guide therapy. DUS has largely supplanted invasive venography or phlebography as the gold standard for LECVD diagnosis due to the fact that invasive venography/phlebography is more costly, more invasive, and requires exposure to iodinated contrast and ionizing radiation. In patients with suspected proximal venous obstruction, MRV or CTV may be useful to guide surgical reconstruction or endovenous intervention while IVUS is often used during contrast venography to confirm the diagnosis and to optimize treatment.

Very few comparative studies of diagnostic testing methods for LECVD are in the recent literature (since the year 2000). After assessment of this literature, we concluded that extreme heterogeneity of patients, comparisons, and outcomes existed in the included diagnostic studies.

In conclusion, evidence was insufficient for any specific diagnostic test method for any of the outcomes studied.

Key Question 2. Treatments for Adult Patients with LE Varicose Veins and/or LE Chronic Venous Insufficiency/Incompetence/Reflux

KQ 2 examines treatments for all adult patients, symptomatic and asymptomatic, with LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux with respect to the following areas:

- The comparative effectiveness of exercise, medical therapy, weight reduction, mechanical compression therapy, and invasive procedures on health outcomes (KQ 2a)
- The diagnostic methods and criteria used in each study (KQ 2b)
- How the comparative effectiveness of treatment varies by patient characteristics, including age, sex, risk factors, comorbidities, characteristics of disease, anatomic segment affected, and characteristics of the therapy (KQ 2c)
- The comparative safety concerns associated with each treatment strategy and how safety concerns vary by patient subgroup (KQ 2d)

Description of Included Studies

We identified 93 studies represented by 118 articles[81-198] that examined treatments for patients with LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux. One article described three separate studies; for ease of citation, we use separate numbered references for the three primary studies throughout the rest of this section.[118,199,200] Twenty-one studies were described in more than one publication. Four articles[106,107,181,198] share the same author. Two articles represent one study.[106,107] Due to uncertain overlap, the remaining two articles are described and counted separately.[181,198] Appendix E provides a key to primary and companion articles. The description of included studies that follows cites only primary articles; companion articles are cited as appropriate under "Detailed Synthesis," below.

Of the 93 included studies, 6 were observational, representing a total of 110,744 enrolled patients.[125,131,183,184,195,198] Eighty-six studies were randomized controlled trials (RCTs), representing a total of 16,267 enrolled patients, and one additional RCT which did not report findings by patient, which represented a total of 130 legs enrolled.[101] One study was conducted in Africa,[153] five in Asia,[140,145,148,151,196] two in Australia/New Zealand,[158,192] three in Latin America,[127,161,170] three in the Middle East,[130,139,186] 68 in the UK/Europe,[82,84,87,89,91,94,97,98,101,103,105,107,111,113,114,117,118,121,123,128,133-138,142-144,146,147,149,150,152,155-157,159,160,162-169,171-183,185,187-189,191,195,197-200] 9 studies in the United States,[124,125,129,131,141,154,184,193,194] and two studies in both the UK/Europe and United States.[97,163] Thirty-eight studies were conducted in multiple centers,[87,89,97,98,107,111,113,117,118,121,124,128-131,133,134,141,146,148,150,157,163,165,171,177,179,183-186,188,193-195,197,199,200] 47 were conducted in a single center,[82,94,101,103,105,114,123,125,127,135,136,138-140,142,144,145,147,149,151-156,158-162,164,166-170,172,174-176,178,182,191,192,196] and eight studies did not report the study site or it was unclear.[137,143,173,180,181,187,189,198]

Nine studies reported government funding,[89,113,118,129,140,146,175,199,200] 14 studies reported industry funding,[82,97,124,141,157,159,163,168,171,174,193,194,197] and 19 studies reported non-government, non-industry funding.[91,107,111,121,123,125,127,130,136,138,143,144,149,152,154,160,165,172,176] Multiple studies

reported a combination of funding sources; specifically, four studies reported a combination of industry and non-government funding,[103,105,114,155] three studies reported a combination of government and industry funding,[98,148,192] one study reported a combination of funding from government, industry, and non-government sources,[133] and one study reported a combination of government and non-government funding.[156] Finally, there were 39 studies that did not report the funding source or it was unclear.[84,94,101,117,128,131,134,135,137,139,142,145,147,150,151,153,158,161,162,164,166,167,169,170,173,177-189,191,195,196,198]

Of the 93 studies relating to KQ 2, 27 were rated as good quality,[89,94,98,105,111,123,124,127,133,135,137,138,141,142,144,148,149,156,157,159,171,177,185,189,193,197,200] 48 were rated as fair quality,[82,84,87,91,97,101,103,107,113,114,117,118,121,128,129,131,134,136,140,143,145-147,150,152,154,156,158,160-162,164-167,169,170,172,173,176,179,181,182,184,188,191,194,196,199] and 18 were rated as poor quality.[125,130,139,151,153,155,163,168,174,175,178,180,183,186,187,192,195,198]

These 93 studies included 11 studies in which patients were identified through clinical assessment,[135,142,144,147,158,171,173,178-180,194] 41 that identified patients through duplex ultrasound,[84,87,89,91,94,97,98,101,103,107,114,117,123-125,127,129,133,134,138,141,145,149-151,153-155,159,160,163,164,168,170,172,174,176,181,185,197,198] 28 which noted a combination of clinical assessment and duplex ultrasound,[111,113,118,121,136,137,140,143,146,148,156,157,162,165,166,169,175,177,182,183,186-189,191,192,199,200] two studies noted a patient CEAP grade between 2-5,[193,196] and six studies where the diagnostic criteria was uncertain.[82,105,130,139,167,184]

Key Points

Surgical Interventions versus Endovenous Interventions

Comparisons Between Surgical and Endovascular Interventions

- There was no long-term difference in effectiveness between RFA and high ligation plus stripping, but RFA was associated with better short-term outcomes (≤30 days), such as less periprocedural pain (SOE=low), faster improvement in symptom scores (SOE=low), and fewer adverse events when compared with high ligation plus stripping. (SOE=low)
- There was no difference in effectiveness between EVLA and surgery, though EVLA was associated with less periprocedural bleeding (SOE=moderate). There were no other significant differences in adverse events (SOE=low).
- There was no difference in effectiveness between sclerotherapy and surgery (SOE=low).

Within Interventions (Endovascular versus Endovascular, Surgery versus Surgery)

Comparisons Between EVLA and Foam Sclerotherapy

- Groups receiving EVLA and foam sclerotherapy both demonstrated improvement in quality-of-life scores and the Venous Clinical Severity Score, however there were no statistically significant differences in improvement between groups. (SOE=low for intermediate term outcomes).

Comparisons Between EVLA and EVLA Plus Phlebectomy

- There was insufficient evidence to support findings for this comparison.

Comparisons Between EVLA and Radiofrequency Ablation (RFA)

- Groups receiving EVLA and RFA both demonstrated improvement in quality-of-life scores; however, there were no statistically significant differences in improvement between groups (SOE=low).

- Both groups demonstrated improvement in the Venous Clinical Severity Score. There was a significant between-group difference in favor of the EVLA group in the short term (SOE=low).
- The RFA group had statistically significantly less periprocedural pain and fewer occurrences of superficial venous thrombosis (statistically significant p-value) and deep venous thrombosis (p-value NR), when compared with the EVLA group (SOE=low).

Comparisons Between Different Surgical Interventions

- There was insufficient evidence to support findings for this comparison.
- The comparative effectiveness of surgical and hybrid procedures is limited by a low number of studies, inconsistency in the procedures utilized, and outcomes assessed.

Different Interventions versus Placebo or Usual Care

Comparisons Between Medical Therapy and Placebo

- There is limited evidence published since 2000 to suggest that pentoxifylline is effective relative to placebo for reducing venous ulcers (SOE=low)
- There was insufficient evidence to support findings all other comparisons.

Detailed Synthesis

KQ 2a Comparisons

We provide a detailed synthesis of the following comparisons. Those in *italics* have low, moderate, or high strength of evidence for their findings:

- Surgical interventions versus endovenous interventions:
  - *Venous stripping plus ligation versus RFA*
  - *Venous stripping plus ligation versus EVLA*
  - *Venous stripping plus ligation versus sclerotherapy*
  - Venous stripping plus ligation versus thermal ablation
  - Minimally invasive venous ligation plus stripping versus sclerotherapy
- Comparisons of different endovascular interventions:
  - *EVLA versus sclerotherapy*
  - Nd:YAG laser ablation versus sclerotherapy
  - *EVLA versus RFA*
  - EVLA plus phlebectomy versus RFA plus phlebectomy
  - EVLA versus EVLA plus phlebectomy
  - EVLA versus EVLA plus ligation
  - EVLA versus EVLA plus sclerotherapy
  - Cyanoacrylate embolization versus RFA
  - Mechanochemical endogenous ablation versus RFA
  - EVLA versus thermal ablation
  - Thermal ablation plus placebo injection versus thermal ablation plus sclerotherapy plus microfoam
- Endovascular interventions versus other therapies:
  - *Endovascular treatment versus placebo*
  - Foam sclerotherapy versus foam sclerotherapy plus mini-ligation
  - *Polidocanol sclerotherapy versus placebo*
  - Sodium tetradecyl sulphate sclerotherapy versus placebo

    - Endovascular treatment versus compression
- Comparisons of different invasive surgical approaches:
    - *High ligation plus stripping with or without phlebectomy versus high ligation plus cryostripping with or without phlebectomy*
    - High ligation plus stripping with or without phlebectomy versus CHIVA
    - Standard ligation plus stripping versus selective ligation
    - Ligation of incompetent veins (without stripping) versus stab avulsion
- Invasive surgical approaches versus hybrid surgical/endovenous approaches:
    - High ligation plus stripping with or without phlebectomy versus compression
    - High ligation plus stripping plus subfascial endoscopic perforating vein surgery versus compression
    - CHIVA versus compression
    - Any surgery versus compression
- Mechanical compression therapies versus placebo/usual care
- Exercise therapy versus usual care
- Balneotherapy versus usual care

Comparisons Between Surgical Interventions and Endovenous Interventions

Venous Stripping Plus Ligation versus RFA

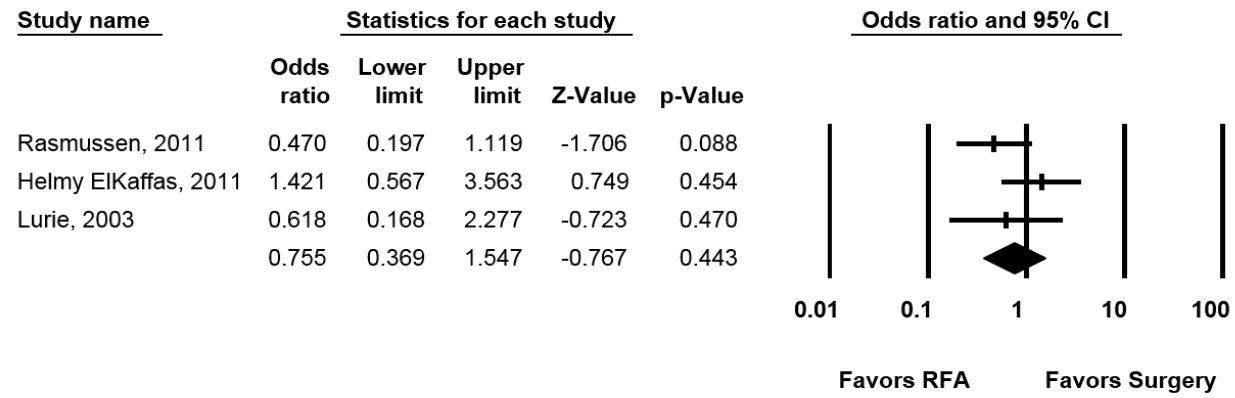
Six RCTs[91,97,98,153,159,189] and two observational studies[131,195] evaluated the effectiveness of venous stripping plus ligation versus RFA in patients with venous reflux/incompetence/varicose veins. Of the RCTs, three were good-quality,[98,159,189] two were fair-quality,[91,97] and one was poor-quality.[153] Note that one of the observational studies[131] was not clear as to whether the ablation was with radiofrequency or laser but is included in the RFA findings.

Effect on Varicose Vein Recurrence/Recanalization and Repeat Intervention

Three RCTs reported long-term reflux recurrence rates at 1-2 years postintervention.[97,98,153] In one study,[98] repeat intervention rates in patients randomized to either RFA (125 limbs) or venous ligation plus stripping (124 limbs) were reported at 3 years. Of those limbs randomized to RFA, 11.1 percent underwent repeat intervention, whereas 15.5 percent of limbs randomized to ligation plus stripping were subject to repeat intervention (no p-value reported).[98] One smaller, fair-quality study[91] also reported repeat intervention rates at 3 years, which were much lower but also not statistically significantly different between groups (1/15 RFA patients versus 1/13 surgery patients underwent repeat intervention; p-value not reported [NR]). A third poor-quality study of 180 patients showed no significant difference in the rates of recurrence (p=0.4) with 12 of 90 patients in the RFA arm and 9 of 90 patients in the surgery arm recurring over 2 years.[153]

A meta-analysis of these three studies demonstrated a reduction in vein recurrence/recanalization rates for patients in the RFA arm but this finding was imprecise and did not reach statistical significance (odds ratio [OR] 0.76, 95% confidence interval [CI], 0.37 to 1.55) (Figure 3).

Figure 3. Forest plot of reduction in varicose vein recurrence/recanalization for RFA versus venous stripping plus ligation



Abbreviations: CI=confidence interval; RFA=radiofrequency ablation

Effect on Reflux

One good-quality European study (57 limbs) reported successful occlusion rates on postoperative day 1 and found no difference between groups (sclerotherapy: 19/20 patients successfully occluded; ligation plus stripping: 20/20 patients successfully occluded; p>0.05).[189]

Effect on Clinical Symptom Scores

The mean decrease in Venous Clinical Severity Score (VCSS) at 50 days follow-up was 5.1 (standard deviation [SD] 1.5) for RFA and 4.4 (SD 1.1) for surgery (p=0.19).[91] One study[97] reported mean VCSS scores at several time points but only found a significant difference, with lower symptom scores with RFA compared to high ligation plus stripping, at 3 days and 1 week postintervention. However, this difference was not apparent at 2-years follow-up.[97] A separate study reported mean VCSS scores at 3 years and also found no difference between groups (RFA mean 0.44, SD 1.82 vs. high ligation plus stripping mean 0.3, SD 1.5; p=NS).[98]

Effect on Patient-Reported Quality of Life

One fair-quality RCT[97] measured quality of life using the Chronic Venous Insufficiency Questionnaire-2 (CIVIQ-2) at baseline, 1-week follow-up, and 2-year follow-up. At 1 week, there was a significantly larger mean within-group change for the RFA group than the surgery group, indicating that the quality of life of the RFA group improved at this time point, whereas quality of life in the surgery group worsened (RFA -9.2, SD 2.3 vs. high ligation plus stripping 3.7, SD 2.5; p<0.0001).[97] At 2 years follow-up, the RFA arm also had lower CIVIQ-2 scores than the surgery arm, indicating a better quality of life.[95]

Two RCTs[98,159] measured quality of life using the Aberdeen Varicose Vein Questionnaire (AVVQ). One study reported AVVQ in two articles[98,99] and found no between-group differences at any follow-up time (3 days, 1 month, 1 year, or 3 years). One study[159] showed that the mean within-group change in score was -8.24 for surgery versus -9.12 for RFA (p=0.53), indicating an improvement in quality of life for both groups at 5 weeks follow-up.

Effect on Lower Extremity Pain

Two RCTs[98,189] reported less pain on a visual analog scale (VAS) in the RFA arms versus surgery arms. One study[98] reported that mean VAS scores were lower in the RFA arm than the surgery arm, indicating less pain in the RFA group at 10 days follow-up (RFA mean 1.21, SD 1.72 vs. surgery mean 2.25, SD 2.23; p-value NR). The other study reported significantly lower cumulative VAS scores over 6 weeks in the RFA arm versus surgery arm but did not indicate the number of time points included in the cumulative score.[189]

Adverse Events

Adverse events were reported in all but one study. Variability of follow-up timing precluded conducting a meta-analysis to quantitatively synthesize the findings of some or all of these studies.

Surgical site infection rates were higher in the ligation plus stripping groups compared to the RFA groups in all studies reporting this outcome. In a multinational study (80 patients), 5.6 percent of patients in the ligation plus stripping group and 0 percent of the patients in the RFA group experienced surgical site infections at 3 days postoperation.[97] A larger (190 patients) but poor-quality study reported 3 out of 90 patients who underwent surgery had a periprocedural surgical site infection, whereas none of the patients who underwent RFA had any procedure-related infections.[153] A retrospective observational study compared patients who underwent RFA (1188 patients) to those who underwent any type of surgical correction for venous incompetence/varicose veins (ligation, ligation plus stripping, phlebectomy, or ligation plus excision) (2580 patients). Those undergoing a surgical intervention had a higher rate of surgical site infection (adjusted OR 2.56; 95% CI, 1.19 to 5.50; p=0.016).[131]

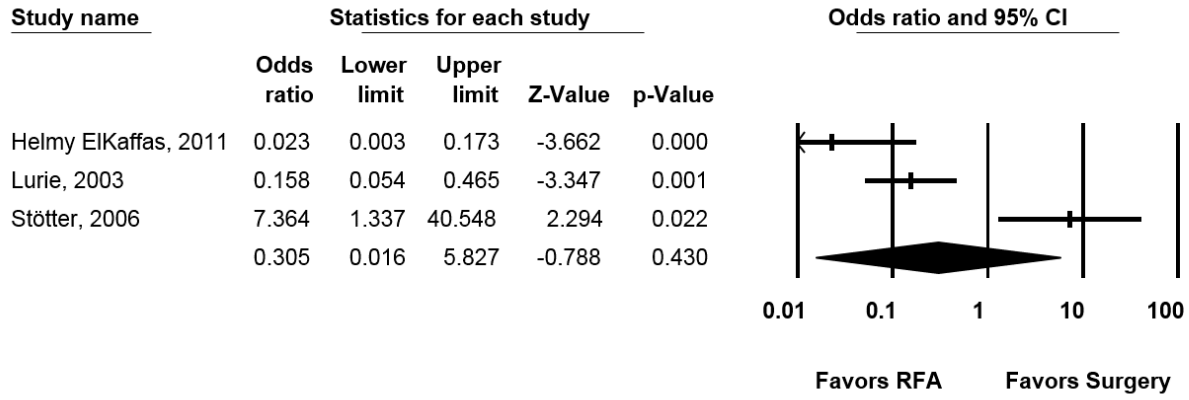
Several blood-related adverse outcomes were reported in various studies, including DVT, pulmonary embolism (PE), superficial thrombophlebitis, hematoma, hemorrhage, and ecchymosis. A large observational study reported that after adjustment for age, gender, race, body mass index, surgeon specialty, and presence of venous ulceration, the odds of DVT were lower for the surgical group than for the RFA group (OR 0.52; 95% CI, 0.28 to 0.97).[131] Two RCTs reported no instances of DVT in the RFA groups and one case of postoperative DVT in each of the surgical groups (surgical event rate: 1/90 patients, RFA event rate: 0/88 patients; p-value NR for one study;[153] 0/121 for RFA, 1/119 surgery; p-value NR for the other[98]).

Additionally, the same two RCTs reported lower rates of superficial thrombophlebitis in the surgery group compared with the RFA group; in a poor-quality study, 6.8 percent of patients randomized to RFA versus 0 percent of patients in surgery were found to have superficial thrombophlebitis,[153] whereas a good-quality study reported 9.9 percent of the RFA group versus 4.2 percent of the surgery group had superficial thrombophlebitis (Fisher exact test p=0.006 across the four arms; p-value NR for arm-to-arm comparison).[98] In the same study, neither group had any reported PEs in the 1-month postintervention time period; however, hemorrhage occurred in one surgical patient and no RFA patients in the same follow-up time period.[98] One study[91] reported 1 out of 15 RFA patients versus 0 out of 13 surgery patients reported an incidence of superficial thrombophlebitis at 3 years follow-up.

One study[97] reported superficial venous thrombosis at three time points—3 days, 1 week, and 3 weeks. Cumulatively, there were five cases of superficial venous thrombosis in the surgical group versus three cases in the RFA group (p-value NR).[97] The three RCTs reporting hematoma outcomes had inconsistent findings. The fair-quality, multinational study reported 1 incident of periprocedural hematoma in each of the RFA and surgery arms (2.3 percent event rate in the

RFA, 2.8 percent in surgery).[97] In contrast, a good-quality European study (60 limbs) reported much higher rates of hematoma within 1 week of surgery in all groups (55 percent of RFA patients, 90 percent in stripping plus ligation, and 90 percent in cryostripping; p-value NR).[189] Alternatively, a poor-quality study in Africa reported much higher rates of hematoma in the surgery arm (33 percent event rate in surgery versus 1.1 percent in RFA; p-value NR).[153] A meta-analysis of these three inconsistent and imprecise findings did not show a difference between strategies (Figure 4).

Figure 4. Forest plot of hematoma effects for RFA versus venous stripping plus ligation



Abbreviations: CI=confidence interval; RFA=radiofrequency ablation

One study reported postprocedural ecchymosis at three time points.[97] At each of three postoperative time points (3 days, 1 week, and 3 weeks), significantly fewer patients in the RFA arm experienced ecchymosis compared with patients within the surgery arm.

One poor-quality observational study reported intraoperative complications as an outcome but did not further specify the types of complications.[195] Rates were low in both groups and statistical significance was not reported (43/31,898 surgery patients vs. 1/3259 RFA patients, p-value NR).

Strength of Evidence

Table 8 summarizes the strength of evidence for the findings described above.

Table 8. KQ 2: Strength of evidence for major outcomes—venous stripping plus ligation versus RFA
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Vein recurrence[a]/ Repeat intervention (Long-term) Insufficient	3 RCTs: 597	Medium	Direct	Inconsistent	Imprecise	Suspected	A meta-analysis of three RCTs[97,98,153] demonstrated a trend towards a reduction in vein recurrence/recanalization rates for patients in the RFA arm, but this finding was imprecise and did not reach statistical significance (OR 0.76 95% CI, 0.37 to 1.55) (Figure 3).
Reflux (Short-term) Insufficient	1 RCT: 57 limbs	Low	Direct	NA	Imprecise	None	This study reported successful occlusion rates 1 day postoperative and found no difference between groups (sclerotherapy: 19/20 patients successfully occluded; ligation plus stripping: 20/20 patients successfully occluded; p>0.05).[189]
Periprocedural Complications (Short-term) Insufficient	1 Obs: 36,096	High	Direct	NA	Imprecise	None	Rates were low in both groups and statistical significance was not reported (43/31,898 surgery patients vs. 1/3259 RFA patients, p-value NR).[195]
Clinical Symptom Scores (VCSS) (Short-, Intermediate-, and Long-term) Low	3 RCTs: 356	Medium	Direct	Consistent	Imprecise	Suspected	For one study, the mean decrease in VCSS at 50 days follow-up was 5.1 (SD 1.5) for RFA and 4.4 (SD 1.1) for surgery (p=0.19).[91] One study[97] reported mean VCSS scores at several time points but only found a significant difference, with lower symptom scores with RFA compared to high ligation plus stripping, at 3 days and 1 week postintervention. However, this difference was not apparent at 2-year follow-up).[97] A separate study reported mean VCSS scores at 3 years and also found no difference between groups (RFA mean 0.44, SD 1.82 vs. high ligation plus stripping mean 0.3, SD 1.5; p=NS).[98]
Patient-Reported Quality of Life (Short-, Intermediate-, and Long-term) Insufficient	3 RCTs: 416	Low	Direct	Inconsistent	Imprecise	Unclear	For one study at 1 week, there was a significantly larger mean within-group change for the RFA group than the surgery group, indicating that the quality of life of the RFA group improved at this time point, whereas quality of life in the surgery group worsened (RFA -9.2, SD 2.3 vs. high ligation plus stripping 3.7, SD 2.5; p<0.0001).[97] At 2 years follow-up, the RFA arm also had lower CIVIQ-2 scores than the surgery arm, indicating a better quality of life.[95] One study reported AVVQ in two articles[98,99] and found no between-group differences at any follow-up time (3 days, 1 month, 1 year, or 3 years). One study[159] showed that the mean within-group change in score was -8.24 for surgery vs. -9.12 for RFA (p=0.53),

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
							indicating an improvement in quality of life for both groups at 5 weeks follow-up.
Reduction in LE Pain (Short- and Intermediate-term) Low	1 RCT: 60 1 RCT: NR	Low	Direct	Consistent	Imprecise	None	Two RCTs[98,189] reported less pain on a VAS in the RFA arms vs. surgery arms. One study[98] reported that mean VAS scores were lower in the RFA arm than the surgery arm, indicating less pain in the RFA group at 10 days follow-up (RFA mean 1.21, SD 1.72 vs. surgery mean 2.25, SD 2.23; p-value NR). The other study reported significantly lower cumulative VAS scores over 6 weeks in the RFA arm vs. surgery arm but did not indicate the number of time points included in the cumulative score.[189]
Adverse Events (Surgical Site Infection) (Short- and Long-term) Low	2 RCTs, 1 Obs: 2850	Medium	Direct	Consistent	Imprecise	Suspected	Surgical site infection rates were higher in the ligation plus stripping groups compared to the RFA groups in all studies reporting this outcome. In a multinational study (80 patients), 5.6% of patients in the ligation plus stripping group and 0% of the patients in the RFA group experienced surgical site infections at 3 days postoperation.[97] A larger (190 patients) but poor-quality study reported 3 out of 90 patients who underwent surgery had a periprocedural surgical site infection, whereas none of the patients who underwent RFA had any procedure-related infections.[153] A retrospective observational study compared patients who underwent RFA (1188 patients) to those who underwent any type of surgical correction for venous incompetence/varicose veins (ligation, ligation plus stripping, phlebectomy, or ligation plus excision) (2580 patients). Those undergoing a surgical intervention had a higher rate of surgical site infection (adjusted OR 2.56; 95% CI, 1.19 to 5.50; p=0.016).[131]
Adverse Events (Blood-Related) (Short-, Intermediate-, and Long-term) Insufficient	2 RCTs, 1 Obs: 5033	Medium	Direct	Inconsistent	Imprecise	Suspected	Several blood-related adverse outcomes were reported in various studies, including DVT, PE, superficial thrombophlebitis, hematoma, hemorrhage, and ecchymosis. A large observational study reported that after adjustment for age, gender, race, body mass index, surgeon specialty, and presence of venous ulceration, the odds of DVT were lower for the surgical group than for the RFA group (OR 0.52; 95% CI, 0.28 to 0.97).[131] Two RCTs reported no instances of DVT in the RFA groups and one case of postoperative DVT in each of the surgical groups (surgical event rate: 1/90 patients, RFA event rate: 0/88 patients; p-value NR for one study;[153] 0/121 for RFA, 1/119 surgery; p-value NR for the other[98]).
Adverse Events (Thrombo-	3 RCTs 695	Medium	Direct	Consistent	Imprecise	Suspected	Two RCTs reported lower rates of superficial thrombophlebitis in the surgery group compared with the RFA group; in a poor-quality study, 6.8% of patients randomized to RFA vs. 0% of patients in surgery were

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
phlebitis) (Short-, Intermediate-, and Long - term) Low							found to have superficial thrombophlebitis,[153] whereas a good-quality study reported 9.9% of the RFA group vs. 4.2% of the surgery group had superficial thrombophlebitis (Fisher exact test p=0.006 across the four arms; p-value NR for arm-to-arm comparison).[98] One study[91] reported 1 out of 15 RFA patients vs. 0 out of 13 surgery patients reported an incidence of superficial thrombophlebitis at 3 years follow-up.
Adverse Events (Hematoma) (Short-term) Insufficient	3 RCTs 318	Medium	Direct	Inconsistent	Imprecise	Suspected	The three RCTs reporting hematoma outcomes had inconsistent findings. The fair-quality, multinational study reported 1 incident of periprocedural hematoma in each of the RFA and surgery arms (2.3% event rate in the RFA, 2.8% in surgery).[97] In contrast, a good-quality European study (60 limbs) reported much higher rates of hematoma within 1 week of surgery in all groups (55% of RFA patients, 90% in stripping plus ligation, and 90% in cryostripping; p-value NR).[189] Alternatively, a poor-quality study in Africa reported much higher rates of hematoma in the surgery arm (33% event rate in surgery vs. 1.1% in RFA; p-value NR).[153] A meta-analysis of these three inconsistent and imprecise findings did not show a difference between strategies (Figure 4).

[a] Vein recurrence refers to the establishment of patency of the venous system; such recurrence often requires repeat intervention.

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; CIVIQ-2=Chronic Venous Insufficiency Questionnaire-2; DVT=deep vein thrombosis; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; PE=pulmonary embolism; RCT(s)=randomized controlled trial(s); RFA=radiofrequency ablation; SD=standard deviation; SE=standard error; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

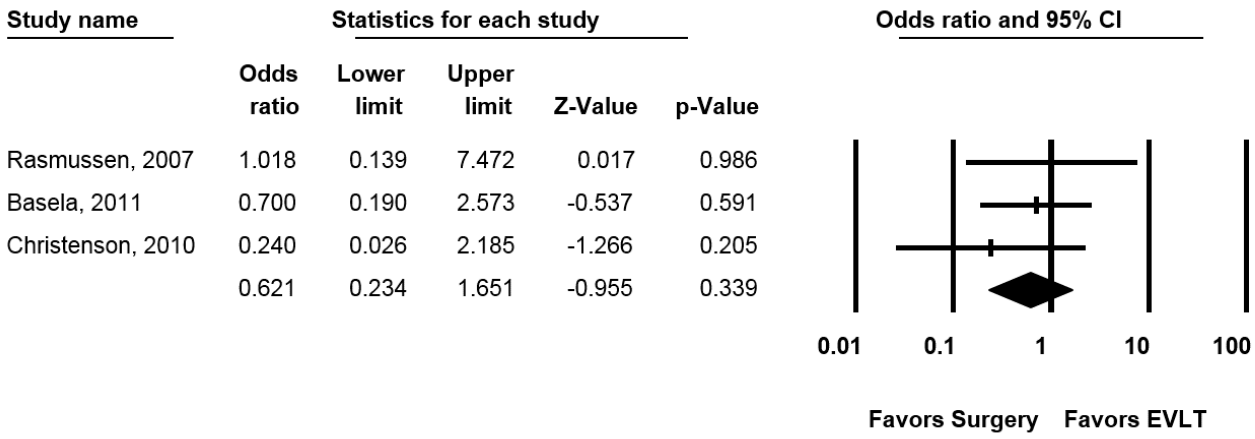
Venous Stripping plus Ligation versus EVLA

Sixteen RCTs[84,87-89,94,98,101,103-105,116,117,120,121,126,139,150,152,168,185,186,196] and one observational study[195] were included in the evaluation of venous stripping plus ligation versus EVLA. One study[94] compared cryostripping versus EVLA, one study[101] compared high ligation plus stripping plus foam sclerotherapy versus EVLA plus foam sclerotherapy, two studies[103,152] compared high ligation plus stripping plus phlebectomy versus EVLA plus phlebectomy, and one study[120,121] compared high ligation plus stripping versus EVLA plus ligation.

Effect on Varicose Vein Recurrence/Recanalization and Repeat Intervention

We performed a meta-analysis on 3 studies representing 491 patients that evaluated short-term superficial thrombophlebitis.[87,152,186] This analysis did not demonstrate a statistically significant difference in superficial thrombophlebitis and was both imprecise and inconsistent across the three studies (Figure 5).

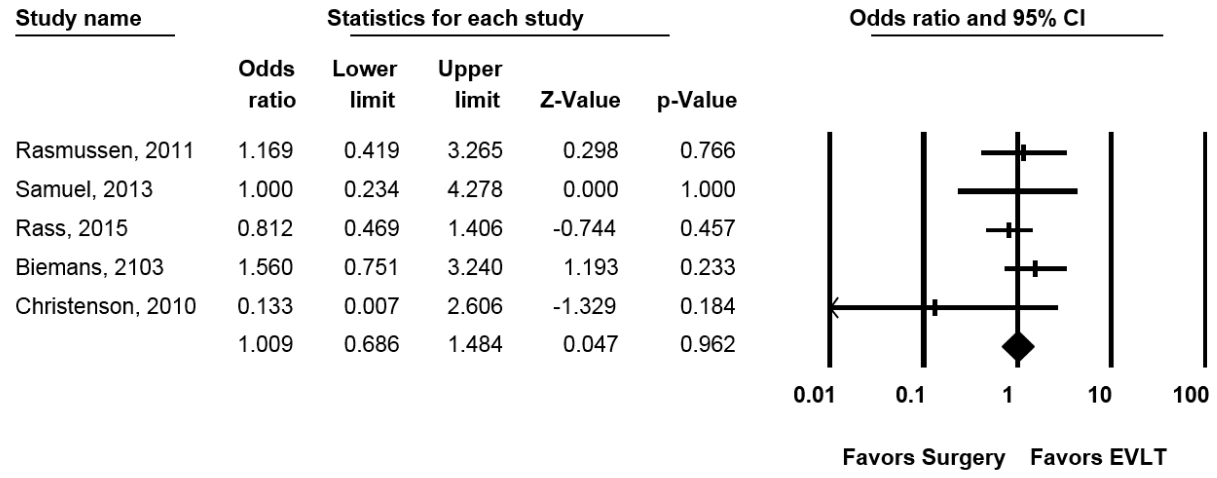
Figure 5. Forest plot of short-term superficial thrombophlebitis for venous stripping plus ligation versus EVLA



Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy

Five studies evaluated long-term superficial thrombophlebitis.[98,105,117,126,152] The findings of these studies were imprecise and inconsistent, demonstrating no difference in superficial thrombophlebitis between the 2 strategies (OR 1.01; 95% CI, 0.69 to 1.48) (Figure 6).

Figure 6. Forest plot of long-term superficial thrombophlebitis for venous stripping plus ligation versus EVLA



Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy

One study reported thrombophlebitis as an outcome at an undefined time point and could not be included for meta-analysis.[196] There was no significant difference in thrombophlebitis occurrence (4/50 surgery patients vs. 3/50 EVLA; p-value NR).

One additional study reported no recurrence as an outcome at 26 weeks, 1 year, and 2 years.[104] Significantly more EVLA patients had no recurrence at any time point (26 weeks, 38/52 surgery patients vs. 51/51 EVLA; p<0.001; 1 year, 38/51 surgery patients vs. 45/48 EVLA; p-value NR; 2 years, 29/44 surgery patients vs. 36/44 EVLA patients; p=0.0020).

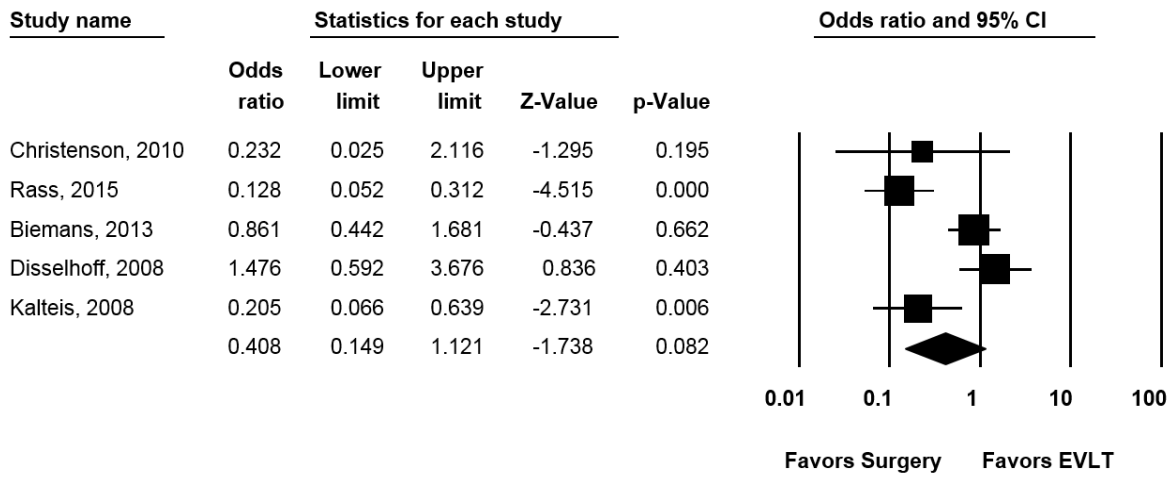
Effect on Reflux/Incompetence

At 2 years, 77 percent (95% CI, 72 percent to 78 percent) of the EVLA patients and 66 percent (95% CI, 60 percent to 67 percent) of cryostripping patients were free of duplex-defined varicose vein recurrence (p=0.253).[94] The same study measured freedom from venous incompetence at 5 years and found a lower rate in the surgery group (51 percent; 95% CI, 39 percent to 66 percent) than the EVLA group (62 percent; 95% CI, 50 percent to 76 percent) but the substantial loss to follow-up for these 5-year findings lowers the quality of the study for this specific outcome to fair.[94] A second study also reported duplex-defined GSV occlusion at 2 years, and its rates were much higher but not statistically significantly different (99/99 surgery patients vs. 88/95 EVLA patients; p=1.00).[152] One study[168] reported abolishment of reflux as an outcome in a three-arm study comparing two different powers of lasers versus surgery. At 3 months' follow-up, reflux was abolished in 41 out of 42 legs in the 12-watt EVLA arm, 26 out of 29 legs in the 14-watt EVLA arm, and 28 out of 32 legs in the high ligation plus stripping arm (p=0.227).[168] Abolishment of reflux was also reported at 12 months; however, >40 percent patient attrition detracts from the power of these results.[168] One study reported cured from reflux as an outcome at an undefined time point and did not report a statistically significant difference between the groups (25/50 surgery patients vs. 32/50 EVLA patients, p-value NR).[196] The same study reported recurrence of reflux at an undefined time point and did not find a statistically significant difference between groups (5/50 surgery vs. 2/50 EVLA, p-value NR).

Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics over a long-term time period.[84,94,117,126,152] The analysis suggested

improvement in reflux/incompetence for surgery compared to EVLA that did not reach statistical significance (OR 0.41; 95% CI, 0.15 to 1.12) (Figure 7).

Figure 7. Forest plot of changes in reflux/incompetence effects for venous stripping plus ligation versus EVLA

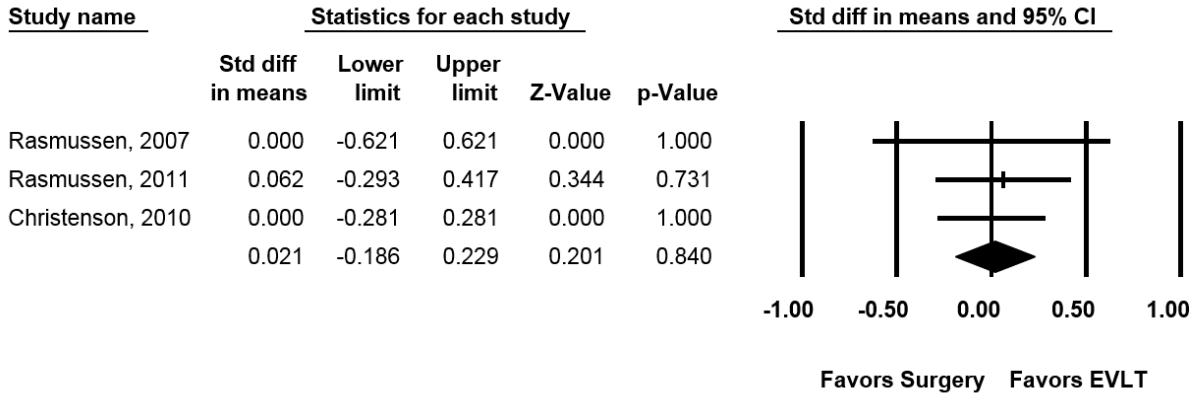


Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy

Effect on Clinical Symptom Scores

We synthesized 3 studies representing 487 patients for treatment effect on long-term VCSS score.[87,98,152] There was no significant difference between treatment strategies (standardized difference in means 0.02; 95% CI, -0.19 to 0.23) (Figure 8).

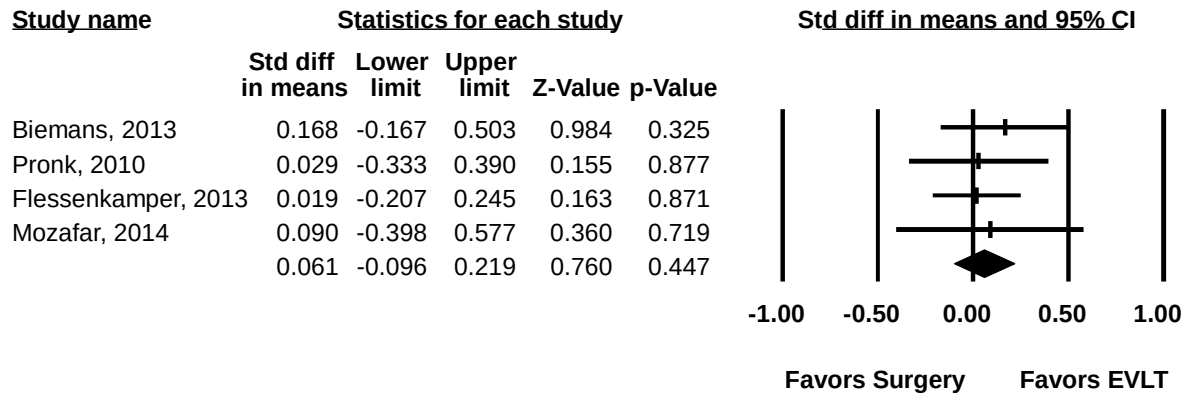
Figure 8. Forest plot of long-term VCSS effects for venous stripping plus ligation versus EVLA



Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

We also explored the CEAP after 12 months in 4 studies representing 867 patients.[101,117,121,139] No difference was found (standardized difference in means 0.06; 95% CI, -0.10 to 0.22) (Figure 9).

Figure 9. Forest plot of CEAP effects for venous stripping plus ligation versus EVLA



Abbreviations: CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

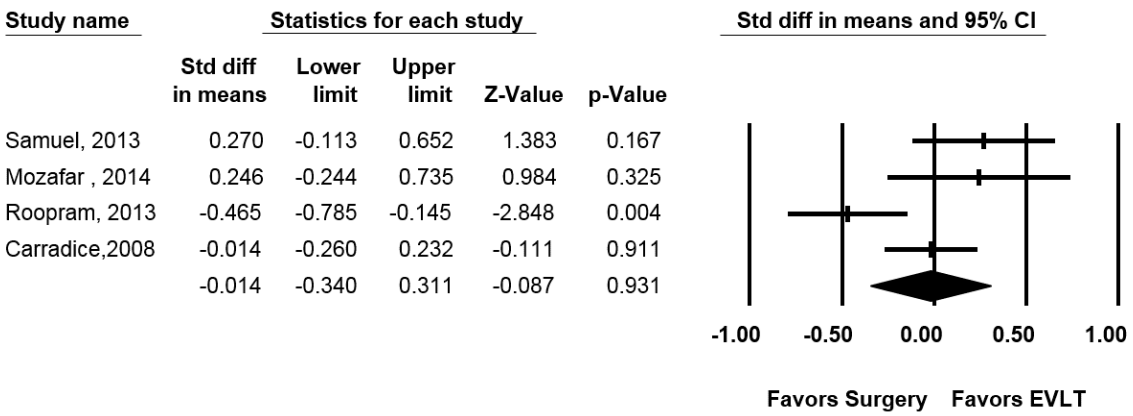
Effect on Patient-Reported Quality of Life

Four studies[89,103,117,185] reported EuroQol 5D (EQ-5D) scores at various time points postintervention. None of the studies reported a statistically significant difference between the surgery and EVLA groups at any time point. In the study with the largest population measuring this outcome,[89] the mean change within groups was 0.111 for EVLA and 0.097 for surgery (p-value NR). Two fair-quality studies[103,117] reported similar scores at baseline and 1 year. In 1 study,[103] the median score at baseline was 0.79 then 1.0 at 1 year for the EVLA group, and the median score at baseline was 0.80 at baseline then 1.0 at 1-year follow-up for the surgery group (p-value NR). The second study to report the same time points had less of an increase; for EVLA, the mean score at baseline was 0.85, then 0.91 at 1 year versus surgery, which at baseline was 0.85, then 0.87 at 1 year (p-value NR).[117] A good-quality study of 175 patients reported no difference between groups at baseline, 2 weeks, or 6 weeks; however, scores for both groups decreased during this time (baseline, EVLA=0.203 vs. surgery=0.187, p=0.67; 2 weeks EVLA=0.201 vs. surgery=0.152, p>0.05; 6 weeks EVLA=0.091 vs. surgery=0.121, p=0.25).[185]

Two RCTs[117,126,150] reported CIVIQ-2 scores at various time points that were not conducive to meta-analysis. Neither study reported a significant difference between EVLA and surgery at any time point, but the mean within-group change was negative for all arms, all time points, and both studies. One fair-quality[117] study reported scores at baseline, 3 months, and 12 months. Mean scores in both groups decreased at both 3- and 12-month follow-up, but no between-group p-values were reported (baseline EVLA=28.1 vs. surgery=25.1; 3 months EVLA=15 vs. surgery=16.2; 12 months EVLA=13.8 vs. surgery=17.3). One study[150] only collected CIVIQ-2 data on the last 100 patients to enroll out of 346 patients in the entire study at 3-, 12-, and 2-year follow-ups. There was no significant difference in mean scores between groups at any time point (3 months EVLA=12.8 vs. surgery=18.0, p=0.11; 12 months EVLA=10.5 vs. surgery=11.1, p=0.73; 2 years EVLA=10.8, surgery=9.5, p=0.55).[150]

We synthesized 4 studies representing 583 patients which evaluated short-term AVVQ effects.[103,105,139,185] These studies showed a -0.01 standardized difference in means (95% CI, -0.34 to 0.31) showing no difference between strategies (Figure 10).

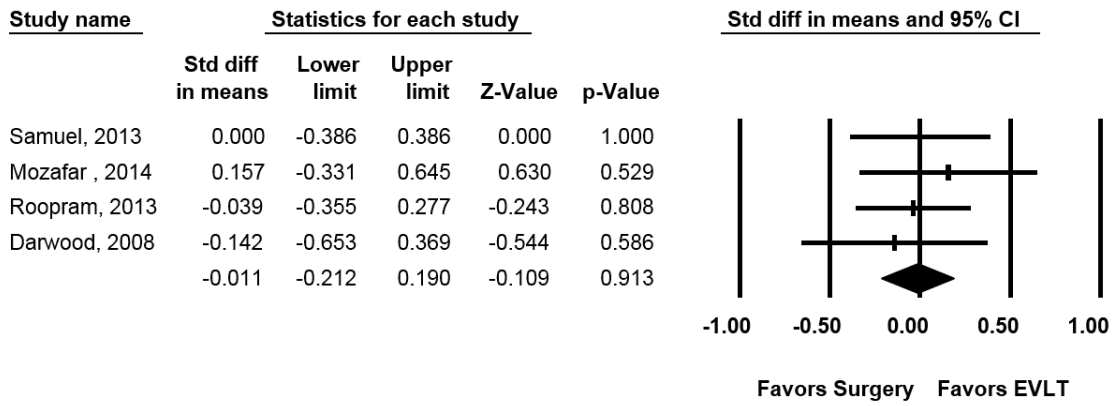
Figure 10. Forest plot of short-term AVVQ effects for venous stripping plus ligation versus EVLA



Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon.[105,139,168,185] Again there was no difference in AVVQ scores (Figure 11).

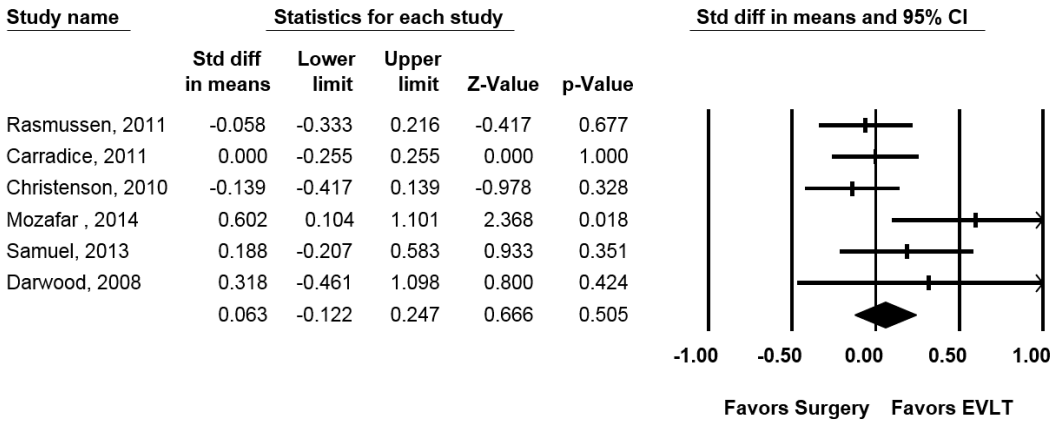
Figure 11. Forest plot of intermediate-term AVVQ effects for venous stripping plus ligation versus EVLA



Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

Finally we synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ.[98,103,105,139,152,168] These studies also consistently found no difference between treatment strategies (Figure 12).

Figure 12. Forest plot of long-term AVVQ effects for venous stripping plus ligation versus EVLA

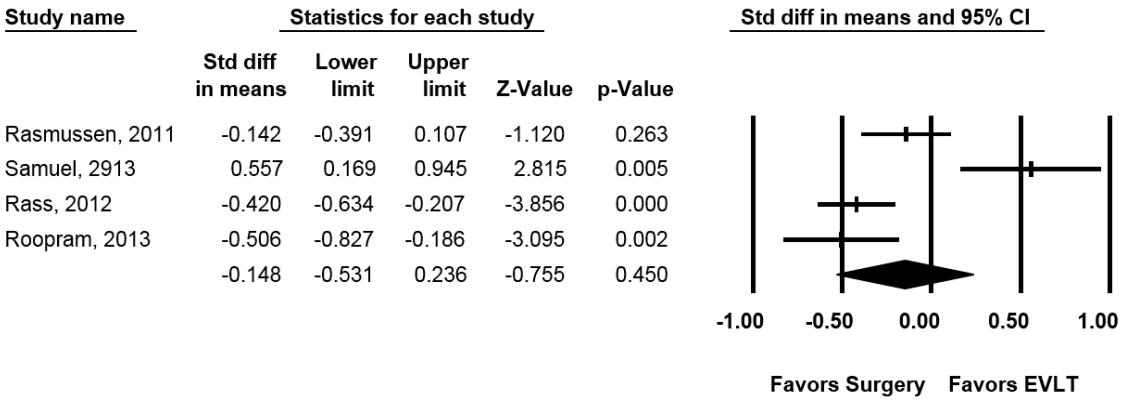


Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

Effect on Pain

Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale.[98,105,150,185] These studies demonstrated a -0.15 standardized difference in means (95% CI, -0.53 to 0.24), showing no difference between treatment strategies (Figure 13).

Figure 13. Forest plot of reduction in LE pain for venous stripping plus ligation versus EVLA



Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy; Std diff=standardized difference

Adverse Events

Six RCTs[94,101,117,121,150,152] reported DVT as an outcome at various time points that precluded meta-analysis. None of the studies reported a significant difference between EVLA and surgery patients. Four studies[94,101,117,152] reported zero cases of DVT in either EVLA or surgery arms, whereas two other studies[121,150] reported one case of DVT in both arms.

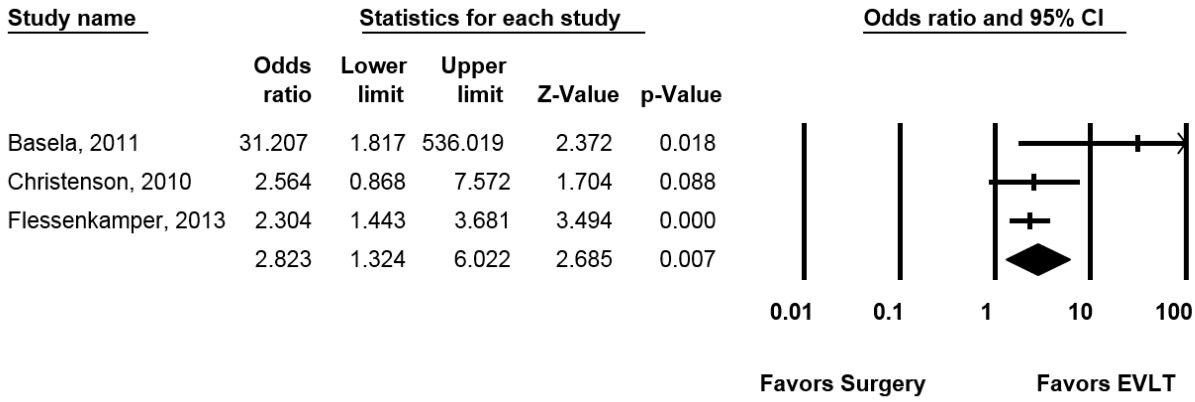
Infection was reported as an outcome in six RCTs[103,117,150,152,168,186] at various time points that precluded meta-analysis. Five studies[103,117,152,168,186] reported higher incidence of infection in the surgery arm but the difference was statistically significant in only two studies.[103,117] In the EVLA arm of 1 fair-quality study, 0/78 patients had infections at 3 months follow-up versus 3/68 surgery

patients (p=0.03).[117] Another fair-quality study reported infections in 2/137 EVLA patients and 8/133 surgery patients (p=0.048).[103] The follow-up time was not described for this study.[103] Three studies[152,168,186] reported infections in the short-term, postoperative period. One poor-quality study[168] reported groin infections requiring antibiotics and found the occurrence in 2/32 surgery patients versus 0/71 EVLA patients (p-value NR). A second poor-quality study reported no statistical difference between groups in terms of infection rates (EVLA=0/90 patients vs. surgery=4/84 patients, p=0.147).[186] A fair-quality study reported no incidence of infection in either arm at 12 days postintervention.[152] Only one study reported a higher incidence of infection in EVLA patients when compared with surgery patients at 12-months follow-up, but the difference was not statistically significant (EVLA=1/185 patients vs. surgery=0/161 patients, p-value NR).

We were able to perform a meta-analysis on 3 studies representing 822 patients that evaluated bleeding (hematoma/ecchymosis) in similar timepoints and populations.[121,152,186] This analysis demonstrated a statistically significant benefit of EVLA compared with surgery regarding reduction in bleeding risk (OR 2.82; 95% CI, 1.32 to 6.02) (Figure 14).

Six other studies included bleeding as an outcome but were not included in the meta-analysis due to different timepoints or type of outcomes. One three-arm study comparing two types of endovenous lasers and ligation plus stripping surgery reported excessive post-operative bruising and found that it only occurred in the surgery patients (0/42 EVLA-1 patients vs. 0/29 EVLA-2 patients vs. 2/32 surgery patients; p-value NR)[168] One study reported occurrence of ecchymosis or bruising at 12 months and found no significant difference between EVLA and surgery (169/185 EVLA patients vs. 145/161 surgery, p=0.71).[150] Only one study reported hemorrhage as a complication at 1 month and there was no significant difference between groups (1/125 EVLA patients vs. 1/119 surgery patients; p-value NR).[98] One study found that occurrence of hematoma was significantly lower in EVLA patients compared to surgery patients at an undefined timepoint (1/137 EVLA patients vs. 11/133 surgery patients; p=0.003).[103] A different study reported residual hematoma at 4-weeks and 16-weeks and found no significant difference between groups (4 weeks: 16/47 EVLA patients vs. 28/48 surgery patients; p=0.24; 16 weeks: 6/47 EVLA patients vs. 5/48 surgery patients; p>0.999).[84] Additionally, this study reported size of hematoma at 4-weeks and found that hematoma size was significantly smaller in EVLA patients compared to surgery patients (EVLA: median 125 cm^2, range 5-180 cm^2 vs. surgery: median 200 cm^2, range 123-269; p=0.001).[84] One fair-quality study reported ecchymosis at an undefined time point and found that occurrence was similar in both groups (4/50 surgery patients vs. 3/50 EVLA patients, p-value NR).[196]

Figure 14. Forest plot of bleeding risk (hematoma/ecchymosis) for venous stripping plus ligation versus EVLA



Abbreviations: CI=confidence interval; EVLT=endovenous laser therapy

Two studies[152,186] reported skin burns occurring immediately postoperatively. Both studies had one instance of skin burn in the EVLA group and none in the surgery group.[152,186] Two studies[152,186] reported postoperative paresthesia and found different event rates. One study found that 1 patient of 99 in the EVLA group versus 1 patient of 100 in the surgery group experienced parasthesias,[152] whereas a different study[103] reported a significantly higher incidence of paresthesia in the surgery group than the EVLA group (13/133 surgery patients vs. 4/137 EVLA patients; p=0.02). A third study reported paresthesia at 12 months postoperative and reported the outcome in 1 of 68 surgery patients versus 0 of 78 EVLA patients (p=NS).[117]

One study[103] reported thromboembolism as an outcome but had zero instances in either arm of the study during an undefined short-term time frame. Superficial venous thrombosis occurred in 4/68 surgery patients versus 3/78 EVLA patients (p=0.85).[117] Two studies[98,152] stated that there was no significant difference in superficial thrombophlebitis for patients who underwent EVLA versus surgery (4/125 EVLA vs. 5/119 surgery; p=NS;[98] 4/99 EVLA vs. 1/100 surgery, p=0.369[152]). One of these two studies[98] and another study[117] found zero instances of PE in either group, suggesting that PE is a rare side effect for either treatment. One poor-quality observational study reported intraoperative complications as an outcome but did not further specify the types of complications.[195] Rates were low in both groups and statistical significance was not reported (43/31,898 surgery patients vs. 4/989 EVLA patients, p-value NR).

Strength of Evidence

Table 9 summarizes the strength of evidence for the findings described above.

Table 9. KQ 2: Strength of evidence for major outcomes—venous stripping plus ligation versus EVLA
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Vein recurrence[a]/ Repeat intervention (Short-term) Insufficient	3 RCTs: 491	High	Direct	Inconsistent	Imprecise	None	We performed a meta-analysis on 3 studies representing 491 patients that evaluated short-term superficial thrombophlebitis.[87,152,186] This analysis did not demonstrate a statistically significant difference in superficial thrombophlebitis and was both imprecise and inconsistent across the three studies (Figure 5).
Vein recurrence[a]/ Repeat intervention (Long-term) Low	5 RCTs: 1261	Low	Direct	Consistent	Imprecise	None	Five studies evaluated long-term superficial thrombophlebitis.[98,105,117,126,152] The findings of these studies were imprecise and inconsistent, demonstrating no difference in superficial thrombophlebitis between the 2 strategies (OR 1.009; 95% CI, 0.686 to 1.484) (Figure 6).
Vein recurrence[a]/ Repeat intervention (undefined timeframe) Insufficient	1 RCT: 50	Medium	Direct	NA	Imprecise	None	One fair-quality study reported ecchymosis at an undefined time point and found that occurrence was similar in both groups (4/50 surgery patients vs. 3/50 EVLA patients, p-value NR).[196]
Improvement in hemodynamics (Long-term) Low	5 RCTs: 887	Low	Direct	Consistent	Imprecise	None	Five studies were combined in a meta-analysis to explore improvement in hemodynamics over a long-term time period.[84,94,117,126,152] The analysis suggested improvement in reflux/incompetence for surgery compared to EVLA which did not reach statistical significance (OR 0.408; 95% CI, 0.149 to 1.121) (Figure 7).
Improvement in hemodynamics (undefined timeframe) Insufficient	1 RCT: 50	Medium	Direct	NA	Imprecise	None	One study reported cured from reflux as an outcome at an undefined time point and did not report a statistically significant difference between the groups (25/50 surgery patients vs. 32/50 EVLA patients, p-value NR).[196] The same study reported recurrence of reflux at an undefined time point and did not find a statistically significant difference between groups (5/50 surgery vs. 2/50 EVLA, p-value NR).
Clinical	3 RCTs:	Medium	Direct	Consistent	Imprecise	None	We synthesized 3 studies representing 487 patients for treatment effect

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
symptom scores (VCSS) (Long-term) Low	487						on long-term VCSS score.[87,98,152] There was no significant difference between treatment strategies (standardized difference in means 0.021; 95% CI, -0.186 to 0.229) (Figure 8).
Clinical symptom scores (CEAP) (Long-term) Moderate	4 RCTs 867	Medium	Direct	Consistent	Precise	Unclear	We also explored the CEAP after 12 months in 4 studies representing 867 patients.[101,117,121,139] No difference was found (standardized difference in means 0.061; 95% CI, -0.096 to 0.219) (Figure 9).
Patient-Reported Quality of Life (EQ-5D) (Short-, Intermediate-, and Long-term) Low	4 RCTs 1436	Medium	Direct	Consistent	Imprecise	None	Four studies[89,103,117,185] reported EQ-5D scores at various time points postintervention. None of the studies reported a statistically significant difference between the surgery and EVLA groups at any time point.
Patient-Reported Quality of Life (CIVIQ-2) (Intermediate and Long-term) Insufficient	2 RCTs 297	Medium	Direct	Consistent	Imprecise	None	Two RCTs[117,126,150] reported CIVIQ-2 scores at various time points that were not conducive to meta-analysis. Neither study reported a significant difference between EVLA and surgery at any time point, but the mean within-group change was negative for all arms, all time points, and both studies.
Patient-Reported Quality of Life (AVVQ) (Short-term) Low	4 RCTs: 583	Medium	Direct	Inconsistent	Imprecise	Unclear	We synthesized 4 studies representing 583 patients which evaluated short-term AVVQ effects.[103,105,139,185] These studies showed a -0.014 standardized difference in means (95% CI, -0.340 to 0.311), showing no difference between strategies (Figure 10).
Patient-Reported	4 RCTs: 426	Medium	Direct	Consistent	Imprecise	Suspected	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon.[105,139,168,185] Again there was no

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Quality of Life (AVVQ) (Intermediate-term) Low							difference in AVVQ scores (standardized difference in means -0.011; 95% CI, -0.212 to 0.190) (Figure 11).
Patient-Reported Quality of Life (AVVQ) (Long-term) Moderate	6 RCTs: 663	Medium	Direct	Consistent	Imprecise	Suspected	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ.[98,103,105,139,152,168] These studies also consistently found no difference between treatment strategies (standardized difference in means 0.063; 95% CI, -0.122 to 0.247) (Figure 12).
Periprocedural Complications (Short-term) Insufficient	1 Obs: 36,096	High	Direct	NA	Imprecise	None	One poor-quality observational study reported intraoperative complications as an outcome but did not further specify the types of complications.[195] Rates were low in both groups and statistical significance was not reported (43/31,898 surgery patients vs. 4/989 EVLA patients, p-value NR).
Reduction in LE Pain (Short-term) Low	4 RCTs: 778	Low	Direct	Inconsistent	Imprecise	None	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a VAS.[98,105,150,185] These studies demonstrated a -0.148 standardized difference in means (95% CI, -0.531 to 0.236), showing no difference between treatment strategies (Figure 13).
Adverse Events (DVT) (Various Timepoints) Insufficient	6 RCTs: 822	Medium	Direct	Consistent	Imprecise	None	Six RCTs[94,101,117,121,150,152] reported DVT as an outcome at various time points that precluded meta-analysis. None of the studies reported a significant difference between EVLA and surgery patients. Four studies[94,101,117,152] reported zero cases of DVT in either EVLA or surgery arms, whereas two other studies[121,150] reported one case of DVT in both arms.
Adverse Events (Venous Infection) (Various Timepoints)	6 RCTs: 822	Medium	Direct	Inconsistent	Imprecise	Suspected	Infection was reported as an outcome in six RCTs[103,117,150,152,168,186] at various time points that precluded meta-analysis. Five studies[103,117,152,168,186] reported higher incidence of infection in the surgery arm but the difference was statistically significant in only two studies.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Insufficient							
Adverse Events (Bleeding risk) Moderate	3 RCTs: 2,275	Medium	Direct	Consistent	Precise	Suspected	We were able to perform a meta-analysis on 3 studies representing 822 patients that evaluated bleeding (hematoma/ecchymosis).[121,152,186] This analysis demonstrated a statistically significant benefit of EVLA compared with surgery regarding reduction in bleeding risk (OR 2.823; 95% CI, 1.324 to 6.022) (Figure 14).

[a] Vein recurrence refers to the establishment of patency of the venous system; such recurrence often requires repeat intervention.

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; CI=confidence interval; CIVIQ-2=Chronic Venous Insufficiency Questionnaire-2; DVT=deep vein thrombosis; EQ-5D=EuroQol 5D; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; SD=standard deviation; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

Venous Stripping plus Ligation versus Sclerotherapy

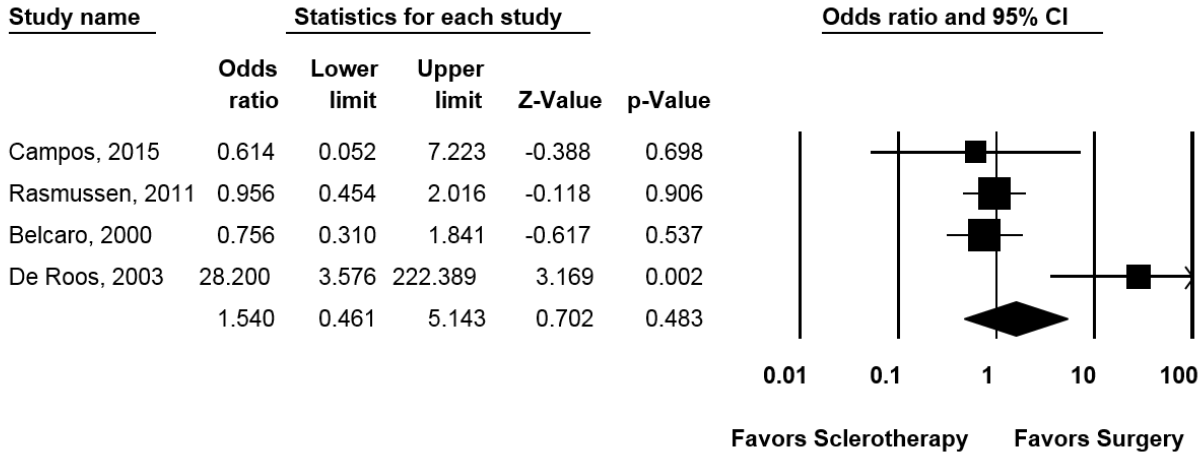
Twelve RCTs[81,82,88,89,98,107,116-118,127,146,151,161,166,187] and one observational study[198] compared venous stripping plus ligation surgery versus foam sclerotherapy. Four studies compared surgery versus liquid sclerotherapy.[176,181,187,199] One study compared venous stripping plus ligation to venous stripping plus ligation plus foam sclerotherapy.[107] Another study compared venous stripping plus ligation to ligation plus sclerotherapy.[166] One observational study compared stripping plus ligation to foam sclerotherapy.[198]

Effect on Recurrence and Repeat Intervention

We synthesized evidence from 4 RCTs (3 RCTs with 395 patients, one additional RCT with 96 limbs) that explored long-term recurrence.[98,127,176,181] These studies did not demonstrate a difference between strategies (OR 1.54; 95% CI, 0.46 to 5.14) and were both inconsistent and imprecise (Figure 15).

One observational study reported recurrence of reflux at 20 year follow-up and found that recurrence rates were significantly lower in the sclerotherapy patients compares to ligation plus stripping patients (38.8 percent stripping plus ligation patients vs. 20.7 percent sclerotherapy patients; $p<0.05$).[198] This same study reported recurrence of varicose veins and found that ligation plus stripping patients had significantly higher recurrence (11.7 percent sclerotherapy patients vs. 47.3 percent ligation plus stripping; $p<0.05$).[198]

Figure 15. Forest plot of reduction in recurrence for sclerotherapy versus venous stripping plus ligation



Abbreviation: CI=confidence interval

Four studies[98,116,117,176,199] reported repeat intervention rates at 3 months, 1 year, and 3 years postintervention. Three studies[98,116,176] reported a higher incidence of repeat intervention in the sclerotherapy arms, but significance was reported in only one study.[98] One good-quality study[98] with four treatment arms (EVLA, RFA, foam sclerotherapy, and high ligation plus stripping) compared rates of repeat intervention at 3 years. A significantly higher percentage of sclerotherapy patients underwent repeat interventions when compared with surgery patients (sclerotherapy=31.6 percent vs. surgery=15.5 percent, $p<0.0001$).[98] Within the 28 days of the intervention, a European study reported that more limbs in the sclerotherapy group had to

undergo repeat intervention due to initial failure in comparison to the phlebectomy group (sclerotherapy=18/48 limbs; phlebectomy=0/48 limbs, p-value NR).[176] In contrast, a different European study reported much lower rates of repeat intervention in the sclerotherapy arm and no difference when compared with the high ligation plus stripping arm (repeat intervention in 1/38 sclerotherapy patients vs. 1/34 surgery patients, p-value NR).[199] In a fair-quality study, at 3-month follow-up, 15/77 sclerotherapy patients and 11/68 surgery patients underwent repeat intervention.[116] Alternatively, this study[116] also reported freedom from repeat intervention rates at 5-year follow-up and found no significant difference between arms (22/77 foam sclerotherapy patients vs. 22/69 ligation plus stripping patients; p=0.546). An observational study found that rates of repeat intervention at 20 years follow-up was significantly higher in the ligation plus stripping arm compared to sclerotherapy (58.55 percent stripping plus ligation patients vs. 21.9 percent sclerotherapy patients; p<0.05).[198]

Effect on Reflux

Only one poor-quality European study reported elimination of reflux as an outcome.[187] At 3 months postintervention, there was no significant between-group difference in the percentage of patients with elimination of reflux (microfoam=83.4 percent; ligation plus stripping=87.2 percent, liquid sclerotherapy=88.8 percent; p>0.05 for ligation plus stripping vs. microfoam; p=0.06 for liquid vs. microfoam).[187] A fair-quality study reported changes in ambulatory venous pressure (AVP) from baseline to 10 years.[107] There were six arms in the study: low-dose liquid sclerotherapy, high-dose liquid sclerotherapy, ligation plus stripping, stab avulsion, foam sclerotherapy, and liquid sclerotherapy plus surgery. There was a statistically significant within-group reduction in venous pressure in all groups; however, the difference between groups was not statistically significant (low-dose sclerotherapy mean change: 9 mmHg; high-dose sclerotherapy mean change: 10 mmHg; ligation plus stripping mean change: 11 mmHg; stab avulsion mean change: 11 mmHg; foam sclerotherapy: 14 mmHg; ligation plus stripping plus sclerotherapy: 11 mmHg).[107] An observational study reported recurrence of reflux in at least 3 major sites at 20 years follow-up and found that rates were significantly lower in the sclerotherapy arm (10.6 percent sclerotherapy patients vs. 45.5 percent surgery patients; p<0.05).[198]

Effect on Clinical Symptoms

Five studies[82,88,89,98,127,146] reported VCSS at various time points that precluded meta-analysis. One good-quality study reported a significant improvement in mean scores (± SD) from baseline to 1-year follow-up for both sclerotherapy and surgery, but there was no significant difference between groups (baseline: sclerotherapy=12.26 ± 3.05, surgery=12.5 ± 1.64; 1 year: sclerotherapy=4.26 ± 3.14, surgery=3.39 ± 1.57; intragroup change p<0.001, between-group p=NS).[127] One study reported baseline and 6-month VCSS scores, and there was an improvement in mean scores (± SD) for both treatment groups (baseline: sclerotherapy=4.9 ± 2.6, surgery=5.1 ± 2.5; 12 months: sclerotherapy=1.6 ± 1.7, surgery=1.4 ± 1.7; p-value NR).[88,89] One good-quality study only reported 3-year follow-up VCSS scores and not baseline scores.[98] The mean score for sclerotherapy was 0.15 (SD 0.4) versus 0.3 (SD 0.5) for surgery (p>0.05).[98] Two studies reported improvement in VCSS scores at different time points.[82,146] In one study, the median improvement was 1 point (range 0-5) in the sclerotherapy group versus 3 points (range 0-4) in the surgery arm, implying a greater median improvement in clinical symptoms for the surgery arm (p-value NR).[82] A 3-year follow-up paper on the same study also reported a median change in VCSS scores and found that both arms improved by 1 point (range 0-9).[81] One fair-quality

study of 393 patients reported improvement in VCSS scores at 2-year follow-up, but there was no statistically significant difference between groups (foam sclerotherapy mean change -1.49, surgery mean change -1.75; p=0.232).[146]

Two studies reported changes in CEAP classification at 3-month follow-up.[82,151] A poor-quality study found that the median within-group change was an improvement of 3 classes for both groups, with no difference between groups.[151] A fair-quality study reported that the median within-group change was an improvement of 1 class for both groups (surgery mean classification change=1, range 0-5; sclerotherapy mean classification change=1, range=0-5; p-value NR).[82]

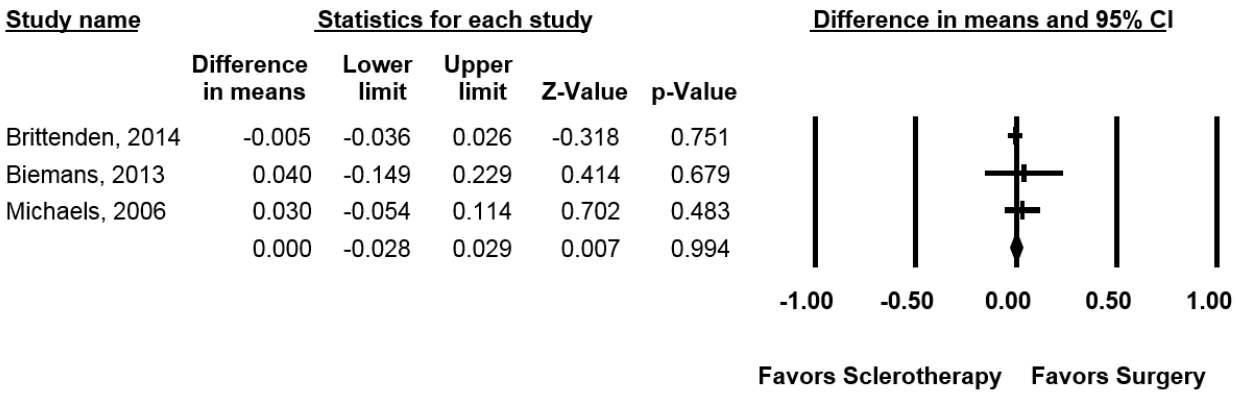
Effect on Patient-Reported Quality of Life

Three good-quality studies[88,89,98,127] reported AVVQ scores at various time points ranging from baseline to 3 years postintervention. All studies showed decreased scores at 3 years, indicating an improvement in symptom scores. One study reported mean AVVQ scores at 3 days, 1 month, 1 year, and 3 years.[98] Mean scores decreased at successive follow-ups, indicating an improvement in PVD-related symptoms; however, no between-group difference was noted at any follow-up time (3 days: sclerotherapy=19.73 [SD 22.19], surgery=21.37 [SD 21.37], p-value NR; 1 month, sclerotherapy=12.74 [SD 18.9], surgery=12.33 [SD 17.6], p-value NR; 1 year, sclerotherapy=6.58 [SD 14.38], surgery=5.34 [SD 13.15], p-value NR; 3 years sclerotherapy=4.76 [SD 5.71], surgery=4.0 [SD 4.87], p-value NR).[98] One study reported baseline and 6-month follow-up, and mean change in scores showed improvement for both groups; however, statistical significance was not reported (baseline: sclerotherapy=17.6 SD 9.9], surgery=18.2 [SD 9.1], p-value NR; 6 months: sclerotherapy=9.1 [SD 7.9], surgery=7.8 [SD 7.5], p-value NR).[88,89] Similarly, 1 study reported baseline and 1-year follow-up for 51 patients randomized to either foam sclerotherapy or high ligation plus stripping surgery.[127] The baseline and 1-year scores were higher in comparison to the previous study described;[88,89] however, the mean change in scores showed improvement in symptom scores for both groups, yet no statistical significance was reported (baseline: sclerotherapy=37.72 [SD 18.17], surgery=40.31 [SD 5.57], p-value NR;12 months: sclerotherapy=15.95 [SD 12.09], surgery=12.3 [SD 7.87], p-value NR).[127]

One poor-quality study reported median within-group change in AVVQ scores at 3-month follow-up. The surgical group had a median within-group improvement score of 7 points, whereas the sclerotherapy group had a 6-point improvement (p-value NR).[151] A fair-quality study reported median within-group changes at 3 years: the surgery group had a larger improvement in AVVQ scores than the sclerotherapy group; however, no p-value was reported to indicate if the difference was significant (sclerotherapy median change=4.97, interquartile range [IQR] 6.19; surgery median change=8.94, IQR 11.51).[81]

We synthesized evidence from 3 RCTs (900 patients) that explored the long-term change in quality of life as measured by EQ-5D.[88,89,117,118] These studies did not demonstrate a difference between strategies (Figure 16).

Figure 16. Forest plot of quality-of-life effects for sclerotherapy versus venous stripping plus ligation



Abbreviation: CI=confidence interval

One fair-quality study reported the mean change in EQ-5D scores at 2-year follow-up and found no difference between the groups (foam sclerotherapy mean change 0.064, surgery mean change 0.061; p=0.889).[146]

Effect on Pain

Four RCTs[88,89,98,187,199] reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies[98,187,199] reported significantly lower pain scores in the sclerotherapy group versus the surgery group. At 10 days follow-up, a good-quality study found that patients in the sclerotherapy arm had a mean VAS score (± SD) of 1.6 (± 2.04) versus 2.25 (± 2.23) for patients in the surgery arm (p<0.0001).[98] One poor-quality study of 217 patients used a VAS scale that ranged from 0-100.[187] Again, the surgery group had a significantly higher mean VAS score when compared with the sclerotherapy group at 1 week postintervention (sclerotherapy=2; surgery=9; p<0.001).[187] A fair-quality study of 49 patients reported that the difference in mean pain scores was significant at 1-year follow-up (sclerotherapy, mean=0.77 [SD 0.18]; surgery, mean=0.83 [SD 0.14]; p<0.05).[199] One study[88,89] reported baseline and 6-month follow-up scores, and the within-group mean improved for both sclerotherapy and surgery (baseline: sclerotherapy mean=5.4 [SD 2.2], surgery mean=5.4 [SD 2.2], p-value NR; 6 months: sclerotherapy mean=2.3 [SD 1.9], surgery mean=1.4 [SD 1.6], p-value NR). One study instead reported a mean change in VAS scores at 2-year follow-up following ultrasound-guided foam sclerotherapy or surgical stripping plus high ligation.[146] Patients in both groups had a decrease in VAS scores, and there was no significant difference between groups (sclerotherapy mean change=-0.36, surgery mean change=-1.8; p=0.577).[146]

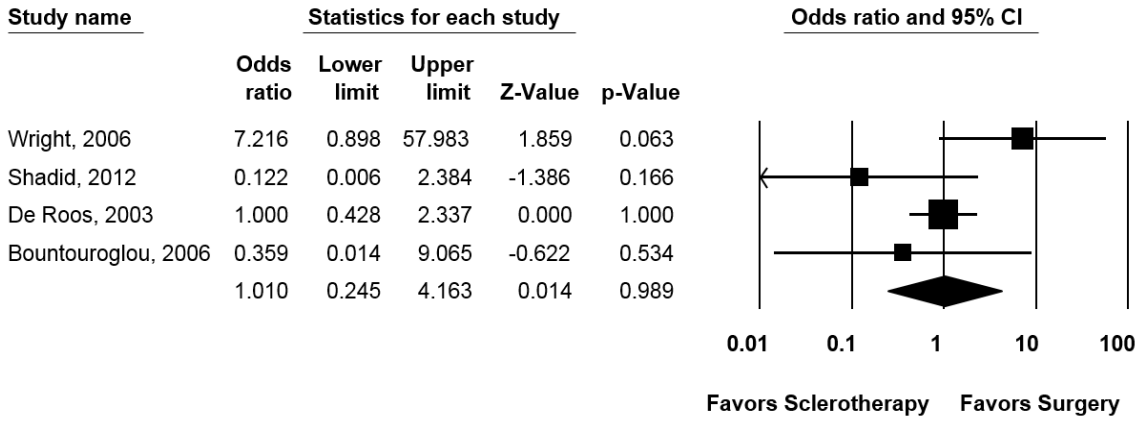
Adverse Events

One study[117] reported no DVTs or PEs in any of three arms (EVLA, sclerotherapy, or surgery) within 3 months of intervention. Another study[98] reported 1 patient with DVT in both the sclerotherapy arm and the ligation plus stripping arm (foam sclerotherapy, 1/124 patients; ligation plus stripping, 1/119 patients; p=NS). This study also reported PE in 1/124 patients in the foam sclerotherapy arm and 0/119 in the surgery arm.[98] A third study reported 1 case of DVT and 1 case of PE out of 230 patients in the sclerotherapy arm and 0 cases out of 200 patients in the surgery arm (p=NS).[146] Only one study reported a significant difference in DVT event rates.

A study of 656 patients in Europe had 3 arms to compare microfoam sclerotherapy, liquid sclerotherapy, and ligation plus stripping. Within 1 week of intervention, patients who underwent microfoam sclerotherapy had a higher incidence of DVT compared with those who underwent ligation plus stripping or liquid sclerotherapy (microfoam sclerotherapy, 2.5 percent event rate; stripping plus ligation, 0 percent event rate; liquid sclerotherapy, 0.8 percent event rate; p-value NR).[187] However, this study is a poor-quality RCT due to selection bias and mixed outcome reporting. One fair-quality study reported no cases of periprocedural DVT in either arm (sclerotherapy, 0/29 patients; surgery, 0/23 patients).[82] An observational study found no significant differences in rates of DVT between groups at 20 years follow-up (1.6 percent ligation plus stripping patients vs. 0.2 percent sclerotherapy patients; p-value NS).[198]

We synthesized evidence from 4 RCTs (3 RCTs with 1142 patients, 1 RCT with 96 limbs) that explored hematomas as an outcome of interest.[82,146,176,187] These inconsistent and imprecise studies did not demonstrate a difference between strategies (OR 1.01; 95% CI, 0.25 to 4.16) (Figure 17).

Figure 17. Forest plot of hematoma effects for sclerotherapy versus venous stripping plus ligation



Abbreviation: CI=confidence interval

Two studies reported hematoma but did not define the timeframe for the outcome and thus were not included in the meta-analysis. A poor-quality RCT reported one case of hematoma in the surgery arm and zero in the sclerotherapy arm and, in addition to not reporting the follow-up timeframe, did not report the total number of patients in either arm.[151] In another fair-quality study, 1/29 surgery patients and 3/27 sclerotherapy patients experienced hematoma within an undefined timeframe postintervention (p-value NR).[161]

Four studies[82,146,151,176] reported superficial thrombophlebitis as an adverse event; however, the various follow-up times precluded meta-analysis. In one study, the rate of superficial thrombophlebitis was high for both groups but the difference was not statistically significant (sclerotherapy, 27.1 percent event rate; phlebectomy, 12.5 percent event rate; p=0.07).[176] A second study reported significantly higher superficial thrombophlebitis events in the sclerotherapy group within 1 week of intervention (sclerotherapy event rate, 17/230 patients; surgery event rate, 0/200 patients; p<0.001).[146] A poor-quality study reported one case of superficial thrombophlebitis in the surgery arm and three cases in the sclerotherapy arm; however, the study did not report the number of patients in each arm.[151] Similarly, a fair-quality study reported that 0/23 surgery patients and 3/28 sclerotherapy patients experienced superficial

thrombophlebitis at 3 months (p-value NR).[82] A 5-year follow-up report of the same study found 3/39 limbs in the sclerotherapy arm and 0/43 limbs in the surgery arm experienced superficial thrombophlebitis (p-value NR).[81]

Six studies[82,117,146,151,161,199] reported wound infections at various time points that were not conducive for meta-analysis. Four studies found no instances of infection in the sclerotherapy arm and one instance of infection in the surgery arms in each study, respectively (sclerotherapy, 0/38 patients; ligation plus stripping, 1/34 patients; p-value NR;[199] sclerotherapy, 0/77 patients; ligation plus stripping, 3/68; p-value NR;[117] sclerotherapy, 0/unknown patients; ligation plus stripping, 1/unknown patients; p-value NR;[151] sclerotherapy, 0/27 patients; surgery, 1/29 patients; p-value NR[161]). A fair-quality study of 73 patients (82 limbs) compared sclerotherapy to surgery with additional mechanical compression therapy for both arms.[82] Two of 30 sclerotherapy patients and 2/28 surgery patients reported periprocedural infection (p-value NR).[82] At 5-year follow-up, groin infections were reported in 2/39 limbs treated with foam sclerotherapy and 2/43 limbs treated with surgery.[82] The fifth study reported a marginally statistically significant difference between groups, with 0/230 sclerotherapy patients and 4/200 surgery patients having wound infections within 1 week of intervention (p=0.031).[146]

Strength of Evidence

Table 10 summarizes the strength of evidence for the findings described above.

Table 10. KQ 2: Strength of evidence for major outcomes—venous stripping plus ligation versus sclerotherapy
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Vein recurrence[a] (Long-term) Low	3 RCTs, 1 Obs: 1,106 1 RCT: 96 limbs	Medium	Direct	Inconsistent	Imprecise	None	We synthesized evidence from 4 RCTs (3 RCTs with 395 patients, 1 RCT with 96 limbs) that explored long-term recurrence. These studies did not demonstrate a difference between strategies (OR 1.54; 95% CI, 0.461 to 5.143) and were both inconsistent and imprecise (Figure 15).[98,127,176,181] Additionally, one observational study reported recurrence of varicose veins and found that ligation plus stripping patients had significantly higher recurrence (11.7% sclerotherapy patients vs. 47.3% ligation plus stripping; p<0.05).[198]
Repeat intervention (Long-term) Insufficient	3 RCTs, 1 Obs: 1,278	Medium	Direct	Consistent	Imprecise	None	Three studies[98,116,176] reported a higher incidence of repeat intervention in the sclerotherapy arms, but significance was reported in only one study.[98] An observational study found that rates of repeat intervention at 20 years follow-up was significantly higher in the ligation plus stripping arm compared to sclerotherapy (58.55% stripping plus ligation patients vs. 21.9% sclerotherapy patients; p<0.05).[198]
Reflux (Long-term) Insufficient	3 RCTs, 1 Obs: 1,365 1 RCT: NR	High	Direct	Inconsistent	Imprecise	Suspected	Only one poor-quality European study reported elimination of reflux as an outcome.[187] At 3 months postintervention, there was no significant between-group difference in the percentage of patients with elimination of reflux (microfoam=83.4%; ligation plus stripping=87.2%, liquid sclerotherapy=88.8%; p>0.05 for ligation plus stripping vs. microfoam; p=0.06 for liquid vs. microfoam).[187] A fair-quality study reported changes in ambulatory venous pressure (AVP) from baseline to 10 years.[107] There were six arms in the study: low-dose liquid sclerotherapy, high-dose liquid sclerotherapy, ligation plus stripping, stab avulsion, foam sclerotherapy, and liquid sclerotherapy plus surgery. There was a statistically significant within-group reduction in venous pressure in all groups; however, the difference between groups was not statistically significant (low-dose sclerotherapy mean change: 9 mmHg; high-dose sclerotherapy mean change: 10 mmHg; ligation plus stripping mean change: 11 mmHg; stab avulsion mean change: 11 mmHg; foam sclerotherapy: 14 mmHg; ligation plus stripping plus sclerotherapy: 11 mmHg).[107] An observational study reported recurrence of reflux in at least 3 major sites at 20 years follow-up and found that rates were significantly lower in the sclerotherapy arm (10.6% sclerotherapy patients vs. 45.5% surgery patients; p<0.05).[198]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Clinical Symptom Scores (VCSS) Insufficient	5 RCTs 1,372	Low	Direct	Inconsistent	Imprecise	Suspected	Five studies[82,88,89,98,127,146] reported VCSS at various time points that precluded meta-analysis. One good-quality study reported a significant improvement in mean scores from baseline to one year follow-up for both sclerotherapy and surgery but there was no significant difference between groups (baseline: sclerotherapy=12.26 ± 3.05, surgery=12.5 ± 1.64; 12 months: sclerotherapy=4.26 ± 3.14, surgery=3.39 ± 1.57; intragroup change p<0.001, between group p=NS).[127] One study reported baseline and 6-month VCSS scores and there was an improvement in mean scores for both treatment groups (baseline: sclerotherapy=4.9 ± 2.6, surgery=5.1 ± 2.5; 12 months: sclerotherapy=1.6 ± 1.7, surgery=1.4 ± 1.7;p not reported).[88,89] One good-quality study only reported 3 year follow-up VCSS scores and not baseline scores.[98] The mean score for sclerotherapy was 0.15 (SD 0.4) versus 0.3 (SD 0.5) for surgery (p>0.05).[98] Two studies reported improvement in VCSS scores at different time points.[82,146] In one study, the median improvement was 1 point (range 0-5) in the sclerotherapy group vs. 3 points (range 0-4) in the surgery arm, implying a greater median improvement in clinical symptoms for the surgery arm (p-value not reported).[82] A 3-year follow-up paper on the same study also reported a median change in VCSS scores and found that both arms improved by 1 point (range 0-9).[81] One fair-quality study of 393 patients reported improvement in VCSS scores at 2 years' follow-up, but there was no statistically significant difference between groups (foam sclerotherapy mean change -1.49, surgery mean change -1.75; p=0.232).[146]
Clinical Symptom Scores (CEAP) Insufficient	2 RCTs: 129	High	Direct	Inconsistent	Imprecise	None	Two studies reported changes in CEAP classification at 3 months' follow-up.[82,151] A poor-quality study found that the median within-group change was an improvement of 3 classes for both groups and that there was no difference between groups.[151] A fair-quality study reported that the median within-group change was an improvement of 1 class for both groups (surgery mean classification change= 1, range 0-5; sclerotherapy mean classification change=1, range=0-5; p-value not reported).[82]
Patient-Reported Quality of Life (AVVQ) Low	3 RCTs: 583	Low	Direct	Consistent	Imprecise	Suspected	Three good-quality studies[88,89,98,127] reported AVVQ as an outcome at various time points ranging from baseline to three years follow-up. All studies showed decreased scores at follow-up, indicating an improvement in symptom scores but no difference between groups.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Patient-Reported Quality of Life (EQ-5D) Moderate	3 RCTs: 900	Medium	Direct	Consistent	Precise	None	We synthesized evidence from 3 RCTs (900 patients) that explored the long-term change quality of life as measured by EQ-5D.[88,89,117,118] These studies did not demonstrate a difference between strategies (difference in means = 0, 95% CI -0.028 to 0.029) (Figure 16).
Reduction of LE Pain Low	3 RCTs: 1,498 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	Four RCTs[88,89,98,187,199] reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies[98,187,199] reported significantly lower pain scores in the sclerotherapy group when compared with the surgery group.
Adverse Events (Presence of DVT) Insufficient	4 RCTs, 1 Obs: 2,507 1 RCT: 82 limbs	Medium	Direct	Inconsistent	Imprecise	Suspected	One study[117] reported no DVTs or PEs in any of three arms (EVLA, sclerotherapy, or surgery) within 3 months of intervention. Another study[98] reported one patient with DVT in both the sclerotherapy arm and the ligation plus stripping arm (foam sclerotherapy, 1/124 patients; ligation plus stripping, 1/119 patients; p-value not significant). This study also reported PE in one of 124 patients in the foam sclerotherapy arm and zero of 119 in the surgery arm.[98] A third study reported one case of DVT and one case of PE out of 230 patients in the sclerotherapy arm and zero cases out of 200 patients in the surgery arm (p-value not significant).[146] Only one study reported a significant difference in DVT event rates. A study of 656 patients in Europe had three arms to compare microfoam sclerotherapy, liquid sclerotherapy, and ligation plus stripping. Within 1 week of intervention, a higher percentage of patients who underwent microfoam sclerotherapy had an incidence of DVT compared with those who underwent ligation plus stripping or liquid sclerotherapy (microfoam sclerotherapy, 2.5% event rate; stripping plus ligation, 0% event rate; liquid sclerotherapy, 0.8% event rate; significance not reported).[187] However, this study is a poor-quality RCT due to selection bias and mixed outcome reporting. One fair-quality study reported no cases of periprocedural DVT in either arm (sclerotherapy, 0/29 patients; surgery, 0/23 patients).[82] An observational study found no significant differences in rates of DVT between groups at 20 years follow-up (1.6% ligation plus stripping patients vs. 0.2% sclerotherapy patients; p-value NS).[198]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Adverse Events (Hematoma) Low	3 RCTs: 1,142 1 RCT: 96 limbs	Medium	Direct	Inconsistent	Imprecise	Suspected	We synthesized evidence from 4 RCTs (3 RCTs with 1,142 patients, 1 RCT with 96 limbs)[82,146,176,187] that explored hematomas as an outcome of interest. These inconsistent and imprecise studies did not demonstrate a difference between strategies (OR = 1.010, 95% CI 0.245 to 4.163) (Figure 17).
Adverse Events (Thrombophlebitis) Insufficient	2 RCTs: 1,084 2 RCTs: 178 limbs	Medium	Direct	Inconsistent	Imprecise	None	Four studies[82,146,151,176] reported superficial thrombophlebitis as an adverse event outcome; however, the various follow-up times precluded meta-analysis. In one study, the rate of superficial thrombophlebitis was high for both groups but the difference was not significant (sclerotherapy, 27.1% event rate; phlebectomy, 12.5% event rate; p=0.07).[176] A second study reported significantly higher superficial thrombophlebitis events in the sclerotherapy group within 1 week of intervention (sclerotherapy event rate, 17/230 patients; surgery event rate=0/200 patients; p<0.001).[146] A poor-quality study reported one case of superficial thrombophlebitis in the surgery arm and three cases in the sclerotherapy arm; however, the study did not report the number of patients in each arm.[151] Similarly, a fair-quality study reported that zero out of 23 surgery patients and three out of 28 sclerotherapy patients experienced superficial thrombophlebitis at 3 months (p-value not reported).[82] A 5-year follow-up report of the same study found three out of 39 limbs in the sclerotherapy arm and zero out of 43 limbs in the surgery arm experienced superficial thrombophlebitis (p-value not reported).[81]
Adverse Events (Wound Infections) Insufficient	6 RCTs: 889	Medium	Direct	Consistent	Imprecise	Suspected	Six studies[82,117,146,151,161,199] reported wound infections at various time points that were not conducive for meta-analysis. Four studies found zero instances of infection in the sclerotherapy arm and one instance of infection in the surgery arms in each study, respectively (sclerotherapy, 0/38 patients; ligation plus stripping, 1/34 patients; p-value not reported)[199] (sclerotherapy, 0/77 patients; ligation plus stripping, 3/68; p-value not reported)[117] (sclerotherapy, 0/unknown patients; ligation plus stripping, 1/unknown patients; p-value not reported)[151] (sclerotherapy, 0/27 patients; surgery, 1/29 patients; p-value not reported).[161]

[a] Vein recurrence refers to the establishment of patency of the venous system; such recurrence often requires repeat intervention.

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; DVT=deep vein thrombosis; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; PE=pulmonary embolism; RCT(s)=randomized controlled trial(s); SD=standard deviation; SE=standard error; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

Venous Stripping plus Ligation versus Thermal Ablation

There was one study comparing venous stripping plus ligation versus steam thermal ablation with a total of 102 patients.[128] Additionally, all 102 patients in the study were treated with mechanical compression therapy.

Effect on Recurrence

At 6 months, six of 52 patients in the steam thermal ablation arm and six of 50 patients in the surgery arm had varicose vein recurrence.[128]

Effect on Clinical Symptoms

The mean baseline VCSS score for the steam thermal ablation group was 7.25 (SD 1.78), and at 6 months postprocedure it was 1.78 ($p<0.05$ for intragroup change). The mean baseline score for the surgery group was 8.28 (SD 2.2) and at 6 months postprocedure it was 2.2 ($p<0.05$ for intragroup change).

Adverse Events

After 1 week, there was no DVT or PE in either group.[128]

Strength of Evidence

Table 11 summarizes the strength of evidence for the findings described above.

Table 11. KQ 2: Strength of evidence for major outcomes—venous stripping plus ligation versus thermal ablation

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Recurrence (Intermediate-term)	1 RCT: 102	Medium	Direct	NA	Imprecise	None	At 6 months, six of 52 patients in the steam thermal ablation arm and six of 50 patients in the surgery arm had varicose vein recurrence.[128]
Insufficient							
Clinical Symptom Scores (VCSS) (Intermediate-term)	1 RCT: 102	Medium	Direct	NA	Imprecise	None	The mean baseline VCSS score for the steam thermal ablation group was 7.25 (SD 1.78), and at 6 months postprocedure it was 1.78 ($p<0.05$ for intragroup change). The mean baseline score for the surgery group was 8.28 (SD 2.2) and at 6 months postprocedure it was 2.2 ($p<0.05$ for intragroup change).
Insufficient							
Adverse Events (Short-term)	1 RCT: 102	Medium	Direct	NA	Imprecise	None	After 1 week, neither group reported any instances of DVT or PE.[128]
Insufficient							

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; PE=pulmonary embolism; RCT(s)=randomized controlled trial(s); SD=standard deviation; SE=standard error; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

Minimally Invasive Venous Ligation plus Stripping versus Sclerotherapy

There was one observational study comparing four arms: minimally-invasive venous ligation plus stripping surgery versus sclerotherapy versus venous ligation plus stripping versus minimally-invasive venous ligation plus stripping surgery plus sclerotherapy.[198] A total of 336 patients were in the minimally-invasive venous ligation plus stripping surgery and sclerotherapy arms.

Effect on Recurrence

One observational study reported recurrence of reflux at 20 year follow-up and found that recurrence rates were not significantly different in the mini-s patients compared to sclerotherapy patients (21.0 percent mini-s patients vs. 20.7 percent sclerotherapy patients; p-value NS).[198] The study also reported recurrence of reflux in at least 3 major sites at 20 years and found that rates were not significantly different between arms (10.6 percent sclerotherapy patients vs. 10.7 percent mini-s patients; p-value NS).[198] This same study reported recurrence of varicose veins and found no difference between arms (11.7 percent sclerotherapy patients vs. 15 percent mini-s; p-value NS).[198]

Effect on Repeat Intervention

An observational study found that rates of repeat intervention at 20 years follow-up was not significantly different between the mini-s arm compared to sclerotherapy (18.9 percent mini-s vs. 21.9 percent sclerotherapy patients; p-value NS).[198]

Adverse Events

There was no significant differences in rates of DVT between groups at 20 years follow-up (0.2 percent mini-s vs. 0.2 percent sclerotherapy patients; p-value NS)[198]

Comparisons Between Different Endovascular Interventions

EVLA versus Sclerotherapy

Three RCTs,[88,89,98,114] two of good quality[88,89,98] and one of fair quality,[114] reported comparisons of EVLA versus endovenous foam sclerotherapy. One of these studies was shared in two publications.[88,89] In all, these studies involved a total of 1,408 participants, comprising patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Individual study sample sizes ranged from 110 to 798. Study follow-up periods ranged from 7 days to 3 years. Three RCTs were conducted in the UK/Europe: one study was conducted at 11 sites,[88,89] one was conducted at 2 sites,[98] and the third was conducted in a single center.[114] One study reported government and industry funding sources,[98] another reported only government funding[88,89] and one reported both an industry and non-government funding source.[114] The mean/median age of study participants ranged from 48.45 to 51 years. The proportion of female patients ranged from 56.7 to 73.75 percent. None of the studies reported the racial or ethnic composition of their study populations. In two studies, the majority of patients had a baseline CEAP class of C2-C3[88,89,98] and in the remaining study the majority of patients had a baseline CEAP class of C2-C4.[114]

Effect on Patient-Reported Quality of Life

Two good-quality RCTs[88,89,98] and one fair-quality RCT[114] reported information on quality of life following EVLA versus endovenous foam sclerotherapy. The studies presented AVVQ scores at 6 weeks,[88] 3 months,[114] 6 months,[88,89] 15 months[114] and at 3 years[98] for each group. The effect size in adjusted data (for minimization covariate: sex, age group, saphenous vein involvement, disease laterality and center) of AVVQ in the EVLA group at 6 weeks was 0.21 and at 6 months was -0.63. The effect size in adjusted data (for minimization covariate: sex, age group, saphenous vein involvement, disease laterality and center) of AVVQ in the foam sclerotherapy group at 6 weeks was -1.71 and at 6 months was -1.06. There was a statistically significant between-group difference regarding effect size in the adjusted data for AVVQ at 6 weeks (p=0.032).[88] The median within-group change of AVVQ in the EVLA group was 14 at 3 months; and the median within-group change for AVVQ in the foam sclerotherapy group was 8 at 3 months. There was a statistically significant between-group difference regarding the median within-group change of AVVQ at 3 months (p=0.01).[114] AVVQ scores improved within each group by 6 months.[89] In the EVLA group, AVVQ improved from a baseline of 17.8 to 7.9 at 6 months. In the foam sclerotherapy group, AVVQ improved from a baseline of 17.6 to 9.1 at 6 months.[89] The median within-group change of AVVQ in the EVLA group was 12.2 at 15 months; and the median within-group change of AVVQ in the foam sclerotherapy group was 9.5 at 15 months. There was no statistically significant between-group difference regarding the median within-group change of AVVQ at 15 months.[114] At 3 years, the mean Aberdeen Varicose Vein Severity Score (AVVSS) in the EVLA group was 4.61 versus 4.76 in the foam sclerotherapy group.[98] The same study also reported the median AVVSS at 3 days, 1 month, and 1 year. In the EVLA group, the median AVVSS was 6.16 at 3 days, 13.15 at 1 month, and 19.73 at 1 year. In the foam sclerotherapy group, the median AVVSS was 6.58 at 3 days, 12.74 at 1 month, and 19.73 at 1 year.[98] One study reported the EuroQol 5D 3L (EQ-5D-3L). The EQ-5D-3L score improved within each group at 6 months.[89] In the EVLA group, scores improved from a baseline of 5 to 1.4 at 6 months. In the foam sclerotherapy group, scores improved from a baseline of 4.9 to 1.6 at 6 months.[89] The majority of studies presented Short Form 36-item Health Survey (SF-36) data for each group.[88,89,98] One study also reported information on quality of life in a subgroup of patients having great saphenous veins equal to or above 8 mm in diameter. In the EVLA group, the median AVVQ was 13.6 at 3 months and 12.3 at 15 months. In the foam sclerotherapy group, the median AVVQ was 11.3 at 3 months and 13.3 at 15 months. There were no statistically significant between-group differences at 3 months (p=0.230) or 15 months (p=0.908).[114]

Effect on Other Standardized Symptom Scores

Two good-quality RCTs[89,98] and one fair-quality RCT[114] presented VCSS data. Within the fair-quality RCT, the median within-group VCSS change in the EVLA group was 3 at 3 weeks and was 5 at 3 months. The median within-group VCSS change in the foam sclerotherapy group was 3 at 3 weeks and was 4 at 3 months. There was not a statistically significant between-group difference regarding median within-group change of VCSS at 3 months (p=0.796).[114] VCSS improved within each group at 6 months,[89] from a baseline of 5 to 1.4 in the EVLA group and from a baseline of 4.9 to 1.6 in the foam sclerotherapy group.[89] The median within-group change of VCSS for both the EVLA and foam sclerotherapy groups was 5 at 15 months. There was not a statistically significant between-group difference regarding median within-group change of VCSS at 15 months (p=0.902).[114] At 3 years, the mean VCSS in the EVLA group was 0.34 compared with 0.15 in the foam sclerotherapy group.[98] One study also reported information on

the effect on VCSS in a subgroup of patients having great saphenous veins ≥8 mm of diameter. In the EVLA subgroup, the median within-group change of VCSS was 5 at 3 months and 4 at 15 months. In the foam sclerotherapy subgroup, the median within-group change of VCSS was 4 at 3 months and 5 at 15 months. There was no statistically significant between-group difference at 3 months (p=0.554) or 15 months (p=0.897).[114] One fair-quality study presented the mean of the Saphenous Treatment Score (STS) for each group. In the EVLA group, the median within-group change of STS was 2 at 3 months and 2 at 15 months. In the foam sclerotherapy group, the median within-group change of STS was 2 at 3 months and 2 at 15 months.[114] There was no statistically significant between-group difference at 3 months (p=0.148) or at 15 months (p=0.866).[114] This study also presented information on the effect on STS in a subgroup of patients having great saphenous veins ≥8 mm of diameter. In the EVLA subgroup, the median within-group change of STS was 1 at 3 months and 2 at 15 months. In the foam sclerotherapy subgroup, the median within-group change of STS was 3 at 3 months and 3 at 15 months.[114] There was a statistically significant between-group difference in favor of foam sclerotherapy at 3 months (p=0.014).[114]

Effect on LE Pain

One study reported 0-10 VAS pain scores for residual varicosities. VAS improved within each group at 6 months.[89] In the EVLA group, VAS pain scores improved from a baseline of 5.5 to 1.8 at 6 months. In the foam sclerotherapy group, VAS improved from a baseline of 5.4 to 2.3 at 6 months.[89] One study presented mean VAS pain scores at 10 days for each group. The foam sclerotherapy group reported less pain compared with the EVLA group at 10 days (utility 1.60 versus 2.58).[98] Additionally, one other study reported median pain scores at 7 days postprocedure. In the EVLA group, the median pain score was 33 versus 14 in the foam sclerotherapy group, which constituted a statistically significant between-group difference in pain in favor of the latter (p=0.005).[114]

Effect on Perioperative/Postoperative Complications

Two studies reported the number of patients with venous thrombosis and venous thromboembolic events for each group.[98,114] In one study,[98] one patient presented with DVT in the foam sclerotherapy group and one patient presented with PE in the foam sclerotherapy group. In the other study,[114] one patient presented with DVT in the EVLA group while no patients presented with PE in either group at 3 months. One study also reported numbers of hemorrhage and superficial thrombophlebitis at 1 month for EVLA and foam sclerotherapy groups, with each group having one patient with hemorrhage.[98] A total of four patients in the EVLA group had superficial thrombophlebitis versus 17 in the foam sclerotherapy group.[98] The other study reported the presence of hematoma and dermal thermal injury in the EVLA group during the postoperative period.[114] Two patients had hematoma and two had dermal thermal injury.[114]

Effect on Improvement in Venous Hemodynamics

One study reported the presence of reflux in veins and failure of procedure at 6 months. At 6 months, the EVLA group had 10 patients with venous reflux, compared with nine in the foam sclerotherapy group. At that same time point, the EVLA group had 9 patients with failure of procedure versus 59 in the foam sclerotherapy group.[89] One study reported recurrence of varicose veins after procedures for each group at 1 year. At 1 year, the number of patients with recurrence of varicose veins was 14 in the EVLA group versus 17 in the foam sclerotherapy group.[98] One study reported postprocedure occlusion rates for each group at 15 months. At 15

months, 31 patients in the EVLA group showed absence of reflux versus 42 in the foam sclerotherapy group: a statistically significant between-group difference in favor of the EVLA group (p=0.001).[114] According to one study, three patients in the EVLA group repeated intervention compared with 28 in the foam sclerotherapy group.[114] In the other study, the percentage of patients that repeated intervention at 3 years was 12.5 percent in the EVLA group, and was 31.6 percent in the foam sclerotherapy group.[98] One fair-quality study presented the median within-group change of venous filling index for each group. In the EVLA group, the median within-group change of venous filling index was 2.6 at 3 months. In the foam sclerotherapy group, the median within-group change of venous filling index was 3.1 at 3 months.[114]

Strength of Evidence

Table 12 summarizes the strength of evidence for the findings described above.

Table 12. KQ 2: Strength of evidence for major outcomes—EVLA versus sclerotherapy

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short-term) Insufficient	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	2 bleeding events in EVLA arm and none in foam sclerotherapy arm.[114]
Bleeding (Intermediate-term) Insufficient	1 RCT 489	Low	Direct	NA	Imprecise	None	At 1 month, one patient presented bleeding in EVLA group and one patient presented bleeding in foam sclerotherapy group.[98]
Changes on standardized symptom scores (Short-term) Insufficient	1 RCT 785	Low	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups.[89]
Changes on standardized symptom scores (Intermediate-term) Low	2 RCTs: 885	Low	Direct	Consistent	Precise	Suspected	VCSS improved in both groups. No statistically difference between groups.[89,114]
Changes on standardized symptom scores (Long-term) Insufficient	1 RCT 489	Low	Direct	NA	Imprecise	None	VCSS improved in both groups. No statistically difference between groups.[98]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term) Insufficient	3 RCTs: 1,374	Low	Direct	Consistent	Imprecise	Suspected	In 3 different RCTs, there was no statistically significant difference in presence of reflux,[89] recurrence of varicoses,[98] or change of venous filling index/VFI.[114]
Improvement in LE venous hemodynamics /reflux severity (Long-term) Insufficient	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	Occlusion rate: Demonstrating a statistically significance in occlusion rates in favor of EVLA arm (p=0.001).[114]
Patient-Reported QOL (Short-term) Insufficient	1 RCT 489	Low	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups.[98]
Patient-Reported QOL (Intermediate-term) Low	2 RCTs: 885	Medium	Direct	Consistent	Precise	Suspected	There was a significant between-groups difference regarding effect size in adjusted data of AVVQ at 6 weeks (p=0.032). There was a significant between-groups difference regarding median within group change of AVVQ at 3 months (p=0.01) both demonstrating a benefit of EVLA.[89,114]
Patient-Reported QOL (Long-term) Low	2 RCTs: 580	Medium	Direct	Consistent	Imprecise	Suspected	QOL improved in both group. No statistically difference between groups.[98,114]
Periprocedural complications (Short-term) Insufficient	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	The number of patients with dermal thermal injury in post operatory period was 2 in EVLA group.[114]

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Qualitative reduction in LE pain (Short-term) Low	2 RCTs: 885	Medium	Direct	Consistent	Imprecise	Suspected	The foam sclerotherapy group reported less pain versus the EVLA group at 10 days (1.60 versus 2.58, respectively). There was a significant between-groups difference in pain in favor of foam sclerotherapy group at 07 days (p=0.005).[89,114]
Qualitative reduction in LE pain (Intermediate-term) Insufficient	1 RCT 412	Low	Direct	NA	Imprecise	None	In the EVLA group, VSA improved from baseline of 5.5 to 1.8 at 6 months. In the foam sclerotherapy group, VAS improved from baseline of 5.4 to 2.3 at 6 months.[89]
Repeat Intervention (Intermediate-term) Insufficient	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	The number of patients that repeated intervention at 15 months was 3 in EVLA group and 28 in foam sclerotherapy group.[114]
Repeat Intervention (Long-term) Insufficient	1 RCT 489	Low	Direct	NA	Imprecise	None	The percentage of patients that repeated intervention at 3 years was 12.5% in EVLA group, and was 31.6% in foam sclerotherapy group.[98]
Thrombo-phlebitis (Short-term) Insufficient	1 RCT 489	Low	Direct	NA	Imprecise	None	The number of patients with superficial thrombophlebitis at 1 month was 4 in EVLA group and was 17 in foam sclerotherapy group.[98]
Venous thrombo-embolic events (Intermediate-term) Insufficient	2 RCTs: 580	Medium	Direct	Inconsistent	Imprecise	Suspected	At 1 month, one patient presented pulmonary embolism in foam sclerotherapy group and no patient presented in EVLA group. At 3 months, no patient presented pulmonary embolism in both groups.[98,114]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Venous thrombosis (Intermediate-term)	2 RCTs: 580	Medium	Direct	Consistent	Imprecise	Suspected	In one RCT, at 1 month, one patient presented deep venous thrombosis in foam sclerotherapy group and no patient presented DVT in EVLA group. In the second RCT, at 3 months, one patient presented deep venous thrombosis in EVLA group and no patient presented DVT in foam sclerotherapy group.[98,114]
Insufficient							

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; PE=pulmonary embolism; QOL=quality of life; RCT(s)=randomized controlled trial(s); SD=standard deviation; SE=standard error; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

Nd:YAG Laser Ablation versus Sclerotherapy

One good-quality RCT reported a comparison of neodymium-doped yttrium aluminum garnet (Nd:YAG) EVLA versus endovenous foam sclerotherapy.[138] This study included 320 patients with symptomatic varicose veins. Follow-up periods ranged from 0 to 3 years. This study was conducted in a single center in the UK/Europe. The study reported both a non-government and non-industry funding source. The mean age of study participants and the proportion of female patients were not reported. The study did not report the racial or ethnic composition of their study populations and the baseline CEAP class.

Effect on Patient-Reported Quality of Life

The study presented percentage of patient satisfaction after the procedure at 3 months and 3 years for each group, with more patients reporting in the Nd:YAG laser ablation group reporting satisfaction than in the foam sclerotherapy group.

Effect on Postoperative Pain

The study reported information on intra-operative pain. In the Nd:YAG laser ablation group, the patients reported predominantly light and moderate pain during the procedure, while patients in the foam sclerotherapy group reported predominantly severe pain during the procedure.

Effect on Perioperative/Postoperative Complications

The study reported rates of general complications at 3 months and at 2 and 3 years following Nd:YAG laser ablation versus foam sclerotherapy. The percentage of complications in the laser ablation group was 7.73 percent at 3 months, 1.16 percent at 2 years, and 0.77 percent at 3 years. The percentage of complications in the foam sclerotherapy group was 6.3 percent at 3 months, and was 0 at 3 years (no data presented for 2-year follow-up). The study also reported the rates of complications by categories including hyperpigmentation, matting, hypopigmentation, and blistering.

Effect on Improvement in Venous Hemodynamics

The study reported procedure efficacy (clearing rates) as determined by 3 blinded physician investigators at 3 months and at 2 years. For each patient, leg veins were defined as follows: Class I (red vessels <0.5 mm in diameter), Class II (red-blue venulectasias of 0.5 to 1.5 mm in diameter) and Class III (blue reticular veins measuring between 1.5 and 4 mm in diameter). Most patients presented several of these types of lesions.

Strength of Evidence

Table 13 summarizes the strength of evidence for the findings described above.

Table 13. KQ 2: Strength of evidence for major outcomes—Nd:YAG laser ablation versus sclerotherapy
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Improvement in LE venous hemodynamics /reflux severity (Long-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	Procedural efficacy: The study reported procedure efficacy (clearing rates) as determined by 3 MD panel at 2 years.[138]
Patient-Reported QOL (Int-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	The study presented percentage of patient satisfaction after the procedure at 3 months for each group. The number of satisfied patients was better in the Nd:YAG laser ablation group than in the endovenous foam sclerotherapy group at 3 months.[138]
Patient-Reported QOL (Long-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	The study presented percentage of patient satisfaction after the procedure at 3 years for each group. The number of satisfied patients was better in the Nd:YAG laser ablation group than in the endovenous foam sclerotherapy group at 3 years.[138]
Periprocedural complications (Int-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	The percentage of complications in the Nd:YAG laser ablation group was 7.73% at 3 months. The percentage of complication in endovenous foam sclerotherapy group was 6.3% at 3 months.[138]
Periprocedural complications (Long-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	The percentage of complications in the Nd:YAG laser ablation group was 1.16% at 2 years; and was 0.77% at 3 years. The percentage of complication in endovenous foam sclerotherapy group was 0 at 3 years.[138]
Qualitative reduction in LE pain (Short-term) Insufficient	1 RCT 517 limbs	Low	Direct	NA	Imprecise	None	In the Nd:YAG laser ablation group, the patients presented predominantly light and moderate pain during the procedure. In the endovenous foam sclerotherapy group, the patients presented predominantly severe pain during the procedure.[138]

Abbreviations: KQ=key question; Int=intermediate; LE=lower extremity; N=number; NA=not applicable; QOL=quality of life; RCT(s)=randomized controlled trial(s)

EVLA versus RFA

Five RCTs, two of good quality,[122,123,149] one of fair quality[154] and two of poor quality,[155,163] reported comparisons of EVLA versus endovenous RFA, associated with compression in all groups. One of these studies was shared in two publications.[122,123] In all, these studies involved 543 patients; four studies included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins, and one study included symptomatic patients with varicose veins.[149] Individual study sample sizes ranged from 66 to 131. Study follow-up periods ranged from 2 days to 1 year. One RCT was conducted in a single U.S. center,[154] three were conducted in a single center in the UK/Europe,[122,123,149,155] and the remaining study was conducted at 6 sites in the United States and the UK/Europe.[163] Two studies reported an industry funding source,[155,163] while three reported non-government/non-industry funding.[122,123,149,154] The mean/median age of study participants ranged from 46.8 to 52 years. The proportion of female patients ranged from 62 to 79.25 percent. None of the studies reported the racial or ethnic composition of their study populations. In two studies, the majority of patients had a baseline CEAP class of C2-C3[149,163] and in two other studies the majority of patients had a baseline CEAP class of C3-C4.[122,123,154] The CEAP class was not reported in the final RCT.[155]

One fair quality observational study[125] reported comparisons of EVLA versus RFA. This study involved 979 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Study follow-up periods ranged from 20 days to an undetermined time. The study was conducted in a single U.S. center and reported a non-government and non-industry funding source. The mean age of participants in the study was 53.2 years. The proportion of female patients in the observational study was 74 percent. The study did not report the racial or ethnic composition of their study populations. The majority of patients had a baseline CEAP class of C2-C3.

One poor quality observational study[195] reported comparisons of EVLA versus RFA. This study was a registry and involved 36,096 patients. The registry was conducted in 84 centers in Germany/Europe. The mean age of participants in the study was 52.8 years. The proportion of female patients in the observational study was 69 percent. The study did not report funding source and racial or ethnic composition of study population. The majority of patients had a baseline CEAP class of C2.

Effect on Patient-Reported Quality of Life

Two studies of good quality presented AVVQ scores for each group.[122,123,149] At 6 weeks the mean between-group change of AVVQ was 0.2 in the EVLA group and -0.3 in the RFA group.[123] At 3 months the mean within-group change of AVVQ was -11.2 in the EVLA group and -10.3 in the RFA group. There was no statistically significant between-group difference ($p=0.12$).[149] AVVQ scores were improved within each group at 6 months. In the EVLA group, AVVQ improved from a baseline of 18.9 to 10.9 at 6 months. In the RFA group, AVVQ improved from a baseline of 20.6 to 10.2 at 6 months. There was no statistically significant between-group difference regarding mean within-group change of AVVQ at 6 months.[122,123] One fair-quality study[154] and one poor-quality study[163] reported scores from the Chronic Venous Insufficiency Questionnaire (CIVIQ) at 2 days, 1 month, and 1 year. The fair-quality study reported the mean CIVIQ scores at 1 month and 1 year for each group. At 1 month, the mean CIVIQ was 87.5 in the EVLA group and 89.3 in the RFA group; at 1 year, the mean CIVIQ was 94.1 in the EVLA group and 93.8 in the RFA group.[154] The poor-quality studied reported mean within-group change in CIVIQ scores at 2 days and 1 month for each group. At 1 month, the

mean within-group change CIVIQ was -7.1 in the EVLA group and -13.5 in the RFA group. At 1 year, the mean within-group change CIVIQ score was -17.5 in the EVLA group and -17.8 in the RFA group. RFA had a larger change and therefore greater improvement than EVLA but the difference was not statistically significant.[163] One study presented the mean improvement of EQ5-D for each group. The mean improvement of EQ-5D was 0.22 in the EVLA group and 0.16 in the RFA group. There was no statistically significant between-group difference (p=0.66)[149] One study also reported SF-36 data for each group.[122,123]

Effect on Other Standardized Symptom Scores

Four studies presented VCSS data following EVLA and endovenous RFA. One poor-quality study reported VCSS data at 2 days and 1 month. In the EVLA group, the mean VCSS was 6.2 at 2 days and 3.2 at 1 month. In the RFA group, the mean VCSS was 4.7 at 2 days and 2.7 at 1 month. There was a statistically significant between-group difference at 2 days (p=0.0009).[163] One fair-quality study reported mean within-group changes of VCSS at 1 week, 1 month, and 1 year. In the EVLA group, the mean within-group change of VCSS was 0.86 at 1 week, 3.82 at 1 month, and 4.69 at 1 year. In the RFA group, the mean within-group change of VCSS was 1.84 at 1 week, 4.21 at 1 month, and 4.90 at 1 year. There was a statistically significant between-group difference at 1 week (p=0.0006).[154] One study of good quality presented VCSS scores at 6 weeks and 6 months for each group.[122,123] At 6 weeks the mean between-group change of AVVQ was 0 in the EVLA group and -0.1 in the RFA group. At 6 months, the mean within-group change of VCSS was 3.3 in the EVLA group and 3.7 in the RFA group. There was no statistically significant between-group difference in the mean within-group change of VCSS at 6 months.[122,123] One good-quality observational study presented the mean change of VCSS at 3 years. The observational study reported the mean change of VCSS. In the EVLA group the mean change of VCSS was 3.8 and in the RFA group, the mean change of VCSS was 3.2—a statistically significant between-group difference in change of VCSS in favor of the EVLA group (p=0.019).[125] One fair-quality study reported the number of patients with clinical class of CEAP ≥3 at 1 year. Before treatment, 21 RFA patients and 24 EVLA patients had a clinical class of CEAP score ≥3. At 1 year, there were 9 patients in the RFA group and there were 12 in the EVLA group (p<0.001). There was a statistically significant between-group difference at 1 year (p<0.001) but no difference in CEAP clinical class improvement between treatment groups during the follow-up.[154]

Effect on LE Pain

Two good-quality RCTs reported differences in 10-point VAS pain scores at 7 and 10 days, respectively, for each group. The study reporting median pain scores at 7 days showed a statistically significant difference in favor of the RFA group, with a median pain score of 13.5 in the EVLA group and 0 in the RFA group (p=0.001).[149] In the other study, the RFA group also reported better improvement in pain score compared with the EVLA group at 10 days (utility -12.3 versus -6.3, respectively). There was a statistically significant between-group difference at 10 days (p=0.01).[122,123]

Effect on Perioperative/Postoperative Complications

Three RCTs reported the number of patients with venous thromboembolic events[149,154,163] for each group. In all studies, one patient presented with DVT in the EVLA group. One good-quality RCT reported that one patient presented with PE in the RFA group.[122,123] A fair-quality observational study reported venous thromboembolic events for each group.[125] There were six

cases of deep venous thrombosis in the RFA group and 19 cases in the EVLA group. There was one case of PE in the EVLA group.[125] The observational study also reported the presence of endovascular heat-induced thrombosis (EHIT). In the EVLA group, 26 patients experienced EHIT; in the RFA group, 10 patients experienced EHIT. There was no statistically significant between-group difference (p=0.106).[125] The same study reported the number of patients with superficial venous thrombosis for each group (EVLA, n=37; RFA, n=11). There was a statistically significant between-group difference in favor of RFA group (p=0.01).[125] One good-quality RCT[122,123] and one fair-quality observational study.[125] reported the number of patients with presence of hematoma and with presence of wound infection for each group. In the RCT, 2 patients in the EVLA group had hematoma (0 patients in the RFA group); and the number of patients with wound infection was 2 in the EVLA group and 4 in the RFA group.[122,123] The observational study reported 45 patients with hematoma in the EVLA group and 5 in the RFA group; it also reported 6 patients with infection in the EVLA group and 2 in the RFA group. There was a statistically significant between-group difference in occurrence of hematoma in favor of RFA group (p<0.001).[125] One fair-quality RCT reported the number of patients with bruising at 1 week and 1 month. There was significantly more bruising in the EVLA group at 1 week (p=0.01). However, there was no statistically significant between-group difference in bruising at 1 month.[154] Two good-quality RCTs reported on the incidence of superficial thrombophlebitis at 1 week[149] and 1 month[122,123] and one poor-quality RCT[163] reported on superficial thrombophlebitis at 2 days and 1 month for each group. In one of the high-quality RCTs, the percentage of patients with superficial thrombophlebitis at 1 week was 2.6 percent in the EVLA group and 1.3 percent in the RFA group (between-group difference NS).[149] The other good-quality RCT reported 5/67 patients with superficial thrombophlebitis in the RFA group and 3/64 in the EVLA group.[122,123] In the poor-quality RCT, the number of patients with superficial thrombophlebitis at 2 days was five in the EVLA group and zero in the RFA group, a statistically significant difference in favor of the latter (p=0.020). At 1 month, neither group had any patients with superficial thrombophlebitis.[163]

One poor quality observational study[195] reported intraoperative and postoperative local complications in each group. Four patients presented intraoperative complications in EVLA group and one patient in RFA group. Nineteen patients presented local postoperative complications in EVLA group and eight patients in RFA group.

Effect on Improvement in Venous Hemodynamics

One good-quality study,[149] one fair-quality study[154] and one poor-quality study[155] reported postprocedure occlusion rates for each group at intervals including 1 week,[154] 30 days,[155] and 3 months.[149] In the fair-quality study, at 1 week, 46 patients (100 percent) in the EVLA group and 48 (100 percent) in the RFA group had venous occlusion.[154] In the poor-quality study, at 30 days, 37 patients in the EVLA group had occlusion versus 38 in the RFA group (difference NS).[155] In the good-quality study, at 3 months, 65 patients in the EVLA group had occlusion versus 68 in the RFA group (p=0.67).[149] The fair-quality study also reported mean number of microphlebectomies at short-term follow-up: 6.5 in the EVLA group; 5.5 in RFA.[154] The same study[154] reported a statistically significant difference in recanalization by treatment are at 1 year, with two EVLA patients showing recanalization versus 11 RFA patients (p=0.002).

Strength of Evidence

Table 14 summarizes the strength of evidence for the findings described above.

Table 14. KQ 2: Strength of evidence for major outcomes—EVLA versus RFA
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Bleeding (Short-term) Low	2 RCTs: 249 1 Obs: 979 limbs	Medium	Direct	Consistent	Imprecise	None	According to *Shepherd et al*, the number of patients with hematoma was 2 in EVLA group and was 0 in RFA group. According to the observational study (Obi) the number of patients with hematoma was 45 in EVLA group and 5 in RFA group. There was a significant between-groups difference regarding hematoma in favor of RFA group (p=<0.001).[122,123,125,154] Gale et al. reported the number of patients with bruising at 1 week. There was a significant more bruising in the EVLA group at 1 week (p=0.01).[154]
Bleeding (Intermediate-term) Insufficient	1 RCT: 118	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT reported the number of patients with bruising at 1 month. There was not significant between-groups difference regarding bruising at 1 month[154]
Changes on standardized symptom scores (Short-term) Low	2 RCTs: 205 1 Obs: 979 limbs	High	Direct	Consistent	Imprecise	None	VCSS improved in both group. Demonstrating statistically difference in favor of EVLA group.[125,154,163]
Changes on standardized symptom scores (Intermediate-term) Low	3 RCTs: 336	Medium	Direct	Consistent	Imprecise	None	VCSS improved in both group. No statistically difference between groups[122,123,154,163]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Long-term) Low	2 RCTs: 249	Medium	Direct	Consistent	Imprecise	None	VCSS improved in both group. No statistically difference between groups[122,123,154]
Improvement in LE venous hemodynamics /reflux severity (Short-term) Insufficient	1 RCT: 118	Medium	Direct	NA	Imprecise	None	Occlusion rate: No statistically difference between groups[154]
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term) Insufficient	2 RCTs: 259	Medium	Direct	Inconsistent	Imprecise	Suspected	Occlusion rate: No statistically difference between groups.[149,155]
Improvement in LE venous hemodynamics /reflux severity (Long-term) Insufficient	1 RCT: 118	Medium	Direct	NA	Imprecise	None	Recanalization: Demonstrating a statistically significance in favor of EVLA group (p=0.002).[154]
Patient-Reported QOL (Short-term) Low	3 RCTs: 372	Low	Direct	Consistent	Imprecise	None	QOL improved in both group. No statistically difference between groups[122,123,149,163]

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-Reported QOL (Intermediate-term) Low	4 RCTs: 490	Medium	Direct	Consistent	Imprecise	None	QOL improved in both group. No statistically difference between groups SOE= high[122,123,149,154,163]
Patient-Reported QOL (Long-term) Insufficient	1 RCT: 118	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups[154]
Periprocedural Complications (Short-term) Insufficient	1 Obs: 36,096	High	Direct	NA	Imprecise	None	One poor quality observational study [195] reported intraoperative and postoperative local complications in each group. Four patients presented intraoperative complications in EVLA group and one patient in RFA group. Nineteen patients presented local postoperative complications in EVLA group and eight patients in RFA group.
Qualitative reduction in LE pain (Short-term) Low	2 RCTs 285	Low	Direct	Consistent	Imprecise	None	Demonstrating statistically significance difference between groups in favor of RFA arm (p=0.001). At 7 days the median pain was 13,5 in the EVLA group and was 0 in the RFA group. RFA showed better improvement of pain score than the EVLA group at 10 days (-12.3 versus -6.3, respectively). There was a significant between-groups difference at 10 days (p=0.01).[122,123,149]
Repeat Intervention (Short-term) Insufficient	1 RCT: 118	Medium	Direct	NA	Imprecise	None	The mean number of microphlebectomies was 6.5 in EVLA group, and was 5.5 in RFA.[154]
Thrombo-phlebitis (Short-term) Insufficient	3 RCTs: 372	Low	Direct	Inconsistent	Imprecise	None	The number of patients with superficial thrombophlebitis at 2 days was 5 in EVLA group. No one patient had superficial thrombophlebitis in RFA group. Demonstrating a significant between-groups difference regarding superficial thrombophlebitis in favor of RFA group at 2 days (p=0.020). At 1 month, no one patient had superficial thrombophlebitis in both group. At 1 week the percentage of patients with superficial thrombophlebitis was 2.6% in EVLA group and 1.3% in RFA group. There was not a significant between-groups difference. Reported the number of patients with superficial thrombophlebitis in each group: 6 in RFA group and 3 in EVLA group.[122,123,149,163]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Venous thrombo-embolic events (Short-term) Insufficient	1 RCT: 154	Low	Direct	NA	Imprecise	None	At 1 week, no patient presented pulmonary embolism in both groups.[149]
Venous thrombo-embolic events (Intermediate-term) Insufficient	2 RCTs: 218 1 Obs: 979 limbs	Medium	Direct	Inconsistent	Imprecise	None	Shepherd et al. reported that one patient presented pulmonary embolism in RFA group and no patient presented PE in EVLA group. The observational study by Obi et al. reported that one patient presented pulmonary embolism in EVLA group and no patient presented in RFA group (timing unclear). Almeida et al. reported that one patient presented deep venous thrombosis in EVLA group and no patient presented DVT in RFA group at 1 month.[122,123,125,163]
Venous thrombosis (Short-term) Insufficient	2 RCTs: 272	1 Fair, 1 Good	Direct	Consistent	Imprecise	None	Nordon et al. reported that no patient presented deep venous thrombosis in both groups at 1 week.[149] Gale et al. reported that one patient presented deep venous thrombosis in EVLA group and no patient presented DVT in RFA group at 1 week.[154]
Venous thrombosis (Intermediate-term) Insufficient	1 Obs: 979 limbs	High	Direct	NA	Imprecise	None	There were 6 cases of deep venous thrombosis in RFA group and 19 cases in EVLA group. The observational study also reported the presence of endovascular heat induced thrombosis (EHIT). In the EVLA, the number of patients with EHIT was 26 and in RFA group the number of patients with EHIT was 10. There was a non-significant between-groups difference (p=0.106). The same study presented the number of patients with superficial venous thrombosis for each group (EVLA group n=37 and RFA group n=11). There was a significant between-groups difference in favor of RFA group (p=0.01) Timing of these events are uncertain.[125]
Venous Wound Infection (Short-term) Insufficient	1 RCT: 134 1 Obs: 979 limbs	High	Direct	Consistent	Imprecise	None	The number of patients with wound infection was 2 in EVLA group and 4 in RFA group. The number of patients with infection was 6 in EVLA group and 2 in RFA group. No statistically difference between groups.[122,123,125]

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; PE=pulmonary embolism; QOL=quality of life; RCT(s)=randomized controlled trial(s); RFA = radiofrequency ablation; SD=standard deviation; SE=standard error; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

EVLA plus Phlebectomy versus RFA plus Phlebectomy

One good-quality RCT[98] (N=762) and 1 fair-quality observational study[184] (N=3,874) reported comparisons of EVLA plus phlebectomy versus endovenous RFA plus phlebectomy. The RCT included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins, while the observational study included patients with LE chronic venous insufficiency/reflux but did not report the presence of varicose veins or presence of symptoms. Study follow-up periods included 3 days to 3 years in the RCT and 1 month in the observational study. Both studies were conducted in the UK/Europe. The RCT was conducted at 2 sites and reported a government and industry funding source.[98] Participant age ranged from 18 to 75 years in the RCT; mean age in the observational study was 52.8 years. The proportion of female patients was 70-77 percent in the RCT and 70.9 percent in the observational study. Neither study reported the racial or ethnic composition of their study populations. The majority of patients in the RCT had a baseline CEAP class of C2-C3.[98]

Effect on Patient-Reported Quality of Life

The RCT presented mean AVVQ scores at 3 years for each group. At 3 years, the mean AVVQ in the EVLA plus phlebectomy group was 4.61 versus 4.43 in the RFA plus phlebectomy group.[98] The same study also reported median AVVSS at 3 days, 1 month, and 1 year. In the EVLA plus phlebectomy group, the median AVSS was 6.16 at 3 days, 13.15 at 1 month, and 19.73 at 1 year. In the RFA plus phlebectomy group, the median AVSS was 5.34 at 3 days, 12.33 at 1 month, and 20.55 at 1 year. This study also presented SF-36 data.[98]

Effect on Other Standardized Symptom Scores

The RCT also presented VCSS data at 3 years' follow-up. At 3 years, the mean VCSS in the EVLA plus phlebectomy group was 0.34 versus 0.44 in the RFA plus phlebectomy group.[98]

Effect on LE Pain

The RCT presented mean VAS pain scores at 10 days for each group, with the RFA plus phlebectomy group reporting less pain than the EVLA plus phlebectomy group (utility 1.21 versus 2.58).[98]

Effect on Perioperative/Postoperative Complications

Both studies reported the number of patients with venous thromboembolic events[98,184] for each group. In the RCT, no patients presented with DVT or PE in either group. In the observational study, ORs for thromboembolic events at 30 days were 1.14 (95% CI, 0.65 to 2.1) in adjusted analysis per age, sex, and surgery procedure in the EVLA group and 1.83 (95% CI, 0.95 to 3.52) in adjusted analysis per subgroup of patients without a concurrent phlebectomy in the EVLA group.[184] The RCT reported rates of hemorrhage and superficial thrombophlebitis at 1 month postprocedure in both groups. One patient in the EVLA plus phlebectomy group experienced hemorrhage versus none in the RFA plus phlebectomy group, while four patients in the EVLA plus phlebectomy group experienced superficial thrombophlebitis versus 12 in the RFA plus phlebectomy group.[98]

Effect on Improvement in Venous Hemodynamics

The RCT also reported recurrence of varicose veins for each group at 1 year (14 in the EVLA plus phlebectomy group versus 9 in the RFA plus phlebectomy group). At 3 years, 12.5 percent

of patients in the EVLA plus phlebectomy group repeated the intervention compared with 11.1 percent in the RFA plus phlebectomy group.[98]

Strength of Evidence

Table 15 summarizes the strength of evidence for the findings described above.

Table 15. KQ 2: Strength of evidence for major outcomes—EVLA plus phlebectomy versus RFA plus phlebectomy
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Bleeding (Intermediate-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	At 1 month, one patient presented bleeding in EVLA group and no patient presented bleeding in RFA group.[98]
Insufficient							
Changes on standardized symptom scores (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups.[98]
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	Recurrence of varicose veins: At 1 year, the number of patients with recurrence of varicose veins was 14 in EVLA +P group and was 9 in RFA+P group.[98]
Insufficient							
Patient-Reported QOL (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups.[98]
Insufficient							
Patient-Reported QOL (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups.[98]
Insufficient							

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Qualitative reduction in LE pain (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The RFA+P group reported less pain versus the EVLA +P group at 10 days (utility 1.21 versus 2.58).[98]
Insufficient							
Repeat Intervention (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The percentage of patients that repeated intervention at 3 years was 12.5% in EVLA+P group, and was 11.1% in RFA+P group.[98]
Insufficient							
Thrombo-phlebitis (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The number of patients with superficial thrombophlebitis at 1 month was 4 in EVLA+P group and was 12 in RFA+P group.[98]
Insufficient							
Venous thrombo-embolic events (Short-term)	1 Obs 3,874	Medium	Direct	NA	Imprecise	None	In the observational study, the odds ratio at 30 days was 1.14 (0.65-2.01) in adjusted analysis per age, sex and surgery procedure in EVLA group and 1.83 (0.95-3.52) in adjusted analysis per subgroup of patients without a concurrent phlebectomy in EVLA group.[184]
Insufficient							
Venous thrombo-embolic events (Intermediate-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	At 1 month, no patient presented pulmonary embolism in EVLA group and, no patient presented pulmonary embolism in RFA group.[98]
Insufficient							
Venous thrombosis (Intermediate-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The study reported the number of patients with venous thrombosis events for each group. In the RCT, no one patient presented deep venous thrombosis in EVLA+P group and in RFA+P group.[98]
Insufficient							

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; Obs=observational study; OR=odds ratio; RCT(s)=randomized controlled trial(s); RFA=radiofrequency ablation; SD=standard deviation

EVLA versus EVLA plus Phlebectomy

Two RCTS, both of fair quality, compared EVLA versus EVLA plus phlebectomy.[145,164] In all, the studies included a total of 184 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Study follow-up periods ranged from 1 week to 1 year. One study was conducted in a single-center in the UK/Europe;[164] the other was conducted in a single center in Asia.[145] Funding source was not reported for either study. The mean age of study participants ranged from 40.2 to 51.8 years, and the proportion of female patients ranged from 53.5 to 76 percent. Neither study reported the racial or ethnic composition of their study populations. In one study, the majority of patients had a baseline CEAP class of C2-C3,[145] and in the other study the baseline CEAP class was not reported.

Effect on Patient-Reported Quality of Life

One study presented median AVVQ scores at 6 weeks and 3 months for each group. At 6 weeks, the median AVVQ was 13.5 for the EVLA group and 7.9 for the EVLA plus phlebectomy group ($p<0.001$); at 3 months, median AVVQ was 9.6 (EVLA) versus 2 (EVLA plus phlebectomy) ($p=0.015$).[164]

Effect on Other Standardized Symptom Scores

One study presented VCSS data at 3 months and 1 year following EVLA. At 3 months, the median VCSS was 2 in EVLA group was 2 versus 0 in the EVLA plus phlebectomy ($p<0.001$); at 1 year, the median AVVQ was 1 in the EVLA group and 0 in the EVLA plus phlebectomy group ($p=0.433$).[164]

Effect on LE Pain

One RCT reported the number of patients with pain at 1 week and 4 weeks for each group. The EVLA group reported fewer patients with pain versus the EVLA plus phlebectomy group at 1 week (utility 11 versus 22) ($p=0.002$). There was a statistically significant between-group difference regarding number of patients with pain at 1 week. No patients in either group reported pain at 4 weeks.[145]

Effect on Perioperative/Postoperative Complications

One RCT reported the incidence of postoperative bleeding. In the EVLA group, 28 patients experienced postoperative bleeding versus 35 patients in the EVLA plus phlebectomy group ($p=0.018$).[145] The same study reported the presence of skin burn, ecchymosis, superficial thrombophlebitis, edema, paresthesia, hematoma, itchiness, and wound infection at 1 and 4 weeks for each group. Both groups had a similar numbers of patients in each category except for itchiness, where 20 patients in the EVLA group experienced itchiness at 1 week versus 29 in the EVLA plus phlebectomy group ($p=0.011$).[145] The other RCT reported the number of patients that required subsequent ambulatory phlebectomy or perforator surgery at 6 weeks. Sixteen patients in the EVLA group required subsequent intervention versus one patient in the EVLA plus phlebectomy group ($p<0.001$).[164]

Effect on Improvement in Venous Hemodynamics

One study reported postprocedural recurrence of varicose veins at 5 years. In the EVLA group, four patients experienced recurrence of varicose veins, versus 12 in the EVLA plus phlebectomy group ($p=0.022$).[145]

Strength of Evidence

Table 16 summarizes the strength of evidence for the findings described above.

Table 16. KQ 2: Strength of evidence for major outcomes—EVLA versus EVLA plus phlebectomy

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Bleeding (Short-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	Demonstrating statistically significance in less bleeding in EVLA arm (p=0.018)).[145]
Insufficient							
Changes on standardized symptom scores (Intermediate-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	VCSS improved in both groups demonstrating statistically difference in favor of EVLA+P group.[145]
Insufficient							
Changes on standardized symptom scores (Long-term)	1 RCT 48	Medium	Direct	NA	Imprecise	Suspected	VCSS improved in both groups, but no statistically significant difference between groups.[164]
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	Recurrence of varicose veins: Demonstrating a statistically significance in favor of EVLA arm (p=0.022)[145]
Insufficient							
Patient-Reported QOL (Intermediate-term)	1 RCT 48	Medium	Direct	NA	Imprecise	Suspected	QOL improved in both group. Demonstrating statistically difference in favor of EVLA+P group at 6 weeks (p<0.001) and 3 months (p=0.015).[164]
Insufficient							

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-Reported QOL (Long-term) Insufficient	1 RCT 132	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups[145]
Periprocedural complications (Short-term) Insufficient	1 RCT 48	Medium	Direct	NA	Imprecise	Suspect	The study reported the presence of skin burn, paresthesia and itchiness at 1 and 4 weeks for each group. In the most of these comparisons, both groups had a similar number of patients in each category with a non-significant between-groups difference. However, for itchiness there was a significant between-groups difference at 1 week in favor of EVLA group (p=0.011).[164]
Qualitative reduction in LE edema (Short-term) Insufficient	1 RCT 134	Medium	Direct	NA	Imprecise	None	Both groups had a similar number of patients with a non-significant between-groups difference.[145]
Qualitative reduction in LE pain (Short-term) Insufficient	1 RCT 132	Medium	Direct	NA	Imprecise	None	The EVLA group reported less patients with pain versus the EVLA+P group at 1 week (utility 11 versus 22). There was a significant between-groups difference regarding number of patients with pain at 1 week (p=0.002). No patient reported pain in both groups at 4 weeks.[145]
Venous wound infection (Short-term) Insufficient	1 RCT 132	Medium	Direct	NA	Imprecise	None	Similar number of patients with wound infection. No significant difference between groups.[145]

Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; NA=not applicable; NR=not reported; NS=not statistically significant; Obs=observational study; OR=odds ratio; QOL=quality of life; RCT(s)=randomized controlled trial(s); SD=standard deviation; VCSS=Venous Clinical Severity Score

EVLA versus EVLA plus Ligation

One fair-quality RCT randomized 449 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins to one of three treatment arms: 159 were assigned to ligation/stripping; 148 to ligation/EVLA; 142 to EVLA alone). Short-term (2-month) results were reported in one publication,[121] while longer term follow-up (mean 3.6 years [max 6 years]) was reported in a second publication.[120] This study was conducted in the UK/Europe at 3 sites and reported non-government, non-industry funding. The mean age of study participants was approximately 48 years; 73 percent of participants were female; and no data on the racial/ethnic composition of the population were reported. The majority of patients were CEAP class C2.

Effect on Perioperative/Postoperative Complications

This RCT reported rates of postprocedural DVT. In the high ligation plus stripping arm, 1/159 patients had DVT versus 0/148 in the high ligation/EVLA arm.[121]

Effect on Improvement in Venous Hemodynamics

Inguinal recurrence on ultrasound was the primary outcome of the short-term follow-up study. In the high ligation/stripping arm, 0/159 patients had inguinal recurrence, versus 10/148 (6.7 percent) in the high ligation/EVLA arm ($p<0.0009$).[121] The long-term follow-up study evaluated reflux into the great saphenous vein (GSV) as measured on ultrasound.[120] In the ligation/stripping group, reflux was present in zero patients at 2 years, five patients (6.6 percent) at 3 years, two patients (3.6 percent) at 4 years, five patients (9.5 percent) at 5 years, and five patients (11.7 percent) at 6 years. In the ligation/EVLA group, reflux was present in 12 (11.7 percent) patients at 2 years, nine patients (13.3 percent) at 3 years, 11 patients (18.4 percent) at 4 years, eight patients (12.8 percent) at 5 years, and four (7.0 percent) at 6 years. The magnitude of reflux (as measured by centimeters of reflux from the saphenous-femoral junction into the GSV) was similar between the high ligation/stripping and high ligation/EVLA arms (pairwise p-value NR).

Effect on LE Pain

This RCT also reported on LE pain at 1 day and 2 months. In the high ligation/stripping arm, 32.7 percent of patients reported pain at 1 day versus 50.0 percent in the high ligation/EVLA arm ($p=0.0069$).[121] At 2 months, 7.8 percent of patients in the high ligation/stripping arm reported persistent pain versus13.5 percent in the high ligation/EVLA arm (p=NS).[121]

Effect on Other Standardized Symptom Scores

The RCT presented Venous Disability Score (VDS) and CEAP data at baseline and at 2 months.[121] VDS scores were similar in both groups at baseline (between-group p-value NR); at 2 months, approximately 85 percent of high ligation/stripping and high ligation/EVLA patients were asymptomatic by VDS (between-group p-value NR). In both groups, >70 percent of the population was CEAP C2 at baseline; by 2 months, approximately 90 percent of high ligation/stripping and high ligation/EVLA patients were CEAP C0-1 (p=NS for between-group difference at baseline and 2 months). CEAP distributions remained similar between the ligation/stripping and ligation/EVLA arms during long-term follow-up.[120] At 12 months, approximately 85 percent of the ligation/stripping group remained at CEAP class C0-1 versus approximately 90 percent of the ligation/EVLA group (between-group p-value NR); these percentages decreased over time in each group, and at 6 years of follow-up, approximately 60

percent of the ligation/stripping group had a CEAP class of C0-1 versus approximately 75 percent of the ligation/EVLA group (between-group p-value NR).

EVLA versus EVLA plus Sclerotherapy

One fair-quality RCT reported a comparison of EVLA above the knee (EVLA AK) versus EVLA above and below the knee (EVLA ABK) versus EVLA above and below the knee plus foam sclerotherapy (EVLA ABK + foam sclerotherapy).[167] This study included 65 patients with LE chronic venous insufficiency/reflux and varicose veins; however, the study did not report the presence of symptoms. Follow-up ranged from 1 week to 12 weeks. This study was conducted in a single center in the UK/Europe; funding source was not reported. The median age of study participants was 42.5 years; 59 percent of participants were female. The study did not report the racial or ethnic composition of their study populations. The majority of patients had a baseline CEAP class of C2.

Effect on Patient-Reported Quality Of Life

The study presented median AVVQ score at baseline and at 6 and 12 weeks for each group. AVVQ scores improved within each group at 6 and 12 weeks. In the EVLA AK group, AVVQ improved from a baseline of 14.8 to 6.4 at 6 weeks; in the EVLA ABK group, AVVQ improved from a baseline of 15.8 to 2.5; and in the EVLA ABK + foam sclerotherapy group, AVVQ improved from 15.1 to 4.1 (p=0.015). At 12 weeks, AVVQ was 3.2 in the EVLA AK group, 1.9 in the EVLA ABK group, and 2.4 in the EVLA ABK + foam sclerotherapy group.

Effect on Repeat Interventions

The study reported the number of patients that required subsequent sclerotherapy at 12 weeks: 14 patients in the EVLA AK group, 4 patients in the EVLA ABK group, and 8 patients in the EVLA ABK + foam sclerotherapy group).

Effect on Improvement in Venous Hemodynamics

The study reported postprocedural occlusion rates below the knee as measured by ultrasound for each group at 1 and 12 weeks. At 1 week, the number of patients with occlusion below the knee was 0 in the EVLA AK group, 23 in the EVLA ABK group, and 19 in the EVLA ABK + foam sclerotherapy group. At 12 weeks, the number of patients with occlusion below the knee was 10 in the EVLA AK group, 23 in the EVLA ABK group, and 22 in the EVLA ABK + foam sclerotherapy group.

Strength of Evidence

Table 17 summarizes the strength of evidence for the findings described above.

Table 17. KQ 2: Strength of evidence for major outcomes—EVLA versus EVLA plus sclerotherapy

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Improvement in LE venous hemodynamics /reflux severity (Short-term)	1 RCT 65	Medium	Direct	NA	Imprecise	None	(Occlusion rate: 23 in EVLA arm and 19 in EVLA + sclerotherapy. No statistically difference between groups.[167]
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	1 RCT 65	Medium	Direct	NA	Imprecise	None	Occlusion rate: 23 in EVLA arm and 22 in EVLA + sclerotherapy. No statistically difference between groups.[167]
Insufficient							
Patient-Reported QOL (Intermediate-term)	1 RCT 65	Medium	Direct	NA	Imprecise	None	There was a significant between-groups difference at 6 weeks in favor of EVLA + foam sclerotherapy arm (p=0.015). .[167]
Insufficient							
Repeat Intervention (Intermediate-term)	1 RCT 48	Medium	Direct	NA	Imprecise	Suspect	The number of patients that required subsequent ambulatory phlebectomy or perforator surgery at 6 weeks. In the EVLA, there were 16 patients that required subsequent intervention. In the EVLA + sclerotherapy group, there was 1 patient that required subsequent intervention. There was a significant between-groups difference at 6 weeks (p<0.001) in favor of EVLA+sclerotherapy.[164]
Insufficient							

Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; SD=standard deviation

Cyanoacrylate (CA) Embolization versus RFA

One fair-quality RCT reported a comparison of CA embolization versus RFA.[129] This study included 242 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Follow-up for this study ranged from 1 day to 3 months. The trial was conducted at 10 U.S. centers and reported a government funding source. The mean age of study participants was 49.8 years; 88 percent of patients were female. The study did not report the racial or ethnic composition of their study populations. The majority of patients had a baseline CEAP class of C2.

Effect on Patient-Reported Quality of Life

The study presented mean AVVQ scores at 1 day and 1 month for each group. AVVQ scores improved from 18.9 at 1 day to 11.9 at 1 month in the CA embolization group and from 19.4 at 1 day to 12.6 at 1 month in the RFA group ($p>0.05$).

Effect on Other Standardized Symptom Scores

The study presented VCSS data at 1 day and 1 month postprocedure. In the CA embolization group, VCSS improved from 5.5 at 1 day to 4.9 at 1 month. In the RFA group, VCSS was 5.6 at 1 day and 5 at 1 month ($p=0.6$).

Effect on Postoperative Pain

The study reported information on postoperative pain using 10-point VAS to present mean pain scores at 24 hours postprocedure and found no statistically significant difference between groups ($p=0.36$).

Effect on Perioperative/Postoperative Complications

The study reported rates of absence postoperative ecchymosis at 3 days postprocedure. At 3 days, 67.6 percent of patients in the CA embolization group were without ecchymosis versus 48.2 percent in the RFA group ($p<0.01$). In addition, 22 patients in the CA embolization group had superficial thrombophlebitis at 3 months compared with 16 patients in the RFA group ($p=0.36$).

Strength of Evidence

Table 18 summarizes the strength of evidence for the findings described above.

Table 18. KQ 2: Strength of evidence for major outcomes—CA embolization versus RFA
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	The percentage of patients without ecchymosis at 3 days was 67.6% in the CA embolization group and 48.2% in RFA group. Demonstrating statistically significance in favored of CA embolization arm ($p<0.01$).[129]

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes on standardized symptom scores (Short-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups.[129]
Changes on standardized symptom scores (Intermediate-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups.[129]
Patient-Reported QOL (Short-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups.[129]
Patient-Reported QOL (Intermediate-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups.[129]
Qualitative reduction in LE pain (Short-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	No significant difference between procedures (p=0.36).[129]
Thrombo-phlebitis (Intermediate-term) Insufficient	1 RCT: 226	Medium	Direct	NA	Imprecise	None	In the CA embolization group, the number of patients was 22 and in the RFA group, the number of patients with superficial thrombophlebitis was 16. There was not a significant between-groups difference at 3 months (p=0.36).[129]

Abbreviations: CA=cyanoacrylate; CI=confidence interval; DVT=deep vein thrombosis; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; RCTs=randomized controlled trials; QOL=quality of life; RFA=radiofrequency ablation; SD=standard deviation; VCSS=Venous Clinical Severity Score

Mechanochemical Endogenous Ablation (MOCA) versus RFA

One study reported in two articles described a comparison of mechanochemical endogenous ablation (MOCA) versus radiofrequency ablation (RFA). One article is a fair-quality RCT[132] and the other is a good-quality RCT.[133] In all, this study included 170 patients with symptomatic lower extremity chronic venous insufficiency/reflux and varicose veins. The first report[132] had a follow-up period of 1 month and the subsequent report[133] had a follow-up of 6 months accounting for the change in study quality. This study was conducted in two centers in Europe/UK. There is a report of government, industry, non-government and non-industry

funding source. The median age of study participants was 50. The proportion of female patients was 30 percent. The study did not report the racial or ethnic composition of their study populations. The patients had a median baseline CEAP of 4.

Effect on Patient-Reported Quality of Life

The final report[133] presented mean AVVQ scores at 1 month and 6 months for each group following mechanochemical endogenous ablation (MOCA) and radiofrequency ablation (RFA). AVVQ scores improved within each group by 1 month and 6 months. In the MOCA group, mean AVVQ improved from baseline of 19.5 to 12.1 at 1 month; and to 11.8 at 6 months. In the RFA group, mean AVVQ improved from baseline of 18.8 to 12.9 at 1 month; and to 9.4 at 6 months. However, there was not a significant between-groups difference at one month (p=0.799) or six months (p=0.511). The study also evaluated Euro Quality of Life scores: EQ-5D QOL and EQ-5D VAS. In the MOCA group, median EQ-5D QOL was 0.761 from baseline to 6 months. In the RFA group, median EQ-5D QOL improved from baseline of 0.730 to 0.761 at 1 month; and remained 0.761 at 6 months. Therefore, there was not a significant between-groups difference at 1 month (p=0.939) and at 6 months (p=0.125). In the MOCA group, median EQ-5D VAS improved from baseline 84.5 to 85 at 1 month; and remained 85 at 6 months. In the RFA group, median EQ-5D VAS improved from baseline of 80 to 87 at 1 month; and to 89 at 6 months. However, there was not a significant between-groups difference at 1 month (p=0.227) and at 6 months (p=0.302).

Effect on Other Standardized Symptom Scores

The final report[133] presented VCSS data at baseline, 1 and 6 months after mechanochemical endogenous ablation (MOCA) and radiofrequency ablation (RFA). In the MOCA group, median VCSS improved from baseline of 6 to 2 at 1 month; and remained 2 at 6 months. In the RFA group, median VCSS was 5 at baseline and improved to 3 at 1 month; and to 2 at 6 months. The between-groups difference was not significantly at 1 month (p=0.096) and at 6 months (p=0.536). The first study[132] presented VDS data at baseline and 1 month after cyanoacrylate embolization and radiofrequency ablation. In the MOCA group, mean VDS was 1.44 at baseline and improved to 0.53 at 1 month. In the RFA group, mean VDS was 1.24 at baseline and improved to 0.69 at 1 month. The between-groups difference was not significantly at 1 month (p=0.451).

Effect on LE Pain

The final report[133] presented medium maximum pain Visual Analog Scale pain scores experienced during endovenous ablation for MOCA group and RFA group. The MOCA group reported significantly less pain versus the RFA group (utility 15 versus 34, p=0.003). As measured on a number scale of 0-10, medium maximum pain VAS was also significantly less in MOCA group than RFA group (utility 3 versus 4, p=0.002).

Effect on Perioperative/Postoperative Complications

The final report[133] described rates of thrombophlebitis during the follow-up after mechanochemical endogenous ablation (MOCA) and radiofrequency ablation (RFA). The number of patients with thrombophlebitis was 3 in the MOCA group and 2 in RFA group. The study also reported the number of patients with venous thrombosis. In the MOCA group, the number of patients was 1 and in the RFA group, the number of patients was 1. There were no significant differences in complications between groups.

Effect on Improvement in Venous Hemodynamics

The final report[133] described overall complete or proximal occlusion rates after procedures for each group at 1 and 6 months. At 1 weeks, the number of patients with occlusion was 93 percent in MOCA group and was 92 percent in RFA group. At 6 months, the number of patients with occlusion was 87 percent in MOCA group and was 93 percent in RFA group. There was no significant difference in occlusion rates at one month (p=0.403) and six months (p=0.483).

Strength of Evidence

Table 19 summarizes the strength of evidence for the findings described above.

Table 19. KQ 2: Strength of evidence for major outcomes—MOCA versus RFA
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Intermediate-term)	1 RCT: 117	Medium	Direct	NA	Imprecise	Suspected	VCSS improved in both groups. No statistically difference between groups.[133]
Insufficient							
Patient-Reported QOL (Intermediate-term)	1 RCT: 117	Medium	Direct	NA	Imprecise	Suspected	QOL improved in both groups. No statistically difference between groups.[133]
Insufficient							
Qualitative reduction in LE pain (Short-term)	1 RCT: 117	Medium	Direct	NA	Imprecise	Suspected	The MOCA group reported significantly less pain versus the RFA group at 6 months, utility 15 versus 34, p=0.003.[133]
Insufficient							
Thrombo-phlebitis (Short-term)	1 RCT: 117	Medium	Direct	NA	Imprecise	Suspected	No significant differences between groups.[133]
Insufficient							

Abbreviations: CI=confidence interval; KQ=key question; LE=lower extremity; MOCA= mechanochemical endogenous ablation; N=number; OR=odds ratio; RCTs=randomized controlled trials; RFA=radiofrequency ablation; SD=standard deviation; VAS=visual analog scale; VCSS=Venous Clinical Severity Score

EVLA versus Thermal Ablation

One fair-quality RCT reported a comparison of EVLA versus endovenous steam ablation (EVSA)[134] in 237 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Follow-up ranged from 2 weeks to 1 year. The study was conducted in three centers in the UK/Europe. The mean age of study participants was 55.5, and 61 percent of participants were female. The study did not report the racial or ethnic composition of their study populations or study funding source. The majority of patients had a baseline CEAP class of C2.

Effect on Patient-Reported Quality of Life

The study presented mean within-group change of AVVQ scores at 12 weeks postprocedure. In the EVLA group, the mean within-group change of AVVQ was -5.47 compared with -5.17 in the EVSA group (difference NS for between-group comparison).

Effect on Other Standardized Symptom Scores

The study presented VCSS data at 12 weeks for each group. In the EVLA group, the mean within-group change of VCSS was -2.51, while inn the EVSA group, the mean within-group change of AVVQ was -2.90 (p-value for between-group comparison=0.242).

Effect on Perioperative/Postoperative Complications

A total of 10 patients in both the EVLA and EVSA groups experienced superficial thrombophlebitis at 2 weeks, while zero patients in the EVLA group and three patients in the EVSA group experienced superficial thrombophlebitis at 12 weeks. The study also reported the mean surface area of occurrences of ecchymosis for each group at 2 and 12 weeks. In the EVLA group, mean surface area was 4.5 cm^2 at 2 weeks versus 1 cm^2 in the EVSA group. At 12 weeks, both groups had mean surface area of ecchymosis of 0 cm^2. One patient in the EVLA group experienced DVT at 2 weeks versus zero patients in the EVSA group.

Effect on Improvement in Venous Hemodynamics

The study also reported rates of occlusion rates on ultrasound after EVLA and EVSA procedures at 12 weeks and 1 year. At 12 weeks, the occlusion rate was 97.1 percent in the EVLA group and was 93.9 percent in EVSA group (p=0.251). At 1 year, the occlusion rate was 96 percent in the EVLA group and was 86.9 percent in EVSA group (p-value for between-group comparison=0.032).

Strength of Evidence

Table 20 summarizes the strength of evidence for the findings described above.

Table 20. KQ 2: Strength of evidence for major outcomes—EVLA versus thermal ablation

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Intermediate-term)	1 RCT: 218	Medium	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups.[134]
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	1 RCT: 218.	Medium	Direct	NA	Imprecise	None	Occlusion rate: The percentage of occlusion rate was 97.1% in EVLA group and was 93.9% in EVSA group. No difference between groups (p=0.251).[134]
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	1 RCT: 218	Medium	Direct	NA	Imprecise	None	Occlusion rate: The percentage of occlusion rate was 96% in EVLA group and was 86.9% in EVSA group. Demonstrating a statistically significance regarding occlusion rates at 1 year in favor of EVLA group (p=0.032).[134]
Insufficient							
Patient-Reported QOL (Intermediate-term)	1 RCT: 218	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically significant difference between groups.[134]
Insufficient							
Thrombo-phlebitis (Short-term)	1 RCT: 218	Medium	Direct	NA	Imprecise	None	The number of patients with superficial thrombophlebitis at 2 weeks was 10 in the EVLA group and 10 in EVSA group.[134]
Insufficient							

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Thrombo-phlebitis (Intermediate-term)	1 RCT: 218	Medium	Direct	NA	Imprecise	None	At 12 weeks, there was 0 patients with superficial thrombophlebitis in EVLA group and there were 3 patients with superficial thrombophlebitis in EVSA group.[134]
Insufficient							

Abbreviations: EVLA=endovenous laser ablation; EVSA=endovenous steam ablation; KQ=key question; LE=lower extremity; N=number; QOL=quality of life; RCTs=randomized controlled trials; VCSS=Venous Clinical Severity Score

Thermal Ablation plus Placebo Injection versus Thermal Ablation plus Sclerotherapy with Microfoam

One fair-quality RCT reported a comparison of endovenous thermal ablation (EVTA) plus placebo injection versus endovascular thermal ablation plus sclerotherapy with microfoam[194] in 117 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Follow-up ranged between 8 weeks and 6 months. The study was conducted in seven centers in USA and reported an industry funding source. The mean age of study participants was 52, and 69 percent of participants were female. The racial or ethnic composition of their study population was predominantly white (93.2 percent). The majority of patients had a baseline CEAP class of C3.

Effect on Patient-Reported Quality of Life

The study presented mean within-group change of m-VEINES-QOL scores at 8 weeks postprocedure. In the EVTA plus placebo group, the mean within-group change of m-VEINES-QOL was 29.8 compared with 31.1 in the EVTA plus sclerotherapy with microfoam. The difference for between-group comparison was not statistically significant (p=0.61).

Effect on Other Standardized Symptom Scores

The study presented VCSS data at 8 weeks for each group. In the EVTA plus placebo group, the mean within-group change of VCSS was -4, while in the EVTA plus sclerotherapy with microfoam, the mean within-group change of AVVQ was -4.2 (p-value for between-group comparison=0.16).

Effect on Perioperative/Postoperative Complications

None patients in the EVTA plus placebo group and 28 patients in the EVTA plus sclerotherapy with microfoam group experienced superficial thrombophlebitis at 8 weeks. The study also reported the deep venous thrombosis occurrence for each group at 8 weeks. One patient in the EVTA plus placebo group and 2 patients in the EVTA plus sclerotherapy with microfoam group experienced deep venous thrombosis.

Effect on Improvement in Venous Hemodynamics

The study reported rates of elimination of sapheno-femoral junction (SFJ) reflux after EVTA plus placebo injection and EVTA plus sclerotherapy with microfoam procedures at 8 weeks. The elimination of SFJ reflux rate was 78.9 percent in the EVTA plus placebo injection group and was 87.3 percent in EVTA plus sclerotherapy with microfoam group. EVTA plus sclerotherapy with microfoam significantly reduced the proportion of patients who received additional treatment for residual varicosities between 8 weeks and 6 months (13.9 percent EVTA plus sclerotherapy with microfoam vs. 23.7 percent EVTA plus placebo, p=0.037).

Comparisons Between Endovascular Interventions and Other Therapies

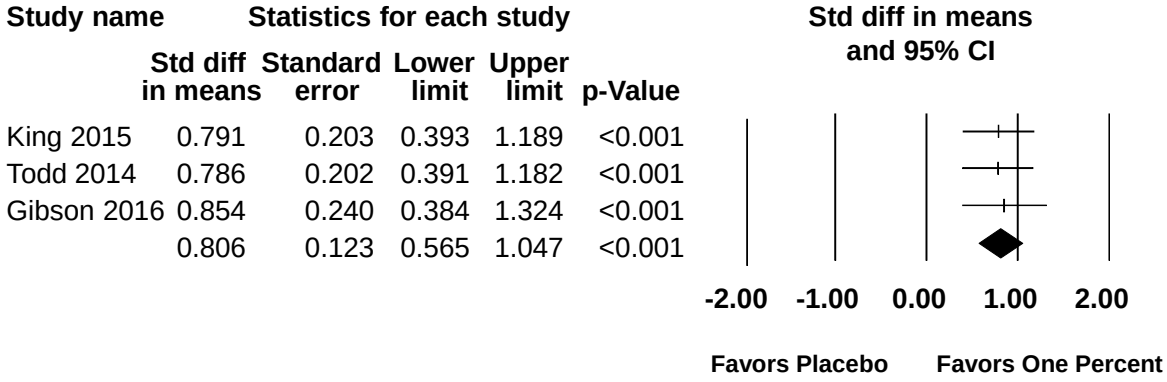
Endovascular Treatment versus Placebo

Three good-quality RCTs[124,141,193] and one fair-quality RCT[174] reported a comparison of different doses of polidocanol endovenous microfoam (PEM) versus placebo. In all, the studies included 621 patients; Three studies[124,141,193] included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins, while one study did not relate the presence of symptoms.[174] Individual study sample sizes ranged from 25 to 284. Follow-up periods ranged from 4 to 12 weeks. The three good-quality studies were conducted in the United States: one comprised 19 sites,[124] another 14 sites,[141] and the third 5 sites[193] The fair-quality study was conducted at a single center in the UK/Europe.[174] All studies reported an industry funding source.[124,141,174] The mean age of study participants ranged from 45.1 to 55.5 years, and the proportion of female patients ranged from 60 to 74.6 percent. The three U.S. studies were predominantly white with over 92 percent of study participants being white in each study.[124,141,193] In all studies, the majority of patients had a baseline CEAP class of C2-C4.

Effect on Other Standardized Symptom Scores

Two good-quality RCTs (King, 2015 #71;Todd, 2014 #1503) presented mean within-group change of VCSS at 8 weeks for each group. The study comparing doses of 0.5 percent and 1 percent PEM versus placebo reported a mean within-group change of VCSS of -5.15 in the 0.5 percent PEM group compared with -5.05 in the 1 percent PEM group and -1.52 in the placebo group.[141] There were statistically significant between-group differences in favor of the 0.5 percent PEM group ($p<0.0001$) and 1 percent PEM group ($p<0.0001$) when compared with placebo.[141] The other study compared pooled doses (0.5 percent, 1 percent and 2 percent) of PEM versus 0.125 percent PEM versus placebo. The mean within-group change of VCSS was -3.96 in the pooled PEM group, -2.97 in the 0.125 percent PEM group, and -.075 in the placebo group. There were statistically significant between-group differences in favor of the pooled PEM group ($p<0.0001$) and 0.125 percent PEM group ($p<0.0001$) compared with placebo.[124] Three good-quality studies [124,141,193] also reported Varicose Veins Symptoms Questionnaire (VVsymQ) or modified VEINES-Sym (m-VEINES-Sym) scores at 8 weeks. In the first study, the 0.5 percent PEM group had a mean VSSymQ score of 83.1 percent; the 1 percent PEM group had a mean score of 77.8 percent; and the placebo group had a mean score of 21.2 percent.[141] There were statistically significant between-group differences in favor of the 0.5 percent PEM group ($p<0.0001$) and 1 percent PEM group ($p<0.0001$) when compared with placebo group.[141] The second study reported the mean within-group change of VVSymQ at 8 weeks. In this study, the mean within-group change of VVSymQ in the 0.5 percent PEM group was -5.44 versus -4.63 in the 1 percent PEM group and in the placebo group. There were statistically significant between-group differences in favor of 0.5 percent PEM group ($p<0.0001$) and 1 percent PEM group ($p<0.0001$) when compared with placebo group.[124] In the third study, the mean within-group change of m-VEINES-Sym at 8 weeks was 14.2 in the placebo arm and 27.1 in the polidocanol arm.[193] After converting to effect sizes, the summary effect of these studies demonstrated a statistically significant standardized difference in means of 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 18).

Figure 18. Forest plot of change in standard symptom score for 1% polidocanol sclerotherapy versus placebo

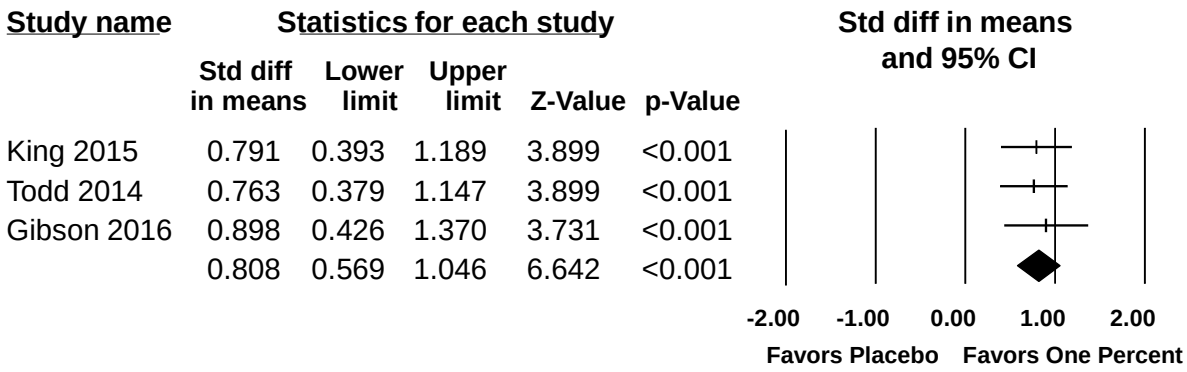


Abbreviations: CI=confidence interval; Std diff=standardized difference

Effect on Patient-Reported Quality of Life

The three good-quality RCTs presented mean within-group changes for the modified or unmodified Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire (mVEINES-QOL and VEINES-QOL) scores at 8 weeks for each group. One study compared doses of 0.5 percent PEM versus 1 percent PEM versus placebo. The mean within-group change of VEINES-QOL scores in the 0.5 percent group was 22.79 in the 0.5 percent group, 20.42 in the 1 percent group, and 7.42 in the placebo group.[141] There was a statistically significant between-group difference in favor of the 0.5 percent group ($p<0.0001$) and 1 percent group ($p<0.0001$) when compared with the placebo group.[141] Another other study compared pooled doses (0.5 percent, 1 percent and 2 percent) of PEM, 0.125 percent PEM, and placebo. The mean within-group change of VEINES-QOL score in the pooled (0.5 percent, 1 percent and 2 percent) PEM group was 21.26, versus 16.28 in the 0.125 percent PEM group, versus 7.67 in the placebo group. There were statistically significant between-group differences in favor of the pooled (0.5 percent, 1 percent and 2 percent) PEM group ($p<0.0001$) and 0.125 percent PEM group ($p=0.0001$) when compared with the placebo group.[124] The last study compared 1% polidocanol to placebo.[193] The mean within-group changes of the m-VEINES-QOL was 13.7 in the placebo group and 26.6 in the 1% polidocanol group. The summary effect of these studies was a statistically significant standardized difference in means of 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 19).

Figure 19. Forest plot of change in VEINES quality-of-life score for 1% polidocanol sclerotherapy versus placebo



Abbreviations: CI=confidence interval; Std diff=standardized difference

Effect on Improvement in Venous Hemodynamics

The two good-quality RCTs presented rates of absence of reflux at 8 weeks for each group. One study compared doses of 0.5 percent and 1 percent PEM versus placebo. In the study comparing 0.5 percent and 1 percent PEM with placebo study, the percentages of patients without reflex were 60 percent, 58 percent, and 1.8 percent, respectively.[141] There were statistically significant between-group differences in favor of the 0.5 percent PEM group (p=0.00043) and the 1 percent PEM group (p=0.0009) when compared with placebo group.[141] In the other study, 123 patient in the pooled (0.5 percent, 1 percent and 2 percent) PEM group showed absence of reflux, compared with 24 in the 0.125 percent PEM group and 3 in the placebo group: a statistically significant between-group difference in favor of the pooled PEM group (p<0.001) when compared with the 0.125 percent PEM group.[124] The fair-quality study reported 11 patients with occlusion in the PEM group at 4 and 12 weeks versus zero patients in the placebo group at 4 and 12 weeks.[174] The same study presented the venoarterial flow index by DUS at 4 and 12 weeks for each group. In the PEM group, mean venoarterial flow index was 1.12 at 4 weeks and 1.06 at 12 weeks; in the placebo group, mean venoarterial flow index was 1.23 at 4 weeks and 1.23 at 12 weeks (p for between-group comparison <0.05).[174]

Foam Sclerotherapy Versus Foam Sclerotherapy plus Mini-ligation

One poor-quality observation study[198] included 711 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins to one of four treatment arms: 158 were assigned to mini-surgery; 152 to ligation/stripping; 178 to foam sclerotherapy; 223 to foam sclerotherapy plus mini-surgery). This study was conducted in the UK/Europe. There is no report of funding source. The mean age of study participants was approximately 43.9 years; 55.69 percent of participants were female; and no data on the racial/ethnic composition of the population were reported. The majority of patients were CEAP class C1-C2.

Effect on Perioperative/Postoperative Complications

This observational study reported rates of postprocedural DVT. Both arms, the foam sclerotherapy group and foam sclerotherapy plus mini-surgery group , had 0.2 percent of patients with DVT. This study also reported rates of edema. Both arms, the foam sclerotherapy group and foam sclerotherapy plus mini-surgery group, had 2.1 percent of patients with presence of edema.

Effect on Improvement in Venous Hemodynamics

The study evaluated recurrence or development of new varicose veins in each group at 20 years. In the foam sclerotherapy arm, 43/178 (24.1 percent) patients had recurrence or developed new varicose veins, versus 35/223 (15.6 percent) in the foam sclerotherapy plus mini-surgery arm. New surgical procedures were needed in 21.9 percent of patients in the foam sclerotherapy group, and in 19.7 percent patients of foam sclerotherapy plus mini-surgery group. New sclerotherapy procedures were needed in 33.1 percent of patients in the foam sclerotherapy group, and in 22.8 percent patients of foam sclerotherapy plus mini-surgery group. The study reported presence of major reflux on ultrasound for each group at 20 years. In the foam sclerotherapy arm, 20.7 percent patients had presence of major reflux, versus 17.9 percent in the foam sclerotherapy plus mini-surgery arm.

Polidocanol Sclerotherapy versus Placebo

In addition to the three good-quality RCTs[124,141,193] and one fair-quality RCT[174] which are described above and reported a comparison of different doses of polidocanol endovenous microfoam (PEM) versus placebo, one additional good-quality RCT[197] reported a comparison of polidocanol sclerotherapy versus placebo in telanlectasias. The study was conducted in 19 centers in UK/Europe and reported an industry funding source.[197] All patients had a baseline CEAP class C1.[197]

Effect on LE Pain

One good-quality RCT[197] reported presence of pain at any time of study, analyzed at 26 weeks, in each group. The placebo group reported less pain versus the polidocanol sclerotherapy group during the study follow-up (utility 5 versus 41). Other good-quality RCT[193] also reported pain in each group at 8 weeks. Two patients experienced pain versus none patient in placebo group.

Effect on Perioperative/Postoperative Complications

One good-quality RCT[197] reported presence of innumerous adverse events in each group at any time of study, analyzed at 26 weeks. The placebo group reported less skin irritation versus the polidocanol sclerotherapy group during the study follow-up (utility 16 versus 66). The placebo group reported less skin discoloration versus the polidocanol sclerotherapy group during the study follow-up (utility 2 versus 65). The placebo group reported less local warmth versus the polidocanol sclerotherapy group during the study follow-up (utility 3 versus 25). The placebo group reported less presence of necrosis versus the polidocanol sclerotherapy group during the study follow-up (utility 0 versus 1). The placebo group reported less erythema versus the polidocanol sclerotherapy group during the study follow-up (utility 0 versus 1). The placebo group reported less presence of haematoma versus the polidocanol sclerotherapy group during the study follow-up (utility 10 versus 58). The placebo group reported less neovascularization versus the polidocanol sclerotherapy group during the study follow-up (utility 2 versus 14). The placebo group reported less skin pruritus versus the polidocanol sclerotherapy group during the study follow-up (utility 2 versus 31). The placebo group reported less skin scars versus the polidocanol sclerotherapy group during the study follow-up (utility 0 versus 1). None patients in both groups experienced presence of local inflammation or ulcers during the study follow-up. The other good-quality RCT[193] reported occurrence of deep venous thrombosis in 10 patients in polidocanol sclerotherapy group. This study also described reduction of peripheral edema in 2 patients in polidocanol sclerotherapy group and in none patients in placebo group.

Effect on Improvement in Venous Hemodynamics

One good-quality RCT presented duplex ultrasound response at 4 weeks for each group. The percentages of patients with response were 90 percent in polidocanol sclerotherapy group versus 0 percent in placebo group. There were statistically significant between-group differences in favor of the polidocanol sclerotherapy group (p=<0.0001) when compared with placebo group.

Sodium Tetradecyl Sulphate Sclerotherapy versus Placebo

One good-quality RCT[197] reported a comparison of sodium tetradecyl sulphate (STS) sclerotherapy versus placebo. The study included 316 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Follow-up period was 26 weeks. The study was conducted in 19 centers in UK/Europe, and reported an industry funding source. The mean age of study participants was 43.5 years. The proportion of female patients was 30.8 percent. All patients had a baseline CEAP class C1.

Effect on LE Pain

The study reported presence of pain at any time of study, analyzed at 26 weeks, in each group. The placebo group reported less pain versus the STS sclerotherapy group during the study follow-up (utility 5 versus 32).

Effect on Perioperative/Postoperative Complications

The study reported presence of innumerous adverse events in each group at any time of study, analyzed at 26 weeks. The placebo group reported less skin irritation versus the STS sclerotherapy group during the study follow-up (utility 16 versus 77). The placebo group reported less skin discoloration versus the STS sclerotherapy group during the study follow-up (utility 2 versus 78). The placebo group reported less local warmth versus the STS sclerotherapy group during the study follow-up (utility 3 versus 22). The placebo group reported less presence of necrosis versus the STS sclerotherapy group during the study follow-up (utility 0 versus 15). The placebo group reported less presence of ulcers versus the STS sclerotherapy group during the study follow-up (utility 0 versus 8). The placebo group reported less erythema versus the STS sclerotherapy group during the study follow-up (utility 0 versus 5). The placebo group reported less presence of local inflammation versus the STS sclerotherapy group during the study follow-up (utility 0 versus 5). The placebo group reported less presence of haematoma versus the STS sclerotherapy group during the study follow-up (utility 10 versus 68). The placebo group reported less neovascularization versus the STS sclerotherapy group during the study follow-up (utility 2 versus 21). The placebo group reported significantly less local skin pruritus versus the STS sclerotherapy group during the study follow-up (utility 2 versus 28). The placebo group reported significantly less local skin scars versus the STS sclerotherapy group during the study follow-up (utility 0 versus 13).

Strength of Evidence

Table 21 summarizes the strength of evidence for the findings described above.

Table 21. KQ 2: Strength of evidence for major outcomes—endovascular treatment versus placebo

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes on standardized symptom scores (Intermediate-term) Moderate	3 RCTs: 621	Low	Direct	Consistent	Precise	Suspected	Two good-quality RCTs[124,141] demonstrated a statistically significance difference of VCSS in favor of 0.5% polidocanol endovenous group (p<0.0001) and 1% polidocanol endovenous group (p<0.0001) when compared with placebo group. Three good-quality studies[124,141,193] also reported Varicose Veins Symptoms Questionnaire (VVsymQ) or modified VEINES-Sym (m-VEINES-Sym) scores at 8 weeks. After converting to effect sizes, the summary effect of these studies demonstrated a statistically significant standardized difference in means of 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 18).
Improvement in LE venous hemodynamics /reflux severity (Short-term) Insufficient	1 RCT: 25	High	Direct	NA	Imprecise	Suspected	Occlusion rate: In the foam sclerotherapy group the number of patients with occlusion was 11 at 4 and 12 weeks. In the placebo group the number of patients with occlusion was 0 at 4 and 12 weeks.[174] VFI: In the foam sclerotherapy group the mean of VFI was 1.12 at 4 weeks and was 1.06 at 12 weeks. The baseline mean of VFI in the foam sclerotherapy group was 1.45. In the placebo group the mean of VFI was 1.23 at 4 weeks and was 1.23 at 12 weeks. There was a significant within group difference in the foam sclerotherapy at 12 weeks (p<0.05).[174]
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term) Moderate	3 RCTs: 465	Medium	Direct	Consistent	Precise	Suspected	Absence of reflux[124,141,174]: In two RCTs, there was a significant between-groups difference in favor of 0.5% polidocanol endovenous group (p=0.00043) and 1% polidocanol endovenous group (p=0.0009) when compared with placebo group. In the second RCT, there was a significant between-groups difference in favor of pooled (0.5%, 1% and 2%) polidocanol endovenous group (p<0.001) when compared with of 0.125% polidocanol endovenous group. In a third RCT, in the foam sclerotherapy group the number of patients with occlusion was 11 at 4 weeks. In the placebo group the number of patients with occlusion was 0 at 4 weeks.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Patient-Reported QOL (Intermediate-term) Moderate	3 RCTs: 621	Low	Direct	Consistent	Precise	Suspected	The three good-quality RCTs[124,141,193] presented mean within-group changes for the modified or unmodified Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire (mVEINES-QOL and VEINES-QOL) scores at 8 weeks for each group. The summary effect of these studies was a statistically significant standardized difference in means 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 19).

Abbreviations: KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; VCSS=Venous Clinical Severity Score; VFI=venous filling index

Endovascular Treatment versus Compression

One fair-quality[160] study compared foam sclerotherapy versus mechanical compression with stockings, and one fair-quality RCT[170] compared EVLA versus mechanical compression with stockings. In total, these two studies comprised 92 patients with LE chronic venous insufficiency/reflux varicose veins and active ulcers. Individual study sample sizes ranged from 18 to 30, and study follow-up ranged from 1 day to 6 months. One study was conducted at a single center in the UK/Europe[160] and one at a single center in Latin America.[170] One study reported non-government and non-industry funding sources,[160] and the other did not report a funding source.[170] The mean/median age of study participants ranged from 57.4 to 69 years. One study reported a 75 percent proportion of female patients[170] while the other study did not report the proportion of females participants.[160] In both studies, the majority of patients had a baseline CEAP class of C6.

Effect on LE Pain

One fair-quality RCT comparing EVLA with compression reported the presence of pain in 9 patients in the compression group versus no patients in the EVLA group during the postintervention period.[170]

Effect on Perioperative/Postoperative Complications

Two studies reported the number of patients with venous thromboembolic events in the respective foam sclerotherapy group or EVLA groups versus the mechanical compression groups.[160,170] In one study[160] one patient presented with DVT in the foam sclerotherapy group at 22 weeks. In the other study,[170] neither group reported instances of venous thrombosis, superficial thrombophlebitis, or wound infection in the postintervention period.[170]

Effect on Improvement in Venous Hemodynamics

The fair-quality RCT of foam sclerotherapy versus compression reported the number of patients with venous occlusion for each group.[160] At 6 weeks, there were 8 patients with venous occlusion in the foam sclerotherapy group versus zero patients with in the mechanical compression group. At 24 weeks, there were 9 patients with venous occlusion in the foam sclerotherapy group and versus zero patients with occlusion in the mechanical compression group.[160]

Effect on Venous Ulcers

Two studies reported on venous wound healing in the foam sclerotherapy or EVLA groups versus the respective mechanical compression groups.[160,170] The study of foam sclerotherapy versus compression presented the number of patients with venous wound healing for each group at 12 and 24 weeks.[160] In the foam sclerotherapy group, there were 12 patients with venous wound healing at 12 weeks and 12 at 24 weeks, compared with 13 patients with venous wound healing at 24 weeks and 17 at 24 weeks in the compression group (p-value for between-group comparison=0.72). The other study, which examined EVLA versus compression, reported the percentage of patients with venous wound healing for each group at 3, 6, 9 and 12 months.[170] In the EVLA group, the percentage of patients with venous wound healing was 62.9 percent at 3 months, 81.5 percent at 6 months, 81.5 percent at 9 months, and 81.5 percent at 12 months. In the compression group, the percentage of patients with venous wound healing was 12 percent at 3 months, 20 percent at 6 months, 16 percent at 9 months, and 24 percent at 12 months. There

was a statistically significant between-group difference at 3 months (p=0.0002) and at 6 months (p=0.0001). The same study reported recurrence of ulceration after procedures for each group at 90 days. At 90 days, the percentage of patients with recurrence of varicose veins was 44.4 percent in the compression group and 0 percent in the EVLA group. Additionally, this study represented the mean ulcer area for each group. At 12 months' follow-up, the mean ulcer area was 2.70 cm^2 in the EVLA group and 12.76 cm^2 in the compression group (p-value for comparison=0.0037).[170]

Strength of Evidence

Table 22 summarizes the strength of evidence for the findings described above.

Table 22. KQ 2: Strength of evidence for major outcomes—endovascular treatment versus compression

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	1 RCT: 30	Medium	Direct	NA	Imprecise	Suspected	At 6 weeks in one small fair-quality RCT[160] there were 8 patients with venous occlusion in the foam sclerotherapy group vs. no patients with occlusion in the mechanical compression group.
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	1 RCT: 30	Medium	Direct	NA	Imprecise	Suspected	At 24 weeks in one small fair-quality RCT[160] there were 9 patients with venous occlusion in the foam sclerotherapy group and there was no patients with occlusion in the mechanical compression group.
Insufficient							
Periprocedural complications (Short-term)	1 RCT: 52	Medium	Direct	NA	Imprecise	Suspected	None of groups had patients with periprocedural complications.[170]
Insufficient							
Qualitative reduction in LE Pain (Short-term)	1 RCT: 52	Medium	Direct	NA	Imprecise	Suspected	In one fair-quality RCT here were 9 patients in the compression group and no patients in the endovenous ablation group.[170]
Insufficient							
Recurrent Ulceration (Intermediate-term)	1 RCT: 52	Medium	Direct	NA	Imprecise	Suspected	At 90 days, the percentage of patients with recurrence of varicose veins was 44.4% in the mechanical compression group and was 0 in the endovenous laser ablation group.[170]
Insufficient							

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Thrombo-phlebitis (Short-term) Insufficient	1 RCT: 52	Medium	Direct	NA	Precise	Suspected	None of groups had patients with superficial thrombophlebitis in either strategy of compression or EVLA.[170]
Venous thrombo-embolic events (Intermediate-term) Insufficient	2 RCTs: 86	Medium	Direct	Consistent	Imprecise	Suspected	In two RCTs, one targeting foam sclerotherapy vs. placebo[160] had one patient suffer a pulmonary embolus related to a new DVT in their untreated, non-trial leg 22 weeks after randomization. In a second RCT of EVLA vs. placebo,[170] no patients with venous thromboembolic events in either group.
Venous thrombosis (Short-term) Insufficient	1 RCT: 216	Medium	Direct	NA	Precise	Suspected	None of groups had patients with venous thrombosis the post-intervention period for each group.[170]
Venous Wound Healing (Intermediate-term) Insufficient	2 RCTs: 86	Medium	Direct	Inconsistent	Imprecise	Suspected	In one fair-quality RCT comparing foam sclerotherapy vs. placebo[160] there was no difference in venous wound healing at 12 weeks. In a second fair-quality RCT which compared EVLA vs. placebo,[170] in the endovenous laser ablation the percentage of patients with venous wound healing was 62.9% at 3 months. In the compression group the percentage of patients with venous wound healing 12% at 3 months. There was a significant between-group difference at 3 months (p=0.0002)
Venous Wound Healing (Long-term) Insufficient	2 RCTs: 86	Medium	Direct	Inconsistent	Imprecise	Suspected	In one-fair quality RCT of foam sclerotherapy vs. placebo[160] there was a nonsignificant between-group difference at 24 weeks (p=0.72). In a second fair-quality RCT of EVLA vs. placebo,[170] there was a significant between-group difference at 6 months benefiting EVLA (p=0.0001).

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials

Comparisons Between Different Invasive Surgical Approaches

High Ligation plus Stripping ± Phlebectomy versus High Ligation plus Cryostripping ± Phlebectomy

Description of Included Studies

Four RCTs, one of good quality[189] and three of fair quality,[165,169,172] reported comparisons of high ligation plus standard stripping (with or without phlebectomy) versus high ligation plus cryostripping (with or without phlebectomy). In all, these studies involved 762 patients; 3 studies exclusively included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins,[165,169,189] while 1 study included patients with LE chronic venous insufficiency/reflux but did not report the presence of varicose veins or presence of symptoms.[172] Individual study sample sizes ranged from 40 to 536. Study follow-up periods ranged from 4 weeks to 9 months. All four RCTs were conducted in the UK/Europe; one was conducted at three sites,[165] two were single-site studies,[169,172] and one did not report the number of sites.[189] Three studies did not report a funding source,[165,169,189] while one reported nongovernment/nonindustry funding.[172]

The mean/median age of study participants ranged from 43 to 55 years. The proportion of female patients ranged from 62 to 75 percent. None of the studies reported the racial or ethnic composition of their study populations. In two studies, the majority of patients had a baseline CEAP class of C2;[165,169] in two studies, baseline CEAP class was not reported.[172,189]

Effect on Perioperative/Postoperative Complications

One fair-quality RCT reported rates of procedural complications with high ligation plus conventional stripping or cryostripping;[165] stripping was described as "problematic" (most commonly GSV perforation or detachment of the GSV from the probe during stripping) in 11 percent of patients receiving conventional stripping versus 34 percent of those receiving cryostripping ($p<0.001$). Three RCTs reported rates of postoperative hematoma (one good quality,[189] and two fair quality[169,172]). Rates differed substantially between studies, suggesting heterogeneity in definitions and precluding meta-analysis. While the good-quality study reported a 90 percent hematoma rate in both groups at 1 week, 1 fair-quality study reported a 43 percent hematoma rate with conventional stripping versus a 51 percent rate with cryostripping,[172] and the other fair-quality study reported a 2.6 percent hematoma rate with conventional stripping versus a 1.5 percent rate for cryostripping.[169] None of these studies made between-group statistical comparisons. Two fair-quality RCTs reported rates of postoperative DVT; one study reported no DVT with conventional stripping versus one with cryostripping,[165] while the other reported no DVT with either procedure (no statistical comparison provided).[169] One fair-quality study reported that superficial thrombophlebitis occurred in one patient after conventional stripping and in two patients after cryostripping (p=NS).[172]

Effect on Postoperative Pain

Three RCTs reported information on postoperative pain following high ligation plus conventional stripping or cryostripping (one good quality,[189] two fair quality[169,172]). These studies used a 10-point VAS, but presented data at varying time points, precluding meta-analysis. Two studies presented mean pain scores at 24 hours postoperatively and found no statistically significant difference between procedures.[169,172] One study presented mean pain scores at 7, 14,

and 28 days postoperatively and found no statistically significant difference between procedures at any time point.[172] One study compared the median cumulative pain scores from 0 to 60 days for patients receiving high ligation and conventional stripping or cryostripping; the median cumulative 0 to 60-day pain score was 7.5 for standard stripping and 10.6 for cryostripping (no p-value provided for pairwise comparison).[189]

Effect on Patient-Reported Quality Of Life

Two fair-quality RCTs reported information on quality of life following high ligation and conventional stripping or cryostripping.[165,169] One study presented mean AVVQ scores at 6 weeks and 6 months for each group, as well as the between-group difference in AVVQ (adjusted for baseline) at 6 months;[165] AVVQ scores improved significantly within each group by 6 months ($p<0.001$), but there was also a statistically significant between-group difference at 6 months of 2.6 favoring conventional stripping ($p=0.001$). Two studies presented SF-36 data at 6 months for each group, as well as between-group difference in SF-36.[165,169] In one study,[165] two SF-36 domains (physical functioning, bodily pain) improved significantly by 6 months in the conventional stripping group, versus 4 domains (physical functioning, role physical, bodily pain, vitality) in the cryostripping group. In the other study,[169] six SF-36 domains (physical functioning, role physical, bodily pain, general health, role emotional, mental health) improved significantly by 6 months in the conventional stripping group, versus 6 domains (physical functioning, bodily pain, general health, vitality, social function, role emotional) in the cryostripping group. However, there was no statistically significant between-group difference in improvement in SF-36 domains in either of these studies.

Effect on Improvement in Venous Hemodynamics

Two RCTs reported on ultrasonographic procedural outcomes (one good quality,[189] one fair quality[165]). The good-quality study reported a 100 percent GSV occlusion rate (20/20) on ultrasound at 24 hours with conventional stripping versus a 90 percent occlusion rate with cryostripping (18/20, p=NS). At 1 year, 0/19 conventional stripping patients had evidence for groin neovascularization with versus 1/19 cryostripping patients. The fair-quality study examined residual GSV on ultrasound at 6 months, and reported 15 percent (33/215) with conventional stripping versus 44 percent (102/230) with cryostripping ($p<0.001$).

High Ligation plus Stripping ± Phlebectomy versus CHIVA

Description of Included Studies

Three studies, one good-quality RCT,[156] one fair-quality RCT,[196] and one poor-quality retrospective cohort study,[183] reported comparisons of high ligation plus stripping (with or without phlebectomy) to a hemodynamic surgery (Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire [CHIVA] method). The good-quality RCT followed 501 patients (3 arms – stripping with clinical marking, stripping with duplex marking, and CHIVA) with symptomatic varicose veins during a 5-year study period. The fair-quality RCT followed 150 patients (3 arms – high ligation and stripping, EVLA, and CHIVA) with symptomatic varicose veins for up to 18 months. The cohort study included 11,026 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins, and followed them for a median of 9 years. Two studies were conducted in the UK/Europe,[156,183] and one in Asia.[196] Both RCTs were conducted at a single site and the cohort study at three sites. The good-quality RCT was government-funded,[156] and funding was not reported for the other studies.

For the RCTs, the mean age of study participants was 46-50 years; females comprised 71 percent of the population in the good-quality RCT,[156] and 36 percent in the fair-quality study.[196] The racial/ethnic compositions of the RCTs' study populations were not reported. For the cohort study, the median age was 46 years; 63.5 percent of the population was female, and the study population's racial/ethnic composition was not reported. The fair-quality RCT included patients with CEAP C2-6;[196] neither of the other studies reported CEAP class at baseline.

Effect on Perioperative/Postoperative Complications

Both RCTs reported rates of procedural complications with high ligation and stripping versus CHIVA.[156,196] In the good-quality study, 6 patients (3.8 percent) in the stripping with clinical marking arm had subcutaneous hemorrhage, versus 7 (4.4 percent) in the stripping with duplex marking arm and 6 (3.8 percent) in the CHIVA arm (p=0.950).[156] In the stripping with clinical marking arm, 1 patient (0.6 percent) had superficial thrombophlebitis, versus 3 (1.9 percent) in the stripping with duplex marking arm and 2 (1.3 percent) in the CHIVA arm (p=0.616); No patients experienced DVT or PE in any arm.[156] In the fair-quality study, 4 patients (8 percent) in the ligation/stripping arm had (ecchymoma), versus 1 (2 percent) in the CHIVA arm (p=NR); 4 patients (8 percent) in the ligation/stripping arm had thrombophlebitis, versus 1 (2 percent) in the CHIVA arm (p=NR).[196]

Effect on Mortality

The good-quality RCT[156] reported that no deaths occurred with high ligation and stripping or CHIVA.

Effect on Improvement in Venous Hemodynamics

The good-quality RCT[156] reported varicose vein recurrence based on DUS assessment. In the stripping with clinical marking arm, 114 patients (68.3 percent) had visible recurrence during the 5-year follow-up, versus 102 (61.1 percent) in the stripping with duplex marking arm and 67 (40.1 percent) in the CHIVA arm. The OR for recurrence for stripping with clinical marking versus CHIVA was 3.21 (95% CI, 2.04 to 5.03, p<0.001) and for stripping with duplex marking versus CHIVA was 2.34 (95% CI, 1.51 to 3.63, p<0.001).

The fair-quality study,[196] reported the "general curative effect" of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the ligation/stripping arm, 25 patients (50 percent) experienced "cure" (not clearly defined), versus 41 (82 percent) in the CHIVA arm (p<0.05); 5 patients in the ligation/stripping arm had "recurrence" (not clearly defined), versus 0 in the CHIVA arm (p<0.01).

The poor-quality cohort study[183] also reported ultrasonographic outcomes, referred to as "duplex abnormalities," or "regions of normal and abnormal venous pressure and irregular disposition in tributary veins." In the stripping arm, 1696 patients (34.0 percent) had duplex abnormalities at the end of the median-9-year follow-up versus 221 (3.7 percent) in the CHIVA arm. The OR for duplex abnormalities at this time point for stripping versus CHIVA was 13.6 (95 percent CI 11.8 to 15.8, p=0.00001); this OR was not adjusted for differences in demographic or clinical factors and minimal information on attrition was reported.

Effect on LE Pain and Edema

The poor-quality cohort study[183] reported the number and percentage of patients reporting LE pain during the 9-year follow-up, though minimal information was provided regarding the means of pain assessment. In the stripping arm, 1121 patients (22.5 percent) were reported to have pain

at the end of the median-9-year follow-up, versus 104 (17.2 percent) in the CHIVA arm. The OR for pain at this time point for stripping versus CHIVA was 16.5 (95% CI, 13.5 to 20.4, p=0.00001); this OR was not adjusted for population differences in demographic or clinical factors. Information on LE edema was likewise reported. In the stripping arm, 1377 patients (27.6 percent) were reported to have edema at the end of the median-9-year follow-up, versus 157 (2.6 percent) in the CHIVA arm. The OR for edema at this time point for stripping versus CHIVA was 14.3 (95% CI, 12.1 to 17.0, p=0.00001); this OR was not adjusted for differences in demographic or clinical factors and minimal information on attrition was reported.

Standard Ligation plus Stripping versus Selective Ligation

Description of Included Studies

One poor-quality observational study compared four arms: selective venous ligation ("minisurgery") versus standard venous ligation plus stripping versus sclerotherapy versus selective venous ligation plus sclerotherapy.[198] A total of 310 patients were included in the standard ligation plus stripping and selective ligation arms.[196] The study was performed in the UK/Europe; number of sites and funding were not reported. The mean age of the population was 43-44 years in the different arms, and females comprised 53 percent to 55 percent of each arm.

Effect on Recurrence

At 20 year follow-up, this study found that major reflux was present on ultrasound in 38.8 percent of standard ligation/stripping patients versus 21.0 percent of selective ligation patients ($p<0.05$).[198] The study also reported reflux at ≥3 major sites in 44.5 percent of standard ligation/stripping patients versus 10.7 percent of selective ligation patients ($p<0.05$), as well as recurrence of varicose veins in 47.3 percent of standard ligation/stripping patients versus 15 percent of selective ligation patients ($p<0.05$).[198]

Effect on Repeat Intervention

At 20 year follow-up, this study found that the rate of repeat intervention was 58.6 percent among standard ligation/stripping patients versus 18.9 percent among selective ligation patients ($p<0.05$).[198]

Adverse Events

There was no significant difference in rates of DVT between groups at 20 years follow-up (1.6 percent with standard ligation/stripping vs. 0.2 percent with selective ligation, p=NR).[198]

Ligation of Incompetent Veins (Without Stripping) versus Stab Avulsion

Description of Included Studies

One fair-quality RCT reported comparisons of six varicose vein treatments, including surgical ligation versus stab avulsion.[107] The RCT recruited 887 patients with symptomatic LE varicose veins (numbers for ligation/stab avulsion arms NR). Patients were followed for 10 years. This study was conducted in the UK/Europe at multiple sites (number NR), and reported nongovernment, nonindustry funding. The mean age of study participants in the ligation and stab avulsion arms was approximately 45, and 69 percent were female. No race or CEAP class data were provided.

Effect on Improvement in Venous Hemodynamics

This RCT reported data on treatment failures (i.e., patients requiring repeat procedure) for ligation versus stab avulsion during the 10-year study period. In the ligation group, 14 percent of patients experienced treatment failure, versus 37 percent in the stab avulsion group. No pairwise statistical comparison was reported. The study also reported data on mean AVP and the mean number of sites of venous incompetence on duplex assessment at baseline and 10 years for ligation and stab avulsion. In the ligation group, mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years, and duplex assessment showed an average of 1 site of incompetence at 10 years, down from 5 at baseline ($p<0.05$ for both within-group comparisons). In the stab avulsion group, mean AVP improved from 54 mmHg at baseline to 43 mmHg at 10 years, and duplex assessment showed 1 site of incompetence at 10 years, down from 6 at baseline ($p<0.05$ for both within-group comparisons). No between-group statistical comparison was reported for AVP or duplex assessment.

Strength of Evidence

Table 23 summarizes the strength of evidence for the findings described above.

Table 23. KQ 2: Strength of evidence for major outcomes—invasive surgery versus invasive surgery
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short-term)	4 RCTs: 751	Medium	Direct	Inconsistent	Imprecise	Suspected	**High ligation/stripping vs. High ligation/cryostripping**[169,172,189]: Hematoma rates differed substantially between studies, suggesting heterogeneity in definitions, no between-group statistical comparisons.
Insufficient	1 RCT: NR						**High ligation/stripping vs. CHIVA**[156,196]: 6 patients (3.8 percent) in the stripping with clinical marking arm had subcutaneous hemorrhage, versus 7 (4.4 percent) in the stripping with duplex marking arm and 6 (3.8 percent) in the CHIVA arm (p=0.950).[156] In the fair-quality study, 4 patients (8 percent) in the ligation/stripping arm had (ecchymoma), versus 1 (2 percent) in the CHIVA arm (p=NR).
Death	1 RCT: 501	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. CHIVA**[156]: No death in any arm.
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Short-term)	1 RCT: 60	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/cryostripping**[189]: 100 percent GSV occlusion rate (20/20) on ultrasound at 24 hours with conventional stripping versus a 90 percent occlusion rate with cryostripping (18/20, p=NS).
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	3 RCTs, 2 Obs: 12,338	Medium	Direct	Inconsistent	Imprecise	None	**High ligation/stripping vs. High ligation/cryostripping**[189]: At 1 year, 0/19 conventional stripping patients had evidence for groin neovascularization with versus 1/19 cryostripping patients.
	1 RCT: NR						**High ligation/stripping vs. High ligation/cryostripping**[165]: 15 percent (33/215) with conventional stripping versus 44 percent (102/230) with cryostripping (p<0.001) had residual GSV on ultrasound at 6 months
Insufficient							**High ligation/stripping vs. CHIVA**[156]: OR for recurrent varicose veins on u/s for stripping with clinical marking versus CHIVA was 3.21 (95% CI, 2.04 to 5.03, p<0.001) and for stripping with duplex marking versus CHIVA was 2.34 (95% CI, 1.51 to 3.63, p<0.001).
							High ligation/stripping vs. CHIVA[183]: OR for duplex abnormalities at 9 years for stripping versus CHIVA was 13.6 (95 percent CI 11.8 to 15.8, p=0.00001); OR was not adjusted

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
							Ligation vs. stab avulsion[107]: In the ligation group, mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years, and duplex assessment showed an average of 1 site of incompetence at 10 years, down from 5 at baseline ($p<0.05$ for both within-group comparisons). In the stab avulsion group, mean AVP improved from 54 mmHg at baseline to 43 mmHg at 10 years, and duplex assessment showed 1 site of incompetence at 10 years, down from 6 at baseline ($p<0.05$ for both within-group comparisons). No between-group statistical comparison was reported for AVP or duplex assessment. **Standard Ligation plus Stripping vs. Selective Ligation**[198]**:** At 20 year follow-up, this study found that major reflux was present on ultrasound in 38.8% of standard ligation/stripping patients vs. 21.0% of selective ligation patients ($p<0.05$).[198] The study also reported reflux at ≥3 major sites in 44.5% of standard ligation/stripping patients vs. 10.7% of selective ligation patients ($p<0.05$).
Improvement in LE venous hemodynamics /reflux severity (Undetermined Timeframe) Insufficient	1 RCT: 150	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. CHIVA**[196]**:** This study, reported the "general curative effect" of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the ligation/stripping arm, 25 patients (50 percent) experienced "cure" (not clearly defined), versus 41 (82 percent) in the CHIVA arm ($p<0.05$); 5 patients in the ligation/stripping arm had "recurrence" (not clearly defined), versus 0 in the CHIVA arm ($p<0.01$).
Patient-Reported QOL (Short-term) Insufficient	1 RCT: 494	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/cryostripping**[165]: No significant between-group difference in improvement in AVVQ or SF-36 domains at 6 weeks.
Patient-Reported QOL (Intermediate-term) Insufficient	2 RCTs: 640	Medium	Direct	Inconsistent	Imprecise	Suspected	**High ligation/stripping vs. High ligation/cryostripping**[165]: AVVQ scores improved significantly within each group by 6 months ($p<0.001$), but there was also a significant between-group difference at 6 months of 2.6 favoring conventional stripping ($p=0.001$); two SF-36 domains improved significantly by 6 months in the conventional stripping group, versus 4 domains in the cryostripping group; no significant between-group difference in improvement in SF-36 domains in either of these studies. **High ligation/stripping vs. High ligation/cryostripping**[169]: 6 SF-36

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
							domains improved significantly by 6 months in the conventional stripping group, versus 6 domains in the cryostripping group; no significant between-group difference in improvement in SF-36 domains in either of these studies
Periprocedural complications (Short-term) Insufficient	1 RCT: 494	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/cryostripping[165]**: Stripping was described as "problematic" (most commonly GSV perforation or detachment of the GSV from the probe during stripping) in 11 percent of patients receiving conventional stripping versus 34 percent of those receiving cryostripping (p<0.001)
Qualitative reduction in LE edema (Long-term) Insufficient	1 Obs: 11,206	High	Direct	NA	Precise	None	**High ligation/stripping vs. CHIVA[183]**: OR for edema at this time point for stripping versus CHIVA was 14.3 (95% CI, 12.1 to 17.0, p=0.00001); OR unadjusted.
Qualitative reduction in LE pain (Short-term) Low	1 RCT: 40 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	**High ligation/stripping vs. High ligation/cryostripping[169]**: No significant difference between procedures at 24 hours. **High ligation/stripping vs. High ligation/cryostripping[172]:** No significant difference between procedures at 7, 14, and 28 days.
Qualitative reduction in LE pain (Intermediate-term) Insufficient	1 RCT: 60	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/cryostripping[189]:** Median cumulative pain scores from 0 to 60 days 7.5 for standard stripping and 10.6 for cryostripping (p=NR for pairwise comparison).
Qualitative reduction in LE pain (Long-term) Insufficient	1 Obs: 11,206	High	Direct	NA	Precise	None	**High ligation/stripping vs. CHIVA[183]**: OR for pain at 9 years for stripping versus CHIVA was 16.5 (95% CI, 13.5 to 20.4, p=0.00001); OR unadjusted.
Repeat intervention (Long-term) Insufficient	1 Obs: 711	High	Direct	NA	Imprecise	None	**Standard Ligation plus Stripping vs. Selective Ligation[198]:** At 20 year follow-up, this study found that the rate of repeat intervention was 58.6% among standard ligation/stripping patients vs. 18.9% among selective ligation patients (p<0.05).

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Thrombo-phlebitis (Short-term)	2 RCTs: 691 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	**High ligation/stripping vs. High ligation/cryostripping[169]**: Superficial thrombophlebitis in one patient after conventional stripping and in two patients after cryostripping. **High ligation/stripping vs. CHIVA[156,196]**: 1 patient (0.6 percent) in the stripping with clinical marking arm had superficial thrombophlebitis, versus 3 (1.9 percent) in the stripping with duplex marking arm and 2 (1.3 percent) in the CHIVA arm (p=0.616).[156] 4 patients (8 percent) in the ligation/stripping arm had thrombophlebitis, versus 1 (2 percent) in the CHIVA arm (p=NR).[196]
Insufficient							
Venous thrombo-embolic events (Short-term)	2 RCTs: 501 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	**High ligation/stripping vs. High ligation/cryostripping[165]**: No DVT with conventional stripping versus one with cryostripping. **High ligation/stripping vs. High ligation/cryostripping[169]**: No DVT with conventional stripping or with cryostripping. **High ligation/stripping vs. CHIVA[156]**: No DVT/PE in any arm.
Insufficient							
Venous thrombo-embolic events (Long-term)	1 Obs: 711	High	Direct	NA	Imprecise	None	**Standard Ligation plus Stripping vs. Selective Ligation[198]:** There was no significant difference in rates of DVT between groups at 20 years follow-up (1.6% with standard ligation/stripping vs. 0.2% with selective ligation, p=NR).[198]
Insufficient							

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; CHIVA= Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; CI=confidence interval; DVT=deep vein thrombosis; GSV=great saphenous vein; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; SD=standard deviation; VCSS=Venous Clinical Severity Score

Comparisons Between Invasive Surgical Approaches and Hybrid Surgical/Endovenous Approaches

High Ligation plus Stripping ± Phlebectomy versus High Ligation plus EVLA

Description of Included Studies

Two fair-quality RCT compared high ligation plus stripping (with or without phlebectomy) to a hybrid procedure, high ligation plus EVLA.[121,196] For one study, one publication reported short-term (2-month) results,[121] while a second publication presented longer-term follow-up (up to 6 years, mean 3.6 years).[120] This RCT randomized 449 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins to 3 treatment arms (n=159 received ligation/stripping, n=148 received ligation/EVLA; the third arm was EVLA alone). The second RCT followed 150 patients (3 arms – high ligation/stripping, ligation/EVLA, and CHIVA) with symptomatic varicose veins for up to 18 months. One study was conducted in the UK/Europe at three sites, and reported nongovernment, nonindustry funding;[121] the other was conducted in Asia.[196] and funding was not reported. The mean age of study participants in the arms of interest was approximately 48 (73 percent female) in one study; [121] no data on the racial/ethnic composition of the population were reported, and the majority of patients were CEAP C2. In the other study,[196] the mean age of study participants was approximately 46 (36 percent female); no racial/ethnic data were reported, and all patients were CEAP C2-6..

Effect on Perioperative/Postoperative Complications

In one RCT,[196] 4 patients (8 percent) in the ligation/stripping arm had bleeding (ecchymoma), versus 3 (6 percent) in the ligation/EVLA arm (p=NR); 4 patients (8 percent) in the ligation/stripping arm had thrombophlebitis, versus 3 (6 percent) in the high ligation/EVLA arm (p=NR). The other RCT reported rates of postprocedural DVT;[121] in the high ligation/stripping arm, 1/159 patients had DVT versus 0/148 in the high ligation/EVLA arm.

Effect on Improvement in Venous Hemodynamics

In one RCT, inguinal recurrence on ultrasound was the primary outcome of the short-term follow-up report;[121] in the high ligation/stripping arm, 0/159 patients had inguinal recurrence, versus 10/148 (6.7 percent) in the high ligation/EVLA arm (p<0.0009). The long-term follow-up report evaluated reflux into the GSV on ultrasound.[120] In the ligation/stripping group, reflux was present in 0 patients at 2 years, 5 (6.6 percent) at 3 years, 2 (3.6 percent) at 4 years, 5 (9.5 percent) at 5 years, and 5 (11.7 percent) at 6 years; in the ligation/EVLA group, reflux was present in 12 (11.7 percent) patients at 2 years, 9 (13.3 percent) at 3 years, 11 (18.4 percent) at 4 years, 8 (12.8 percent) at 5 years, and 4 (7.0 percent) at 6 years. The magnitude of reflux (as measured by centimeters of reflux from the saphenous-femoral junction into the GSV), was similar between the high ligation/stripping and high ligation/EVLA arms (pairwise between-group p-value NR).

The other RCT,[196] reported the “general curative effect” of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the ligation/stripping arm, 25 patients (50 percent) experienced “cure” (not clearly defined), versus 32 (64 percent) in the ligation/EVLA arm (p=NR); 5 patients in the ligation/stripping arm had “recurrence” (not clearly defined), versus 2 in the ligation/EVLA arm (p<0.05).

Effect on LE Pain

This RCT reported on LE pain at 1 day and 2 months. In the high ligation/stripping arm, 32.7 percent of patients endorsed pain, versus 50.0 percent in the high ligation/EVLA arm (p=0.0069).[121] In the high ligation/stripping arm, 11/141 patients (7.8 percent) had persistent pain, versus 19/141 (13.5 percent) in the high ligation/EVLA arm (p=NS).[121]

Effect on Other Standardized Symptom Scores

This study presented VDS and CEAP data at baseline and 2 months.[121] VDS scores were similar in both groups at baseline (between-group p-value NR); by 2 months, approximately 85 percent of high ligation/stripping and high ligation/EVLA patients were asymptomatic by VDS (between-group p-value NR). In both groups >70 percent of the population was CEAP C2 at baseline; by 2 months, approximately 90 percent of high ligation/stripping and high ligation/EVLA patients were CEAP C0-1 (p=NS between-group difference at baseline and 2 months). CEAP distributions remained similar between the ligation/stripping and ligation/EVLA arms during long-term follow-up.[120] By 12 months, approximately 85 percent of the ligation/stripping group remained at C0-1, versus approximately 90 percent of the ligation/EVLA group (between-group p-value NR); these percentages decreased over time in each group, and by 6 years of follow-up, approximately 60 percent of the ligation/stripping group had a CEAP class of C0-1, versus approximately 75 percent of the ligation/EVLA group (between-group p-value NR).

CHIVA versus High Ligation plus EVLA

Description of Included Studies

One fair-quality RCT compared CHIVA to a hybrid procedure, high ligation plus EVLA.[196] This RCT followed 150 patients (3 arms – high ligation/stripping, ligation/EVLA, and CHIVA) with symptomatic varicose veins for up to 18 months; it was conducted in Asia, and funding was not reported. The mean age of study participants was approximately 46 (36 percent female); no racial/ethnic data were reported, and all patients were CEAP C2-6.

Effect on Perioperative/Postoperative Complications

One patient (2 percent) in the CHIVA arm had bleeding (ecchymoma), versus 3 (6 percent) in the ligation/EVLA arm (p=NR); one patient (2 percent) in the CHIVA arm had thrombophlebitis, versus 3 (6 percent) in the ligation/EVLA arm (p=NR).

Effect on Improvement in Venous Hemodynamics

This RCT reported the "general curative effect" of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the CHIVA arm, 41 patients (82 percent) experienced "cure" (not clearly defined), versus 32 (64 percent) in the ligation/EVLA arm (p=NR); no patients in the CHIVA arm had "recurrence" (not clearly defined), versus 2 in the ligation/EVLA arm (p=NR).

High Ligation/Stripping ± Phlebectomy versus High Ligation/Foam Sclerotherapy

Description of Included Studies

One fair-quality RCT compared high ligation and stripping to a hybrid procedure, high ligation plus reverse foam sclerotherapy,[166] with the goal of describing perioperative/postoperative complications. The RCT randomized 82 patients (90 limbs) with symptomatic chronic venous insufficiency/reflux and varicose veins to 3 treatment arms, with n=60 receiving ligation/stripping (n=30 standard stripping and n=30 invagination stripping) and n=30 receiving ligation/foam sclerotherapy. This single-center RCT was conducted in the UK/Europe, and did not report a funding source. The median age of study participants was 44 (73 percent female); no data on the racial/ethnic composition of the population were reported. All patients were reported to be CEAP C2-3.

Effect on Perioperative/Postoperative Complications

The only outcome of interest reported by this RCT[166] was bleeding (postoperative blood loss). Each of the ligation/stripping arms reported a median of 25 mL of blood loss (IQR 25-35 mL for standard stripping, 20-35 mL for invagination stripping) versus 15 mL (IQR 10-20 mL) in the ligation/foam sclerotherapy arm ($p< 0.001$ for difference between ligation/foam sclerotherapy and ligation/stripping).

Standard Ligation plus Stripping ± Phlebectomy versus Selective Ligation plus Sclerotherapy

Description of Included Studies

One poor-quality observational study compared four arms: selective venous ligation ("minisurgery") versus standard venous ligation plus stripping versus sclerotherapy versus selective venous ligation plus sclerotherapy.[198] A total of 375 patients were included in the standard ligation plus stripping and selective ligation plus sclerotherapy arms.[196] The study was performed in the UK/Europe; number of sites and funding were not reported. The mean age of the population was 43-44 years in the different arms, and females comprised 53percent to 55 percent of each arm.

Effect on Recurrence

At 20 year follow-up, this study found that major reflux was present on ultrasound in 38.8 percent of standard ligation/stripping patients vs. 17.9 percent of selective ligation/sclerotherapy patients ($p<0.05$).[198] The study also reported reflux at ≥3 major sites in 44.5 percent of standard ligation/stripping patients versus 10.3 percent of selective ligation/sclerotherapy patients ($p<0.05$), as well as recurrence of varicose veins in 47.3 percent of standard ligation/stripping patients versus 9.8 percent of selective ligation/sclerotherapy patients ($p<0.05$).[198]

Effect on Repeat Intervention

At 20 year follow-up, this study found that the rate of repeat intervention was 58.6 percent among standard ligation/stripping patients versus 19.7 percent among selective ligation/sclerotherapy patients ($p<0.05$).[198]

Adverse Events

There was no significant difference in rates of DVT between groups at 20 years follow-up (1.6 percent with standard ligation/stripping vs. 0.2 percent with selective ligation/sclerotherapy, p=NR).[198]

Selective Ligation versus Selective Ligation plus Sclerotherapy

Description of Included Studies

One poor-quality observational study compared four arms: selective venous ligation ("minisurgery") versus standard venous ligation plus stripping versus sclerotherapy versus selective venous ligation plus sclerotherapy.[198] A total of 381 patients were included in the selective ligation and selective ligation plus sclerotherapy arms.[196] The study was performed in the UK/Europe; number of sites and funding were not reported. The mean age of the population was 43-44 years in the different arms, and females comprised 53 percent to 55 percent of each arm.

Effect on Recurrence

At 20 year follow-up, this study found that major reflux was present on ultrasound in 21 percent of selective ligation patients versus 17.9 percent of selective ligation/sclerotherapy patients (p=NR).[198] The study also reported reflux at ≥3 major sites in 10.7 percent of selective ligation patients versus 10.3 percent of selective ligation/sclerotherapy patients (p=NR), as well as recurrence of varicose veins in 15 percent of selective ligation patients versus 9.8 percent of selective ligation/sclerotherapy patients (p=NR).[198]

Effect on Repeat Intervention

At 20 year follow-up, this study found that the rate of repeat intervention was 18.9 percent among selective ligation patients versus 19.7 percent among selective ligation/sclerotherapy patients (p=NR).[198]

Adverse Events

There was no significant difference in rates of DVT between groups at 20 years follow-up (0.2 percent with selective ligation vs. 0.2 percent with selective ligation/sclerotherapy, p=NR).[198]

Ligation of Incompetent Veins (without Stripping) versus Ligation/Sclerotherapy

Description of Included Studies

Two fair-quality RCTs compared surgical ligation of incompetent veins without stripping versus a hybrid procedure, surgical ligation plus sclerotherapy.[107,181] One study randomized 887 patients with symptomatic LE varicose veins to 6 treatment arms (numbers for the ligation and ligation/sclerotherapy arms NR),[107] and the other study randomized 150 patients across 3 arms (n=42 received ligation, n=40 received ligation plus sclerotherapy; the third arm was sclerotherapy alone).[181] Patients were followed for 10 years in both RCTs. Both were conducted in the UK/Europe at multiple sites (number NR); one RCT reported nongovernment, nonindustry funding,[107] while the other did not report funding.[181]

In one RCT,[107] mean age of study participants in the ligation and ligation/sclerotherapy arms was approximately 43 (68 percent female); in the other,[181] mean age in both arms was 53 (48 percent female). Neither study reported race or CEAP class data.

Effect on Improvement in Venous Hemodynamics

Both fair-quality RCTs reported data on treatment failures. One RCT defined treatment failure as requiring a repeat procedure by the end of the 10-year study period;[107] 14 percent of patients experienced treatment failure with ligation, versus 8 percent with ligation/sclerotherapy. No pairwise between-group statistical comparison was reported. The other RCT defined treatment failure as saphenous-femoral junction incompetence at 10 years.[181] Of the patients with available data at 10 years, 0/33 receiving ligation and 0/31 receiving ligation/sclerotherapy experienced treatment failure. Both RCTs also reported data on AVP. In one study, mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years in both the ligation and ligation/sclerotherapy groups ($p<0.05$ for within-group differences, no between-group comparison reported).[107] In the other, the ligation group's mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years versus 54 to 35 mmHg in the ligation/sclerotherapy group ($p<0.05$ for within-group differences, no between-group comparison reported).[181] Finally, one RCT reported the mean number of sites of venous incompetence on duplex assessment at baseline and 10 years;[107] in both groups, duplex assessment showed an average of 1 site of incompetence at 10 years, down from 5 at baseline ($p<0.05$ for both within-group comparisons, no between-group comparison reported).

High Ligation/Stripping ± Phlebectomy versus High Ligation/Endovenous Microwave Therapy

Description of Included Studies

One fair-quality RCT compared high ligation and stripping to a hybrid procedure, high ligation plus endovenous microwave ablation (EMA).[140] The RCT randomized 200 patients with symptomatic chronic venous insufficiency/reflux and varicose veins to 2 treatment arms, ultimately analyzing 188 (206 limbs). Patients were followed for 2 years. This single-center RCT was conducted in Asia, and reported government funding. The median age for participants was approximately 59 (53 percent female); no data on the racial/ethnic composition of the population were reported. All patients were reported as CEAP C3-6.

Effect on Improvement in Venous Hemodynamics

This RCT[140] assessed recurrence on ultrasound. In the ligation/stripping arm, 10/98 limbs (10.2 percent) had evidence for recurrence at 6 months versus 3/108 (2.8 percent) in the ligation/EMA arm ($p<0.03$). At 2 years, 24 limbs (28.2 percent) In the ligation/stripping arm had evidence for recurrence versus 14 (14.3 percent) in the ligation/EMA arm ($p<0.02$).

Effect on Patient-Reported Quality Of Life

AVVQ scores during 2-year follow-up were reported.[140] In the ligation/stripping arm, mean AVVQ improved from a baseline of 28.86 to 2.14 at 2 years versus 31.18 to 2.44 in the ligation/EMA arm ($p<0.001$ for within-group change over time, between-group p=NS).

Effect on Other Standardized Symptom Scores

VCSS scores during 2-year follow-up were reported.[140] In the ligation/stripping arm, mean VCSS improved from a baseline of 6.02 to 1.48 at 2 years versus 6.62 to 1.38 in the ligation/EMA arm ($p<0.001$ for within-group change over time, between-group p=NS).

Strength of Evidence

Table 24 summarizes the strength of evidence for the findings described above.

Table 24. KQ 2: Strength of evidence for major outcomes—invasive surgery versus hybrid approaches
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Bleeding (Short-term) Insufficient	1 RCT: 449	Medium)	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/foam sclerotherapy[120,121,196]: T**he ligation/stripping arms reported a median of 25 mL of blood loss versus 15 mL in the ligation/foam sclerotherapy arm (p< 0.001 for difference between ligation/foam sclerotherapy and ligation/stripping).
Bleeding (Undetermined Timeframe) Insufficient	1 RCT: 150	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[196]:** In one RCT, 4 patients (8 percent) in the ligation/stripping arm had bleeding (ecchymoma), versus 3 (6 percent) in the ligation/EVLA arm (p=NR); 4 patients (8 percent) in the ligation/stripping arm had thrombophlebitis, versus 3 (6 percent) in the high ligation/EVLA arm (p=NR). **CHIVA vs. High Ligation plus EVLA[196]:** One patient (2 percent) in the CHIVA arm had bleeding (ecchymoma), versus 3 (6 percent) in the ligation/EVLA arm (p=NR); one patient (2 percent) in the CHIVA arm had thrombophlebitis, versus 3 (6 percent) in the ligation/EVLA arm (p=NR).
Changes on standardized symptom scores (Short-term) Insufficient	1 RCT: 449	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** By 2 months, approximately 85 percent of high ligation/stripping and high ligation/EVLA patients were asymptomatic by VDS. By 2 months, approximately 90 percent of high ligation/stripping and high ligation/EVLA patients were CEAP C0-1 (no between-group p-values reported).
Changes on standardized symptom scores (Long-term) Insufficient	2 RCTs: 637	Medium	Direct	Unclear	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** By 12 months, approximately 85 percent of the ligation/stripping group remained at C0-1, versus approximately 90 percent of the ligation/EVLA group; by 6 years of follow-up, approximately 60 percent of the ligation/stripping group had CEAP C0-1, versus approximately 75 percent of the ligation/EVLA group (no between-group p-values reported). **High ligation/stripping vs. High ligation/microwave ablation[140]:** In the ligation/stripping arm, mean VCSS improved from a baseline of 6.02 to 1.48 at 2 years versus 6.62 to 1.38 in the ligation/EMA arm (p<0.001 for within-group changes, between-group p=NS).

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Improvement in LE venous hemodynamics /reflux severity (Short-term) Insufficient	1 RCT: 449	Medium	Direct	NA	Precise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** In the high ligation/stripping arm, 0/159 patients had inguinal recurrence at 2 months, versus 10/148 (6.7 percent) in the high ligation/EVLA arm (p<0.0009).
Improvement in LE venous hemodynamics /reflux severity (Long-term) Insufficient	3 RCTs.: 496 limbs 1 RCT: NR 1 Obs: 375	Medium	Direct	Unclear	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** In the ligation/stripping group, reflux was present in 0 patients at 2 years, 5 (6.6 percent) at 3 years, 2 (3.6 percent) at 4 years, 5 (9.5 percent) at 5 years, and 5 (11.7 percent) at 6 years; in the ligation/EVLA group, reflux was present in 12 (11.7 percent) patients at 2 years, 9 (13.3 percent) at 3 years, 11 (18.4 percent) at 4 years, 8 (12.8 percent) at 5 years, and 4 (7.0 percent) at 6 years. The magnitude of reflux was similar between the arms (pairwise between-group p-value not reported). **High ligation vs. High ligation/foam sclerotherapy[107]:** Mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years in both groups (no between-group comparison reported); in both groups, duplex assessment showed an average of 1 site of incompetence at 10 years, down from 5 at baseline (p<0.05 for both within-group comparisons, no between-group comparison reported). **High ligation vs. High ligation/foam sclerotherapy[181]:** Of the patients with available data at 10 years, 0/33 receiving ligation and 0/31 receiving ligation/sclerotherapy experienced SFJ incompetence; ligation group's mean AVP improved from 55 mmHg at baseline to 44 mmHg at 10 years versus 54 to 35 mmHg in the ligation/sclerotherapy group (no between-group comparison reported). **High ligation/stripping vs. High ligation/microwave ablation[140]:** At 2 years, 24 limbs (28.2 percent) in the ligation/stripping arm had recurrence versus 14 (14.3 percent) in the ligation/EMA arm (p<0.02). **Standard Ligation plus Stripping ± Phlebectomy vs. Selective Ligation plus Sclerotherapy[198]:** At 20 year follow-up, this study found that major reflux was present on ultrasound in 38.8% of standard ligation/stripping patients vs. 17.9% of selective ligation/sclerotherapy

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
							patients (p<0.05).[198] The study also reported reflux at ≥3 major sites in 44.5% of standard ligation/stripping patients vs. 10.3% of selective ligation/sclerotherapy patients (p<0.05). **Selective Ligation vs. Selective Ligation plus Sclerotherapy[198]:** At 20 year follow-up, this study found that major reflux was present on ultrasound in 21% of selective ligation patients vs. 17.9% of selective ligation/sclerotherapy patients (p=NR).[198] The study also reported reflux at ≥3 major sites in 10.7% of selective ligation patients vs. 10.3% of selective ligation/sclerotherapy patients (p=NR), as well as recurrence of varicose veins in 15% of selective ligation patients vs. 9.8% of selective ligation/sclerotherapy patients (p=NR).
Improvement in LE venous hemodynamics /reflux severity (Undetermined Timeframe) Insufficient	1 RCT: 150	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[196]: R**eported the "general curative effect" of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the ligation/stripping arm, 25 patients (50 percent) experienced "cure" (not clearly defined), versus 32 (64 percent) in the ligation/EVLA arm (p=NR); 5 patients in the ligation/stripping arm had "recurrence" (not clearly defined), versus 2 in the ligation/EVLA arm (p<0.05). **CHIVA vs. High Ligation plus EVLA[196]:** This RCT reported the "general curative effect" of each intervention, as well as varicose vein recurrence (timing of assessment not reported). In the CHIVA arm, 41 patients (82 percent) experienced "cure" (not clearly defined), versus 32 (64 percent) in the ligation/EVLA arm (p=NR); no patients in the CHIVA arm had "recurrence" (not clearly defined), versus 2 in the ligation/EVLA arm (p=NR).
Patient-Reported QOL (Long-term) Insufficient	1 RCT: 188	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/microwave ablation[140]:** In the ligation/stripping arm, mean AVVQ improved from a baseline of 28.86 to 2.14 at 2 years versus 31.18 to 2.44 in the ligation/EMA arm (p<0.001 for within-group changes, between-group p=NS).
Qualitative reduction in LE pain (Short-term) Insufficient	1 RCT: 412	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** In the high ligation/stripping arm, 32.7 percent of patients endorsed pain, versus 50.0 percent in the high ligation/EVLA arm (p=0.0069). In the high ligation/stripping arm, 11/141 patients (7.8 percent) had persistent pain, versus 19/141 (13.5 percent) in the high ligation/EVLA arm (p=NS).

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Repeat Intervention (Long-term) Insufficient	1 Obs: 711	High	Direct	NA	Imprecise	None	**Standard Ligation plus Stripping ± Phlebectomy vs. Selective Ligation plus Sclerotherapy[198]:** At 20 year follow-up, this study found that the rate of repeat intervention was 58.6% among standard ligation/stripping patients vs. 19.7% among selective ligation/sclerotherapy patients (p<0.05). **Selective Ligation vs. Selective Ligation plus Sclerotherapy[198]:** At 20 year follow-up, this study found that the rate of repeat intervention was 18.9% among selective ligation patients vs. 19.7% among selective ligation/sclerotherapy patients (p=NR).
Venous thrombo-embolic events (Short-term) Insufficient	1 RCT: 449	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. High ligation/EVLA[120,121]:** In the high ligation/stripping arm, 1/159 patients had DVT versus 0/148 in the high ligation/EVLA arm.
Venous thrombo-embolic events (Long-term) Insufficient	1 Obs: 711	High	Direct	NA	Imprecise	None	**Standard Ligation plus Stripping ± Phlebectomy vs. Selective Ligation plus Sclerotherapy[198]:** There was no significant difference in rates of DVT between groups at 20 years follow-up (1.6% with standard ligation/stripping vs. 0.2% with selective ligation/sclerotherapy, p=NR). **Selective Ligation vs. Selective Ligation plus Sclerotherapy[198]:** There was no significant difference in rates of DVT between groups at 20 years follow-up (0.2% with selective ligation vs. 0.2% with selective ligation/sclerotherapy, p=NR).

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; CHIVA= Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; CI=confidence interval; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; GSV=great saphenous vein; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; SD=standard deviation; VCSS=Venous Clinical Severity Score

Comparisons Between Invasive Surgical Approaches and Compression

High Ligation/Stripping ± Phlebectomy versus Compression

Description of Included Studies

Five RCTs, 2 of good quality[108,111,200] and 3 of fair quality,[136,188,191] reported comparisons of surgery (high ligation and stripping with or without phlebectomy) to compression. One of the good-quality RCTs was described in two publications.[108,111] In all, these studies involved 1029 patients; all exclusively included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Individual study sample sizes ranged from 76 to 500. Study follow-up periods ranged from 7 weeks to 3 years. All five RCTs were conducted in the UK/Europe; two were conducted at two sites,[188,200] one was multicenter but did not report the number of sites,[108,111] and two were single-site studies.[136,191] Two studies reported nongovernment/nonindustry funding,[108,111,136] one reported government funding,[200] and two did not report a funding source.[188,191]

The mean/median age of study participants ranged from 47 to 73 years. The proportion of female patients ranged from 58 to 87.5 percent. None of the studies reported the racial or ethnic composition of their study populations. In two studies, all patients had CEAP C6 disease,[188,191] in one study, the majority of patients had a baseline CEAP class of C3;[136] and in two studies, baseline CEAP class was NR.[108,111,200]

Effect on Perioperative/Postoperative Complications (Surgery Patients Only)

One good-quality RCT reported that one of 242 surgical patients developed a postoperative hematoma, one experienced a DVT, and one developed superficial thrombophlebitis.[108,111]

Effect on Venous Wound Healing and Ulcer Recurrence

Three RCTs reported venous wound healing rates with surgery versus compression (one good-quality study,[108,111] one fair-quality study[188,191]). In the good-quality study, the ulcer healing rate at 24 weeks was 65 percent in both groups (p=0.8); the overall ulcer healing rate over 3 years was 93 percent in the surgery group and 89 percent in the compression group (p=0.737). In one fair quality study,[188] a strategy involving surgery and flavonoid therapy strategy resulted in significantly higher rates of complete ulcer healing at seven weeks relative to compression and flavonoid therapy (7/27 versus 2/27, p=0.03). In the other fair-quality study,[191] the overall ulcer healing rate over 6 months was 68 percent in the surgery group and 64 percent in the compression group (p=0.75), hazard ratio (HR) 0.8 (95% CI, 0.46 to 1.39). The good-quality RCT reported ulcer recurrence among subgroups with ulcer healing during the study or recently healed ulcers prior to study entry; the recurrence rate was 12 percent in the surgery group versus 28 percent with compression alone (p<0.0001).

Effect on Venous Wound Infection

Two RCTs reported on venous wound infection (one good quality,[200] one fair quality[191]). The good-quality study reported 12 wound infections in the 81 surgery patients by 1 year, versus 0 in the 101 compression patients (p=NR). The fair-quality study reported 1 episode of cellulitis requiring intravenous antibiotics in the 37 surgery patients by 6 months, versus 2 in the 39 compression patients (p=NR).

Effect on Mortality

Two RCTs reported mortality data (1 good quality,[108,111] one fair quality[191]). The good-quality study reported 0 deaths in the 242 surgery patients by 1 year and specified that none occurred within 30 days of surgery or related to surgery; mortality in the compression group was not reported. This good-quality study also reported 3-year death rates for both groups, which were 16 percent in the surgery group versus 19 percent in the compression group (p=0.245). The fair-quality study reported no deaths in either group over 6 months.

Effect on Patient-Reported Quality Of Life

Three RCTs reported information on quality of life after high ligation and stripping or compression (one good-quality,[200] two fair-quality[136,191]); because each study utilized different instruments and measurement time points, meta-analysis was not attempted. The good-quality study[200] reported EQ-5D results; at 1 year, surgery patients reported significantly superior quality of life versus the compression group (utility 0.87 versus 0.78, p<0.05), but at 2 years there was no between-group difference (utility 0.84 versus 0.85, p=NS). One fair-quality study[136] presented mean AVVQ scores at 1 and 2 years for each group. In the surgery group, AVVQ improved from a baseline of 16.3 to 8.1 at 1 year and 7.1 at 2 years (improvement described as statistically significant, p=NR). In the compression group, AVVQ was 14.6 at baseline, 13.1 at 1 year, and 13.4 at 2 years (p=NS). No between-group comparison was reported. The other fair-quality study[191] presented SF-36 data at 3 and 6 months for each group, as well as information on the between-group difference in SF-36 at 3 and 6 months. In the surgery group, one SF-36 domain (physical functioning) improved significantly by 3 and 6 months, while 2 other domains (role physical, general health) improved significantly by 6 months (all p<0.05). In the compression group, no SF-36 domains improved by 3 months, but 3 domains (role physical, bodily pain, role emotional) improved significantly by 6 months (all p<0.05). Comparing mean SF-36 scores between surgery and compression patients, surgery patients scored better in physical functioning at 3 and 6 months and in general health at 6 months, while compression patients scored better in bodily pain and role emotional at 6 months (all p<0.05). This study also presented mean Charing Cross Venous Ulcer Questionnaire (CCVUQ) scores at 3 and 6 months for each group. In the surgery group, CCVUQ improved from a baseline of 60.4 to 56.0 at 3 months (p<0.05) and 41.1 at 6 months (p<0.05). In the compression group, CCVUQ improved from a baseline of 63.0 to 50.2 at 3 months (p=NS) and 45.5 at 6 months (p<0.05). There was no statistically significant between-group difference in CCVUQ at any time point.

Effect on Improvement in Venous Hemodynamics

One good-quality RCT reported ultrasonographic procedural outcomes with high ligation and stripping (± calf varicosity avulsion) versus compression,[108,111] specifically describing the number of legs with incompetent calf perforating veins at 3 months and 1 year. Among surgery patients, 51 percent had incompetent calf perforating veins at baseline, 41 percent at 3 months (p<0.001), and 42 percent at 1 year (p=0.001). Among compression patients, 42 percent had incompetent calf perforating veins at baseline; this number increased to 46 percent at 3 months (p=0.144), and 59 percent at 1 year (p=0.01). No between-group comparison was reported.

Effect on LE Pain

One good-quality RCT presented mean LE pain scores (visual analog scale) at 1 and 2 years for surgery and compression patients;[200] surgery patients reported significantly less pain versus

the compression group at 1 year (utility 0.82 versus 0.75, p<0.05) and at 2 years (utility 0.81 versus 0.75, p<0.05).

Effect on Other Standardized Symptom Scores

One fair-quality study presented VCSS, Venous Segmental Disease Score (VSDS), and CEAP data at 1 and 2 years after high ligation and stripping or compression.[136] In the surgery group, VCSS improved from a baseline of 4.8 to 0.8 at 1 year and 0.6 at 2 years (p<0.05). In the compression group, VCSS was 4.6 at baseline, 3.6 at 1 year, and 3.5 at 2 years (p=NS). The between-group difference significantly favored surgery (p<0.05). In the surgery group, VSDS improved from a baseline of 8.2 to 0.6 at 1 year and 0.9 at 2 years (p<0.05). In the compression group, VSDS was 7.7 at baseline, 7.2 at 1 year, and 7.0 at 2 years (p=NS). The between-group difference again significantly favored surgery (p<0.05). All patients began the study with a CEAP classification of C2-C3. At 2-year follow-up, 80.0 percent (56/70) of compression patients remained at C2-C3 as opposed to the 29.4 percent (20/68) in the surgery group (p=NR).

High Ligation plus Stripping plus Subfascial Endoscopic Perforating Vein Surgery (SEPS) versus Compression

Description of Included Studies

One fair-quality RCT[112,113] reported a comparison of a combination surgery strategy (high ligation plus stripping plus SEPS) versus compression. An initial report[113] provided data with a mean follow-up of 28 months, and a subsequent report provided 97-month follow-up of this population.[112] This study analyzed 170 patients (196 limbs) with symptomatic LE chronic venous insufficiency with venous ulcers, 73 of whom were included in the long-term follow-up report (80 limbs). This RCT was conducted at 12 sites in the UK/Europe. The original study utilized government funding, and the follow-up study reported nongovernment/nonindustry funding.

The mean/median age of study participants of approximately 66 years, and approximately 60 percent of patients were reported as female. Data regarding the population's racial/ethnic composition was not reported. All enrolled patients had a baseline CEAP class of C6.

Effect on Venous Wound Healing and Ulcer Recurrence

This RCT reported venous wound healing rates with combination surgery versus compression. Among surgery patients, 83 percent of limbs experienced ulcer healing within the timeframe of the initial study, versus 73 percent for compression patients (p=NS);[113] at long-term follow-up, all but 4.4 percent of surgery patients' limbs achieved some degree of ulcer healing versus 2.9 percent with compression (p=NS).[112] By the end of the initial study,[113] 72 percent of surgery patients' limbs were deemed ulcer-free, versus 53 percent with compression (p=0.11); at long-term follow-up,[112] 48.9 percent of surgery patients' limbs were ulcer-free, versus 2.9 percent for compression patients (p=NR). At long-term follow-up, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression (p=NR).

Effect on Mortality

This RCT reported incidence of mortality in the combination surgery group and compression group. A total of 23 patients died within the timeframe of the original study;[113] these patients contributed 8 limbs to the surgical group and 17 to the compression group (both legs were

randomized for 2 patients), p=NR. No deaths were felt to relate to the allocated treatment or venous ulcers.

CHIVA versus Compression

Description of Included Studies

One poor-quality RCT[175,190] yielded 2 reports comparing CHIVA surgery versus compression. The RCT recruited 80 patients with symptomatic LE chronic venous insufficiency with primary venous ulcers, and randomized 45. Patients were followed for a mean of 1 year in the first report,[190] and 3 years in the second.[175] This study was conducted in the UK/Europe at a single site, and did not report a funding source. The mean age of study participants was not reported, nor were data on sex, race, or CEAP class (though all patients are described as having LE ulcers).

Effect on Venous Wound Healing

These reports described venous wound healing outcomes after CHIVA surgery versus compression. In the CHIVA group, 100 percent of patients experienced wound healing in a mean of 29 days; with compression, 96 percent experienced wound healing in a mean of 61 days.[190] The rate of ulcer healing did not differ between groups (p=NS), though the difference in time to healing was statistically significant ($p<0.005$).

Effect on Improvement in Venous Hemodynamics

Air plethysmography was used to compare "venous function" with CHIVA surgery versus compression. No between-group differences in venous function (venous volume, venous filling index, ejection fraction, or residual volume fraction) were noted at baseline in the poor-quality study.[190] By 6 months, venous volume, venous filling index, and residual volume fraction all improved significantly in the CHIVA group (all $p<0.001$); no improvements were observed in the compression group. No between-group statistical comparisons were reported. By 3 years follow-up, only residual volume fraction remained improved; no parameters were improved in the compression group. No between-group statistical comparisons were reported at 3 years.

Effect on Patient-Reported Quality of Life

In the poor-quality study's CHIVA group,[190] all SF-36 domains improved significantly by 6 months (all $p<0.001$), while 4 domains (role physical, vitality, social functioning, role emotional) improved in the compression group (all $p<0.05$). Comparing SF-36 domains between CHIVA and compression patients, CHIVA patients had significantly better scores in 5 domains (role physical, vitality, social functioning, role emotional, mental health) at 6 months (all $p<0.05$).

Effect on Recurrent Ulceration

This study reported recurrent ulceration at 3 years.[175] A significantly higher number of patients in the compression arm (9 out of 24 patients) had recurrent ulcerations compared to 2 out of 27 surgery patients ($p\leq0.005$).

Effect on Repeat Intervention

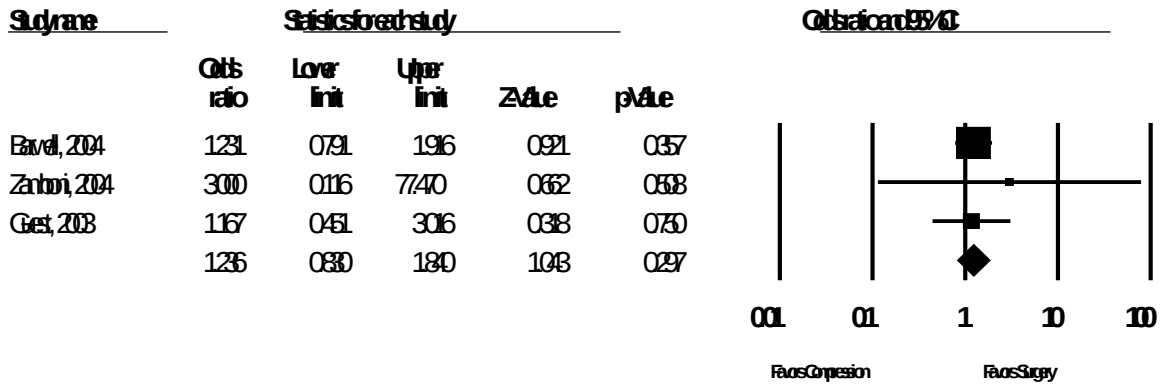
Two patients in the CHIVA arm underwent repeat interventions within 6 months of initial intervention.[175]

Meta-Analysis of Any Surgery versus Compression

Effect on Wound Healing

Due to conceptual heterogeneity in study design (surgical procedures utilized, outcomes selected, outcome definitions, outcome timing, analytic approaches, etc.), there was limited opportunity for quantitative synthesis of data relating to comparisons of surgery and compression. However, we were able to meta-analyze data from 3 studies[111,190,191] that examined the effect of surgical approaches versus compression on intermediate-term wound healing outcomes (2 months). One good-quality[111] and one fair-quality study[191] examined high ligation and stripping procedures and one poor-quality study[190] examined CHIVA surgery. The summary effect of these studies was a non-statistically significant OR of 1.24 (95% CI, 0.83 to 1.84) favoring surgery (Figure 20).

Figure 20. Forest plot of wound healing for surgical approaches versus compression



Abbreviation: CI=confidence interval

Strength of Evidence

Table 25 summarizes the strength of evidence for the findings described above.

Table 25. KQ 2: Strength of evidence for major outcomes—invasive surgery versus compression
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Bleeding (Short-term) Insufficient	1 RCT: 500	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[108,111]: One of 242 surgical patients developed a postoperative hematoma, no compression patients.
Changes on standardized symptom scores (Long-term) Insufficient	1 RCT: 143	Medium	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[136]: Between-group difference in VCSS at 1 and 2 years significantly favored surgery (p<0.05), and the between-group difference in VSDS at 1 and 2 years significantly favored surgery (p<0.05). At 2-year follow-up, 80.0 percent (56/70) of compression patients remained at C2-C3 as opposed to the 29.4 percent (20/68) in the surgery group (p=NR).
Death (Long-term) Low	2 RCTs: 526 1 RCT: 196 limbs	Medium	Direct	Consistent	Imprecise	None	**High ligation/stripping vs. compression**[108,111]: 16 percent in the surgery group versus 19 percent in the compression group (p=0.245) at 3 years. **High ligation/stripping vs. compression**[191]: No deaths in either group over 6 months. **High ligation/stripping/SEPS vs. compression**[112,113]: A total of 23 patients died within 28 months; these patients contributed 8 limbs to the surgical group and 17 to the compression group (both legs were randomized for 2 patients), p=NR.
Improvement in LE venous hemodynamics/reflux severity (Intermediate-term) Low	2 RCTs: 258	Medium	Direct	Consistent	Imprecise	Suspected	**High ligation/stripping vs. compression**[108,111]: Number of legs with incompetent calf perforating veins dropped from 51 to 41 percent at 3 months among surgery patients (p<0.001), but increased from 42 to 46 percent among compression patients (p=0.144). No between-group comparison reported. **CHIVA vs. compression**[175,190]: By 6 months, venous volume, venous filling index, and residual volume fraction improved significantly in the CHIVA group (all p<0.001); no improvements observed in the compression group. No between-group statistical comparisons reported.
Improvement in LE venous hemodynamics/r	2 RCTs: 258	Medium	Direct	Inconsistent	Imprecise	Suspected	**High ligation/stripping vs. compression**[108,111]: Number of legs with incompetent calf perforating veins dropped from 51 to 42 percent at 1 year among surgery patients (p=0.001), but increased from 42 to 59

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
eflux severity (Long-term)	1 RCT: 61 limbs						percent among compression patients (p=0.01). No between-group comparison reported.
Insufficient							**CHIVA vs. compression**[175,190]: By 3 years follow-up, only residual volume fraction improved with CHIVA; no parameters were improved with compression. No between-group statistical comparisons reported at 3 years.
Patient-Reported QOL (Intermediate-term)	2 RCTs: 156	Medium	Direct	Inconsistent	Imprecise	Suspected	**High ligation/stripping vs. compression**[200]: Comparing mean SF-36 scores, surgery patients scored better in physical functioning at 3 and 6 months and in general health at 6 months, while compression patients scored better in bodily pain and role emotional at 6 months (all p<0.05); no statistically significant between-group difference in CXVUQ at 3 or 6 months.
Insufficient							**CHIVA vs. compression**[175,190]: Comparing SF-36 domains between CHIVA and compression patients, CHIVA patients had significantly better scores in 5 domains (role physical, vitality, social functioning, role emotional, mental health) at 6 months (all p<0.05).
Patient-Reported QOL (Long-term)	2 RCTs: 308	Medium	Direct	Inconsistent	Imprecise	None	**High ligation/stripping vs. compression**[200]: At 1 year, surgery patients reported superior quality of life (EQ5D) versus compression (utility 0.87 versus 0.78, p<0.05); at 2 years there was no between-group difference (utility 0.84 versus 0.85, p=NS).
Insufficient							**High ligation/stripping vs. compression**[136]: No between-group comparison in AVVQ at 1 or 2 years reported.
Qualitative reduction in LE pain (Long-term)	1 RCT: 199	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[200]: Surgery patients reported significantly less pain versus the compression group at 1 year (utility 0.82 versus 0.75, p<0.05) and at 2 years (utility 0.81 versus 0.75, p<0.05).
Insufficient							
Recurrent Ulceration (Long-term)	2 RCTs: 127	Medium	Direct	Consistent	Imprecise	Suspected	**High ligation/stripping vs. compression**[108,111]: Recurrence rate was 12 percent in the surgery group versus 28 percent with compression alone (p<0.0001).
Low	1 RCT: 196 limbs						**High ligation/stripping/SEPS vs. compression**[112,113]: At long-term follow-up, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression (p=NR).

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
							CHIVA vs. compression[175,190]: A significantly higher number of patients in the compression arm (9 out of 24 patients) had recurrent ulcerations compared to 2 out of 27 surgery patients (p≤0.005).
Repeat Intervention (Long-term) Insufficient	1 RCT: 21	Medium	Direct	NA	Imprecise	Suspected	**CHIVA vs. compression**[175,190]: Two patients in the CHIVA arm underwent repeat interventions within 6 months of initial intervention.
Thrombo-phlebitis (Short-term) Insufficient	1 RCT: 500	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[108,111]: One of 242 surgical patients developed postoperative superficial thrombophlebitis.
Venous thrombosis (Short-term) Insufficient	1 RCT: 500	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[108,111]: One of 242 surgical patients developed a postoperative DVT.
Venous Wound Healing (Intermediate-term) Insufficient	4 RCTs: 545 1 RCT: 196 limbs	Medium	Direct	Inconsistent	Imprecise	Suspected	**High ligation/stripping vs. compression**[108,111]: Ulcer healing rate at 24 weeks was 65 percent in both groups (p=0.8). **High ligation/stripping vs. compression**[188]: Surgery and flavonoid therapy resulted in significantly higher rates of complete ulcer healing at seven weeks relative to compression and flavonoid therapy (7/27 versus 2/27, p=0.03). **High ligation/stripping vs. compression**[191]: Overall ulcer healing rate over 6 months was 68 percent in the surgery group and 64 percent in the compression group (p=0.75), HR 0.8 (95% CI, 0.46 to 1.39). **High ligation/stripping/SEPS vs. compression**[112,113]: Among surgery patients, 83 percent of limbs experienced ulcer healing within the 28 months, versus 73 percent for compression patients (p=NS); 72 percent of surgery patients' limbs were deemed ulcer-free, versus 53 percent with compression (p=0.11). **CHIVA vs. compression**[175,190]: In the CHIVA group, 100 percent of

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients or Limbs**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
							patients had wound healing in a mean of 29 days; with compression, 96 percent experienced wound healing in a mean of 61 days. The rate of ulcer healing did not differ between groups (p=NS), though the difference in time to healing was statistically significant (p<0.005).
Venous Wound Healing (Long-term) Insufficient	1 RCTs: 446 1 RCT: 196 limbs	Medium	Direct	Inconsistent	Imprecise	None	**High ligation/stripping vs. compression**[108,111]: Overall ulcer healing rate over 3 years was 93 percent in the surgery group and 89 percent in the compression group (p=0.737). **High ligation/stripping/SEPS vs. compression**[112,113]: All but 4.4 percent of surgery patients' limbs achieved some degree of ulcer healing versus 2.9 percent with compression (p=NS); 48.9 percent of surgery patients' limbs were ulcer-free, versus 2.9 percent for compression patients (p=NR).
Venous Wound Infection (Long-term) Insufficient	1 RCT: 76	Low	Direct	NA	Imprecise	None	**High ligation/stripping vs. compression**[191]: 1 episode of cellulitis requiring IV antibiotics in the 37 surgery patients by 6 months, versus 2 in the 39 compression patients (p=NR).

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CHIVA= Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; CI=confidence interval; DVT=deep vein thrombosis; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; SD=standard deviation; SEPS= subfascial endoscopic perforating vein surgery; VCSS=Venous Clinical Severity Score

Comparisons Between Mechanical Compression Therapies and Placebo or Usual Care

Description of Included Studies

Eleven RCTs (1522 patients) compared mechanical compression with either placebo compression or no compression.[130,135,142,144,148,157,162,173,180,182,192] All of these studies were performed outside of the United States. They included a good-quality study (321 patients) conducted in Hong Kong that compared two different bandaging interventions to usual care for elderly patients with venous leg ulcers.[148] Another good-quality study (60 patients) assessed the effectiveness and safety of adding a 3-week course compression therapy to foam sclerotherapy among patients with varicose saphenous veins in France.[157] Three good-quality studies (total of 373 patients) that used a placebo taping procedure as a comparator among a sample of postmenopausal women were conducted by the same group of investigators in Spain.[135,142,144] Three studies were rated as fair quality: one study (104 patients) conducted in the Netherlands compared GSV stripping plus elastic bandaging for 3 days postoperatively with GSV stripping plus elastic bandaging for 4 weeks,[162] one study (111 patients) conducted in the Netherlands evaluated the effectiveness of a 2-week course of elastic stockings after endovenous laser therapy for primary varicosities,[182] and one study (200 patients) conducted in Ireland compared the effects of four-layer compression bandaging for treating venous leg ulcers with other available treatments on health-related quality of life during a 6-week course of treatment.[173] We also identified 3 poor-quality studies: one study randomized 100 patients in Saudi Arabia to compression stockings for 1 month versus standard medical therapy,[130] one study randomized 153 patients in Australia with recently healed leg ulcers to below-knee compression stockings versus no compression therapy,[192] and one publication reporting on 2 studies (100 patients) conducted in the UK evaluated the effectiveness of intermittent pneumatic compression as an adjuvant to compression bandaging for treating and preventing venous ulcer disease.[180]

Variability across studies in terms of the study interventions, outcome measures, duration of treatment, and timing of follow-up assessments precluded conducting a meta-analysis to quantitatively synthesize the findings of some or all of these studies.

Results

The 3-arm RCT conducted in Hong Kong assessed quality-of-life aspects, ulcer-related pain, and patients' functional status at baseline and after 24 weeks of treatment with a four-layer compression bandaging, short-stretch compression bandaging, or usual care without bandaging.[148] Relative to usual care, both compression bandaging interventions significantly reduced ulcer-related pain and improved functional status as measured by the Frenchay Activities Index, and quality of life as measured by the Short Form 12-item Health Survey (SF-12) and the CCVUQ at 24 weeks. The mean time to ulcer healing was 10.4 weeks (SD 0.8) for the four-layer bandaging, 9.8 weeks (SD 0.77) for the short-stretch compression bandaging, and 18.3 weeks (SD 0.86) for usual care ($p<0.001$ for comparisons between either compression group with usual care).

The study conducted in France conducted clinical and DUS assessments and administered quality-of-life and symptom questions 14 and 28 days after foam sclerotherapy interventions.[157]

Abolition of venous reflux was successful for all of the subjects, and there were no between-group differences for quality of life, symptoms, or adverse effects.

One of the three studies conducted in Spain assessed pain and quality of life (as assessed by the Chronic Venous Insufficiency Questionnaire-20 [CIVIQ-20]) 48 hours after study enrollment.[135] Compression therapy was not associated with pain reduction relative to placebo compression, but the CIVIQ-20 score was significantly improved in the compression arm relative to the placebo arm at 48 hours (between-group change score: -8.76; 95% CI, -12.55 to -4.96). The other two studies conducted in Spain reported significant improvement in several symptoms (e.g., swelling, claudication, muscle cramps, and body pain) but not in pain or quality of life, associated with compression therapy relative to placebo compression at 4 weeks.[142,144] It is unclear whether these three studies have overlapping patients.

The study that compared GSV stripping plus elastic bandaging with elastic bandaging alone was designed as an equivalence trial; this study did not identify significant between-group differences in edema, pain, complications, or return to work 4 weeks after undergoing GSV stripping.[162] The study that compared elastic stockings to no compression therapy after endovenous laser therapy found no statistically significant between-group differences at 6 weeks in time to return to work, AVVQ scores, SF-36 scores, leg circumference measurements, or risk of complications. However, patients who received compression therapy did report a small but statistically significant reduction in postoperative pain and use of analgesics compared with controls.[182] The study that evaluated the effects of four-layer compression bandaging for treating venous leg ulcers demonstrated significant improvements in the physical, social, and global domains of the CIVIQ associated with compression bandaging relative to usual care only.[173]

The study that compared compression stockings for 1 month with usual medical therapy for varicose veins demonstrated that compression stockings were associated with improved CEAP clinical scores.[130] The study that compared below-knee compression stockings with no compression therapy demonstrated reduced lipodermatosclerosis and ulcer recurrence associated with compression stockings at 6 months but not at 12 months[192] Finally, the two studies reported in the publication that evaluated intermittent pneumatic compression found that intermittent pneumatic compression as an adjuvant to compression therapy was associated with a higher rate of healing of venous ulcers (0.14 cm^2/day) relative to compression therapy alone (0.05 cm^2/day; $p<0.05$). Intermittent pneumatic compression was not, however, found to decrease the incidence of ulcer recurrence.[180]

Strength of Evidence

Table 26 summarizes the strength of evidence for the findings described above.

Table 26. KQ 2: Strength of evidence for major outcomes—mechanical compression therapies versus placebo or usual care
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design) N Patients or Limbs	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes on standardized symptom scores (Short-term)	6 RCTs: 637	Medium	Direct	Inconsistent	Imprecise	Suspected	1 poor-quality RCT representing 100 patients[130] and 1 good-quality RCT representing 123 patients[142] demonstrated significant improvement at 30 days associated with compression therapy. The other 4 RCTs did not demonstrate a difference between interventions.[135,144,157,162]
Strength of Evidence: Insufficient							
Improvement in LE venous hemodynamics / reflux severity (Intermediate-term)	1 RCT: 120	Low	Direct	NA	Imprecise	None	No significant improvement in LE venous hemodynamics at 1 month.[144]
Strength of Evidence: Insufficient							
Patient-Reported QOL (Intermediate-term)	5 RCTs: 894	Low	Direct	Inconsistent	Imprecise	None	1 fair-quality RCT representing 200 patients demonstrated significant improvement in patient-reported QOL at 6 weeks.[173] The other 4 RCTs did not demonstrate a difference between interventions.[135,142,144,148]
Strength of Evidence: Insufficient							
Qualitative reduction in LE edema (Intermediate-term)	2 RCTs: 219	Medium	Direct	Inconsistent	Imprecise	None	1 good-quality RCT representing 123 patients demonstrated a significantly lower proportion of patients reporting LE edema at 1 month.[142] The other fair-quality RCT did not demonstrate a difference between interventions.[162]
Strength of Evidence: Insufficient							

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Qualitative reduction in LE pain (Intermediate-term) Insufficient	4 RCTs: 675	Low	Direct	Inconsistent	Imprecise	None	1 good-quality RCT representing 123 patients demonstrated a significantly lower proportion of patients reporting LE pain at 1 month.[142] The other 3 RCTs did not demonstrate a difference between interventions.[144,148,182]
Recurrent ulceration (Intermediate-term) Insufficient	3 RCTs: 376	Medium	Direct	Consistent	Imprecise	None	No significant differences in recurrent ulceration at 1- months in 2 RCTs.[142,180] A poor-quality RCT representing 153 patients reported a lower proportion of patients with recurrent ulceration at 6 months associated with compression stockings relative to no compression.[192]
Recurrent ulceration (Long-term) Insufficient	1 RCT: 153	Medium	Direct	Consistent	Imprecise	None	No significant differences in recurrent ulceration at 12 months.[192]
Venous wound healing (Intermediate-term) Insufficient	3 RCTs: 621	Medium	Direct	Inconsistent	Imprecise	None	1 poor-quality RCT representing 100 patients demonstrated significant improvement in venous wound healing.[180] The other 2 RCTs did not demonstrate a difference between interventions.[148,173]

Abbreviations: KQ=key question; LE=lower extremity; N=number; NA=not applicable; QOL=quality of life; RCT(s)=randomized controlled trial(s)

Comparisons Between Medical Therapies and Placebo or Usual Care

Six RCTs (1149 patients) evaluated the effectiveness of medical therapies in patients with LE venous ulcers. A good-quality study conducted in Italy randomized 254 patients with LE edema due to chronic venous insufficiency to medical management with coumarin and troxerutin versus placebo.[177] Upon completion of the 16-week trial, patients in the active medical intervention group reported improved scores on an undefined quality-of-life index instrument (p=0.004) relative to controls. Another good-quality RCT conducted in the UK randomized 245 patients with a venous leg ulcer of at least 1 cm in length and 8 weeks in duration to either pentoxifylline, sustained-release, 400 mg tablets three times daily or placebo tablets.[171] Patients were then further randomized to receive either knitted viscose or hydrocolloid dressings, and then further randomized to either four-layer or adhesive single layer bandages for 6 months. The notable findings from this factorial RCT were that there was no evidence of interaction between pentoxifylline, bandages, and dressings for the primary outcome of ulcer healing; pentoxifylline was associated with a not statistically significant increase in ulcer healing relative to placebo (62 percent vs. 53 percent; p=0.21); four-layer bandages were associated with significantly higher healing rates relative to single layer bandages (67 percent vs. 49 percent; p=0.009); and there was no difference in healing between knitted viscose and hydrocolloid dressings (58 percent vs. 57 percent; p=0.88). The effectiveness of the same dose of pentoxifylline (1200 mg per day) relative to usual care was also demonstrated by a smaller (80 patients), poor-quality study conducted in Macedonia; this study reported complete healing of ulcers in 57.5 percent of patients who received pentoxifylline plus local therapy (without mechanical compression) versus 27.5 percent in patients who received local therapy alone after 24 weeks of treatment (p=0.013).[178] These two studies demonstrate that there is limited evidence since 2000 to suggest that pentoxifylline is effective relative to placebo for reducing venous ulcers with low SOE.

A fair-quality study conducted in Spain compared a daily dose of 300 mg of aspirin plus gradual compression therapy versus compression therapy alone among 51 patients with venous ulcers.[147] The rate of ulcer recurrence over the 42-week study period was lower in the aspirin group (25 percent) compared with the no aspirin group (33 percent) (statistical significance NR). A fair-quality study (235 patients) conducted in Italy demonstrated that a 90-day course of sulodexide plus local wound care and compression bandaging was associated with a higher rate of ulcer heating (52.5 percent) than placebo drug plus local wound care and compression bandaging (32.7 percent; p=0.004).[179] Another fair-quality study (284 patients) conducted in Italy demonstrated that 12 months of daily subcutaneous injections of the low molecular weight heparin drug nadroparin was associated with a higher rate of ulcer healing (83.90 percent) at 12 months than usual care only (60.56 percent; p<0.00001), with the greatest between-group difference in ulcer healing rates observed among patients 80 years or older.[143] The recurrence rate of venous ulcers at 5 years was also apparently lower in the nadroparin group (26.76 percent) relative to usual care only (59.15 percent; p-value NR). Given the diversity of treatments, outcomes, and small number of patients, there was insufficient SOE for these studies.

Comparisons Between Exercise Therapy and Other Strategies

A fair-quality RCT conducted in New Zealand compared a 12-week progressive resistance exercise program using heel raises plus compression therapy to usual care plus compression therapy among 40 patients with venous leg ulcers.[158] At 12 weeks, 38 percent of patients in the exercise group and 53 percent in the usual care group had healed ulcers, with an OR of healing at

12 weeks of 0.55 (OR 0.55; 95% CI, 0.16 to 1.95). The mean change in ulcer area from baseline to 12 weeks was -1.47 cm^2 in the exercise group and -2.92 cm^2 in the usual care group (p=0.08).

Table 27 summarizes the strength of evidence for these findings.

Table 27. KQ 2: Strength of evidence for major outcomes—exercise therapy versus usual care
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Venous wound healing (Intermediate-term)	1 RCT: 40	Medium	Direct	NA	Imprecise	Suspected	No differences in venous wound healing at 12 weeks.[158]
Insufficient							
Exercise-related harms (Intermediate-term)	1 RCT: 40	Medium	Direct	NA	Imprecise	Suspected	No differences in exercise-related harms at 12 weeks.[158]
Insufficient							

Abbreviations: KQ=key question; N=number; NA=not applicable; RCT=randomized controlled trial

Other Approaches

A good-quality RCT conducted in France evaluated the effectiveness of balneotherapy (bathing therapy in a spa setting) among 425 patients with primary or post-thrombotic chronic venous disorders without active ulcers.[137] Patients were randomized to a customized 3-week spa treatment course or a waitlist control group. The incidence of leg ulcers during the 1-year follow-up period was 9.3 percent in the balneotherapy group and 6.1 percent in the control group (between-group difference NS). Balneotherapy was, however, associated with significant improvements in the VCSS (-1.2 vs. -0.6, p=0.04), the EQ-5D score (+0.01 vs. -0.07, p<0.001), and the CIVIQ-2 Scale (-2.0 vs. +0.2, p=0.008) relative to the control group at the 1-year follow-up assessment.

Table 28 summarizes the strength of evidence for these findings.

Table 28. KQ 2: Strength of evidence for major outcomes—balneotherapy versus usual care
Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Intermediate-term)	1 RCT: 425	Low	Direct	NA	Imprecise	None	No differences in standardized symptom scores at 6 months.[137]
Insufficient							

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Long-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	Balneotherapy associated with improvement in the VCSS (-1.2 vs. -0.6, p=0.04) at 1 year[137]
Patient-Reported QOL (Intermediate-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	No differences in patient-reported QOL at 6 months.[137]
Patient-Reported QOL (Long-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	Balneotherapy associated with improvement in the EQ-5D score (+0.01 vs. -0.07, p<0.001), and the CIVIQ-2 Scale (-2.0 vs. +0.2, p=0.008) at 1 year.[137]
Adverse drug reactions (Long-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	No differences in exercise-related harms at 18 months.[137]
Venous thromboembolic events (Long-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	No differences in thromboembolic events at 18 months.[137]
Recurrent ulceration (Long-term) Insufficient	1 RCT: 425	Low	Direct	NA	Imprecise	None	No significant differences in improvement in recurrent ulceration at 1 year.[137]

Abbreviations: KQ=key question; N=number; NA=not applicable; QOL=quality of life; RCT=randomized controlled trial; VCSS=Venous Clinical Severity Score

Key Question 3. Treatments for Adult Patients with LE Chronic Venous Thrombosis/Obstruction

KQ 3 examines treatments for all adult patients, symptomatic and asymptomatic, with LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome) with respect to the following areas:

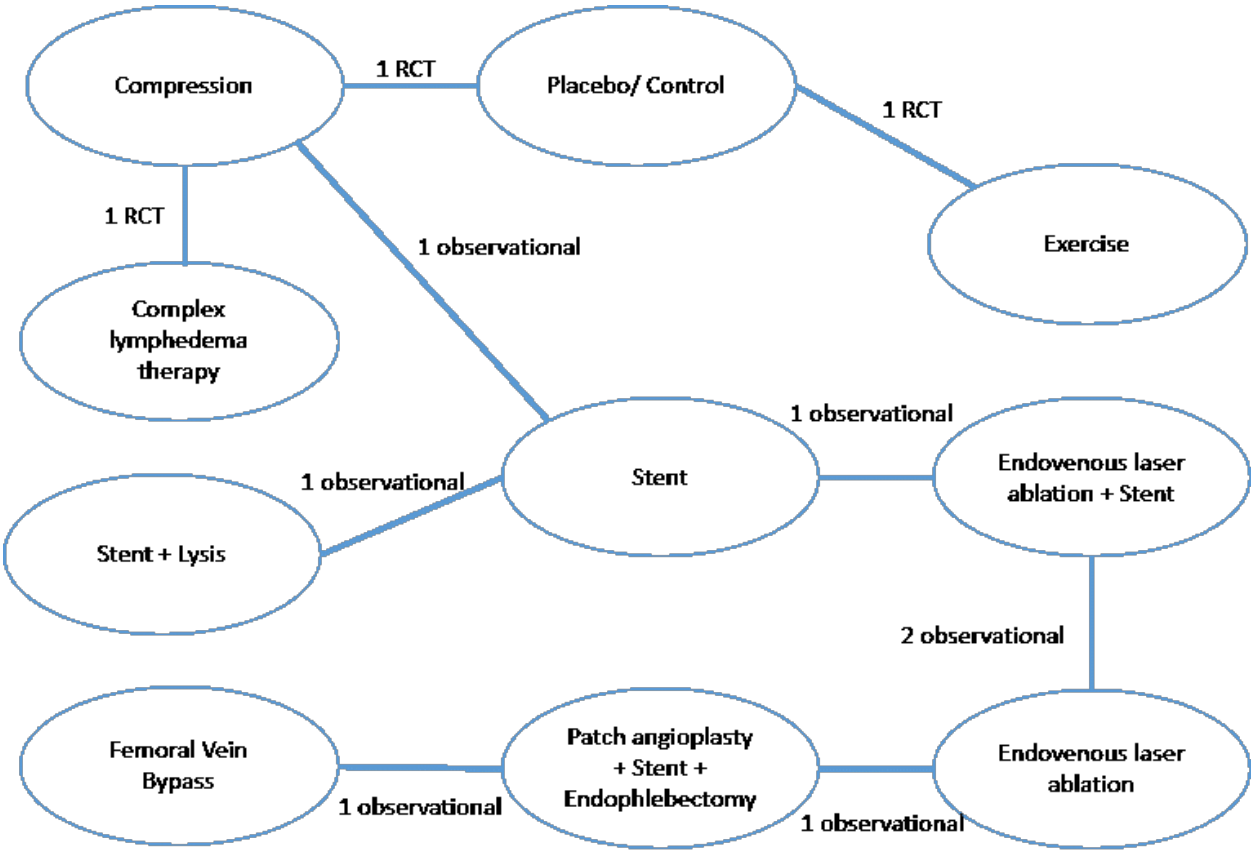
- The comparative effectiveness of exercise, medical therapy, mechanical compression therapy, and invasive procedures on health outcomes (KQ 3a)
- The diagnostic methods and criteria used in each study (KQ 3b)
- How the comparative effectiveness of treatment varies by patient characteristics, including age, sex, risk factors, comorbidities, characteristics of disease, anatomic segment affected, and characteristics of the therapy (KQ 3c)
- The comparative safety concerns associated with each treatment strategy and how safety concerns vary by patient subgroup (KQ 3d)

Description of Included Studies

We identified eight studies that examined the treatments for patients with LE chronic venous thrombosis/obstruction.[201-208] In seven of the studies, all patients were symptomatic at baseline, and in one only a small minority had unclear symptom severity.[208] Three of the studies were RCTs, representing a total of 109 patients.[202,204,205] Sample sizes of the remaining 5 observational studies ranged from 20 to 216 patients. Four studies were conducted in the United States,[202,203,206,208] two in Canada,[204,205] and two in Asia.[201,207] All but one study[204] reported conducting the studies at a single center. Three studies reported government funding.[201,204,207] Two studies reported a combination of funding from government, industry, or nongovernment sources.[202,205] Three studies did not report the funding source or the funding source was unclear.[203,206,208] All eight studies were conducted in a specialty practice. Of the three RCTs, two were rated as good quality,[202,204] and one was rated as poor quality.[205] Of the five observational studies, three were rated as fair quality,[201,203,207] and the other two were rated as poor quality.[206,208]

Figure 21 is a network map summarizing the comparisons that were assessed in the included studies and detailed in this analysis. Each line represents a study, and the nodes represent study interventions.

Figure 21. KQ 3 treatment comparisons



Abbreviations: KQ=key question; RCT=randomized controlled trial

Key Points

- *KQ 3a Effectiveness of interventions:* Given overall variable study quality, inconsistent selection of endpoints, and small sample sizes, insufficient strength of evidence limits ability to make any conclusions regarding effectiveness of any of the studied interventions.
- *KQ 3b Diagnostic methods:* Post-thrombotic syndrome is diagnosed for the purpose of clinical studies through a variety of ways including patient symptoms standardized to a vein-specific quality-of-life score, imaging (most commonly ultrasound), or a combination of the two assessments.
- *KQ 3c Modifiers of effectiveness:* There was insufficient evidence to make any conclusions about modifiers of effectiveness of the comparators in the clinical trials.
- *KQ 3d Safety concerns*: Study design limitations do not allow for any conclusive findings regarding the safety of endovenous stenting in patients with post-thrombotic syndrome.

Detailed Synthesis

Effectiveness of Interventions

Exercise Training plus Patient Education/Engagement versus Patient Education/Engagement Alone

One study, an RCT rated good quality, compared a standardized education and phone call follow-up protocol (control arm) to an exercise training program consisting of strengthening, stretching, and aerobic components (15 total one-on-one sessions) plus the control intervention.[204] This study included 43 patients with post-thrombotic syndrome (22 randomized to the control arm and 21 to exercise training), and 39 completed the study. Study duration was 6 months. The mean age in the study was 47 years, and 56 percent were female. Racial and ethnic demographics of study participants were not reported. The study was conducted at two sites, both in Canada. The funding source was the government.

Effect on Patient-Reported Quality of Life

The VEINES-QOL instrument was used to assess the effect of venous disease, including DVT, on quality of life. In addition to VEINES-QOL, the SF-36 Physical and Mental Component scores were used to assess within-patient changes by group. Results of exercise versus control group are displayed in Table 29, demonstrating a significant effect on VEINES-QOL and SF-36 Physical Component, but not on the SF-36 Mental Component score.

Table 29. Effects of exercise therapy versus control on quality-of-life scores

QOL Instrument	Mean Treatment Effect (95% CI)	P-value	Age- and Sex-Adjusted P-value
VEINES-QOL	+4.6 (0.54 to 8.7)	0.03	0.05
SF-36 Physical Component	+5.4 (0.5 to 10.4)	0.03	0.09
SF-36 Mental Component	+0.4 (-4.2 to 4.9)	0.87	0.68

Abbreviations: CI=confidence interval; QOL=quality-of-life; SF-36=Short Form 36-item Health Survey; VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire

Effect on Post-Thrombotic Syndrome Severity

The Villalta score was used to assess severity of post-thrombotic syndrome, and results are displayed in Table 30, demonstrating no change.

Table 30. Effect of exercise therapy versus control on post-thrombotic syndrome severity

Instrument	Mean Treatment Effect (95% CI)	P-value	Age- and Sex-Adjusted P-value
Villalta score	-2.0 (-4.6 to 0.6)	0.14	0.12

Abbreviation: CI=confidence interval

Compression Stockings versus Noninvasive Care (Placebo or Lymphedema Care)

Two RCTs assessed the use of compression stockings versus noninvasive care. These studies involved 66 patients. One RCT (rated poor quality due to incomplete reporting of methods) compared compression stockings (30-40 mmHg) to placebo stocking (1-2 sizes too large) over a duration of 2 years.[205] The other RCT (rated good quality) compared compression stocking therapy to a regimen of complex lymphedema therapy, which included compression stockings, over a duration of 3 months.[202] The mean age of study participants ranged from 48-49 years, with minimum and maximum of 18-82 years. The proportion of female patients was 42-60 percent. Racial and ethnic demographics of study participants were not reported. Both studies were single center; one was conducted in the United States and the other in Canada. Funding sources for the studies included government, nongovernment, and industry.

Effect on Patient-Reported Quality of Life

No improvement in pain or swelling or worsening symptoms (considered treatment failure) was seen in 61 percent of subjects treating with active stockings, compared to 59 percent of subjects treated with placebo stockings (p>0.99) in a study of 35 patients.[205] In the RCT of compression stockings versus complex lymphedema therapy, there also were no significant changes in VEINES-QOL or VEINES-QOL/symptom score within or between treatment arms (Table 31).[202]

Table 31. Effect of compression stockings versus noninvasive care on quality of life

QOL Instrument	Treatment	Baseline	1 month	3 months	P-Value, Baseline to 3 Months	P-Value, Between Treatments
VEINES-QOL score	Complex lymphedema therapy	51 ± 7	50 ± 6	50 ± 6	0.17	0.43
	Compression stockings only	49 ± 6	50 ± 6	50 ± 7	0.84	
VEINES-QOL/ symptom score	Complex lymphedema therapy	49 ± 7	49 ± 6	49 ± 7	0.55	0.96
	Compression stockings alone	51 ± 7	49 ± 8	50 ± 8	0.64	

Abbreviations: CI=confidence interval; QOL=quality-of-life; VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire

Effect on Post-Thrombotic Syndrome Severity

In the RCT of compression stockings versus complex lymphedema therapy, there were no significant between-group changes in post-thrombotic syndrome severity as measured by Villalta score (Table 32).[202]

Table 32. Effect of compression stockings versus noninvasive care on post-thrombotic syndrome severity

Instrument	Treatment	Baseline	1 month	3 months	P-Value, Baseline to 3 Months	P-Value, Between Treatments
Villalta score	Complex lymphedema therapy	9.9 ± 7.1	7.5 ± 4.7	7.6 ± 4.3	0.05	0.61
	Compression stockings alone	10.9 ± 5.3	8.9 ± 5.2	7.7 ± 6.2	0.03	

Compression Stockings versus Endovenous Stenting

One retrospective observational study assessed the use of endovenous stenting compared with compression therapy (30-40 mmHg) alone in post-thrombotic syndrome patients with iliofemoral obstruction with 3-month follow-up.[201] This study assessed 216 patients with moderate or severe post-thrombotic syndrome (Villalta score ≥10); approximately 40 percent in the stenting group and 44 percent in the compression therapy group had venous ulcers at baseline. The study was rated fair quality due to selection bias for patients in the group receiving compression therapy alone. The median age of patients was 44 years, ranging from 28 to 81 years. The proportion of female patients was 59 percent. Racial and ethnic demographics were not reported. The study occurred in a single center in Asia. Funding source of the study was government.

Effect on Post-Thrombotic Syndrome Severity

Post-thrombotic syndrome severity was assessed by Villalta score change before and after intervention. The median change in Villalta score among patients receiving endovascular stenting was +13 (range: 2-24), compared to median change of +9 for patients receiving compression therapy (range: 3-20) ($p<0.01$). Median pain score (range) as assessed by visual analog scale (0-10, 10 being the worst) and edema score (0-3, 3 being the worst) before and after treatment are displayed in Table 33.

Table 33. Effect of endovenous stenting versus compression therapy on edema and pain scores

Score	Endovenous Stenting	Compression Therapy	P-Value, Between Treatment Groups
Edema score before	3 (0-3)	3 (0-3)	0.212
Edema score after	1 (0-3)	1 (0-3)	0.070
Pain score before	7 (1-9)	6.5 (1-9)	0.13
Pain score after	3 (0-6)	4 (0-7)	0.007

Effect on Venous Wound Healing

Recurrence-free ulcer healing rates was 87 percent in the stenting group compared to 71 percent in the compression group ($p<0.01$). Data on ulcer size or new ulcers were not available.

Endovenous Procedures (Stenting and EVLA) Performed Alone versus Combination Endovenous Therapies (Stenting, EVLA, or Thrombolytics)

Three studies (all retrospective observational studies) assessed effectiveness of treating post-thrombotic syndrome/May-Thurner syndrome with endovenous management strategies. One study compared stenting to stenting with catheter-directed thrombolysis,[206] one compared EVLA alone to combined EVLA/stenting,[207] and another evaluated stenting alone (in patients with less evidence of obstruction) versus stenting combined with saphenous ablation (in patients with

greater evidence of obstruction).[208] Patients with venous reflux disease were further evaluated for obstruction with computed tomography angiography or transfemoral venography in patients with visible pelvic collateral veins or exercise-induced pain or edema,[207] IVUS,[208] or varying use of all these modalities, including additional use of MRI.[206] The studies included 419 patients, and follow-up ranged from 1-5 years. Two were rated fair quality and one was of poor quality due to comparison of interventions among varying subgroups of patients.[208] The mean age was 43-51 years in two studies,[206,207] and in another was presented as a median of 59 years.[208] Approximately 63 percent of all subjects were female. Race and ethnicity were not reported for any of the studies. Two studies were at single centers in the United States,[206,208] with unclear funding source, and another was a single center study in Asia with government funding source.[207]

Effect on LE Venous Hemodynamics

In the study assessing stenting with thrombolysis versus stenting alone, 58 percent (7/12) of chronic subjects receiving the combined treatment had patency of vein versus 100 percent (8/8) of subjects receiving stenting alone at 12 months as viewed by color flow on ultrasound.[206] In the study of combined EVLA and stenting versus EVLA alone, over 5.9 years follow-up, patients receiving combined therapy had deep venous reflux present on Doppler ultrasound from 51 percent at baseline to 35 percent post-treatment (p=0.254), and in patients receiving EVLA alone, deep venous reflux was present in 33 percent at baseline and 27 percent post-treatment (p=0.218).[207] Over the same follow-up and with Doppler ultrasound, superficial venous reflux disease prevalence improved from 58 percent to 10 percent (p<0.001) in the combined treatment group, and changed from 67 percent to 52 percent in the EVLA alone treatment group (p=0.099).

Effect on Patient-Reported Quality of Life

Quality-of-life changes were assessed in two of the studies.[206,207] For chronic subjects who received thrombolysis with stenting compared to stenting alone, quality of life was qualitatively assessed by whether symptoms worsened, stayed the same, or improved.[206] As demonstrated in Table 34, stenting alone improved pain and edema symptoms in a greater proportion of patients as compared to stenting plus catheter-directed thrombolysis (p-value NR).

Table 34. Effect of stenting plus catheter-directed thrombolysis versus stenting alone on quality of life

Outcome	Stenting plus Catheter-Directed Thrombolysis	Stenting Alone
Improved pain and edema symptoms	38%	75%
Stable/partially improved pain and edema symptoms	50%	25%
Worsened pain and edema symptoms	12%	0%

For 207 subjects who received stenting for concomitant superficial venous reflux disease at the time of EVLA for May-Thurner syndrome, pain and edema were assessed using the CIVIQ assessment components (Table 35).[207] Treatment effect comparisons were not reported, but EVLA plus stent did demonstrate a statistically significant decrease in pain and edema assessments (after vs. before treatment).

Table 35. Effect of stenting plus catheter-directed thrombolysis versus stenting alone on pain and edema

Outcome	EVLA + Stent			EVLA Alone		
	Before	After	P-Value	Before	After	P-Value
Pain (0-10)	4.92 ± 1.17	1.12 ± 0.88	<0.001	4.5 ± 1.57	3.37 ± 1.16	0.059
Edema (0-3)	2.17 ± 0.84	0.6 ± 0.7	<0.001	2.08 ± 1.0	1.52 ± 0.850	0.16

Abbreviations: EVLA=endovenous laser ablation

Effect on Venous Wound Healing

Venous wound healing was assessed by presence of ulcer before and after treatment for the stenting plus EVLA compared to EVLA alone study.[207] Among patients who received stenting plus EVLA, 16 percent had venous ulcer before treatment and 2 percent had ulcer at follow-up (p=0.001). Among patients receiving EVLA alone, 13 percent had venous ulcer before treatment and 6 percent had ulcer at follow-up (p=0.151).

In the study assessing endovenous stenting with and without EVLA, the saphenous vein was ablated if the refluxing saphenous vein was small or obstructive features were dominant.[208] All subjects had venous ulcers pretreatment. Among subjects who received combination therapy with EVLA and stenting, 78 percent had venous wound/ulcer healing, compared to 38 percent who had venous wound/ulcer healing with stenting alone (p-value NR).

Femorofemoral Vein Bypass versus Hybrid Reconstruction (Patch Angioplasty, Stent and Femoral Vein Endophlebectomy)

One retrospective study compared femorofemoral vein bypass (also known as Palma procedure) with hybrid reconstruction (endophlebectomy with patch angioplasty and stenting) for patients with post-thrombotic syndrome.[203] Subjects who had symptoms from DVT for at least 6 months and Villalta score of at least 5 met criteria for intervention, and they had follow-up for approximately 2.5 years. Overall, 34 patients included in the study received 1 of the 2 treatments (25 received vein bypass graft and 9 received the hybrid reconstruction). Fifty-seven percent were female. The mean age was 43 years, ranging from 16-81 years. Race and ethnicity of the patients were not provided. The study (rated good quality) was single center and took place in the United States. The funding source was not reported.

Effect on LE Venous Hemodynamics

The primary patency of the vein was assessed with ultrasound, computed tomographic venography, or MRV (based on last imaging available). In subjects who received the femorofemoral vein bypass procedure, the 5-year primary patency was 70 percent and secondary patency was 78 percent. In subjects who received hybrid reconstruction with endophlebectomy and patch angioplasty and stenting, the 2-year primary patency was 0 percent and secondary patency was 30 percent (p-value not reported).

Modifiers of Effectiveness

One RCT (good quality) and three retrospective studies (two fair quality and one poor) reported variations in treatment effectiveness by subgroup.[201-203,208] The RCT examined compression therapy versus complex lymphedema therapy (including compression stockings).[202] The retrospective studies examined EVLA versus EVLA with stenting,[208] endovenous stenting versus compression therapy,[201] and femorofemoral vein bypass versus hybrid reconstruction.[203]

Findings are summarized in Table 36. Subgroups analyzed included patients with severe baseline post-thrombotic syndrome,[201,202,204] use of compression stockings leading into and during study,[202,208] size of ulcer and severity of venous reflux at baseline,[208] and post-thrombotic syndrome patients with the additional diagnosis of May-Thurner syndrome.[203] Only patients with moderate to severe post-thrombotic syndrome at baseline experienced significant improvement with complex lymphedema therapy.[202] Only patients with severe post-thrombotic syndrome at baseline benefited from endovascular stenting.[201] In the study assessing complex lymphedema therapy versus compression stockings alone, the use of compression stockings prior to study initiation decreased the treatment effect for both compression stocking and complex lymphedema therapy arms.[202] Stockings were not seen to influence ulcer healing, but overall patients with smaller-sized ulcers have significantly higher rates of healing in the EVLA versus combined EVLA plus stenting study.[208] The diagnosis of May-Thurner syndrome in patients with post-thrombotic syndrome undergoing femorfemoral vein bypass had higher risk for losing venous patency postsurgery.

We found no studies reporting subgroup results by race, age, or sex. Given the heterogeneity of the subgroups, interventions and clinical outcomes, the SOE for modifiers of effectiveness was insufficient.

Table 36. KQ 3 findings for subgroups of interest

Study Population	Study Design N Analyzed Comparison Quality	Subgroup	Results Reported by Authors
Garg, 2011[203] Patients with obstruction of iliofemoral veins and inferior vena cava, using MRI, ultrasound, or computed tomographic venogram	Observational N=60 Femorofemoral vein bypass vs. endophlebectomy, patch angioplasty, stenting Fair	Diagnosis of May-Thurner Syndrome	Relative risk of secondary patency loss after femorofemoral vein bypass=6.7 (p=0.04).
Holmes, 2014[202] Patients with prior history of DVT and clinical diagnosis of post-thrombotic syndrome	RCT N=31 Complex lymphedema therapy vs. compression stockings only Good	Moderate or severe post-thrombotic syndrome Wearing compression stockings prior to study start	Improvement in severity versus mild post-thrombotic syndrome: Villalta score change -9.9 vs. 0.5, p=0.02 among complex lymphedema arm, and -7.8 vs. 01.7, p=0.08 among compression stocking arm. Overall, post-thrombotic severity decreased by -8.8 if not wearing, versus by -1.5 if wearing (p=0.07)

Study Population	Study Design N Analyzed Comparison Quality	Subgroup	Results Reported by Authors
Raju, 2013[208] Patients with venous ulcers who failed conservative therapy (CEAP 6), swelling and pain, and diagnosed obstruction with venography and IVUS	Observational N=192 EVLA vs. EVLA with endovenous stenting Poor	Compression stocking use after intervention Small (<500 mm^2) vs. Large (≥500 mm^2) ulcers	No difference in ulcer healing with and without stockings (% healed at 5 months: 65 vs. 59%, p=0.76; at 50 months: 80 vs. 71%, p=0.71) At 6 months, 86% of small ulcers had healed, vs. 23% of large ulcers
Yin, 2015[201] Patients with moderate or severe post-thrombotic syndrome with iliofemoral obstruction	Observational N=216 Endovenous stenting vs. compression stockings Fair	Post-thrombotic syndrome severity at baseline (moderate [Villalta score 10-14] and severe [Villalta score ≥15]) subgroups	Villalta score change, median (range): Moderate: stenting 7 (2-10) vs. compression 6 (3-9) (p=0.22); Severe: stenting 17 (15-24) vs. compression 12 (9-20) (p<0.01)

Abbreviations: CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; DVT=deep vein thrombosis; EVLA=endovenous laser ablation; IVUS=intravascular ultrasound; KQ=key question; MRI=magnetic resonance imaging; N=number of patients; RCT=randomized controlled trial

Safety Concerns

No adverse events were reported in the trial of exercise training in post-thrombotic syndrome patients.[204] About 62 percent of the patients attended 60 percent or more of the trainer sessions, and the mean number of trainer sessions attended was 9.5 of a maximum of 15 sessions. Reasons for not adhering to the regimen were not provided, and given the small size of the study, the safety and tolerability of exercise training in post-thrombotic syndrome are unknown. The overall rate of technical success in endovenous stenting without complications in patients with post-thrombotic syndrome was reported to be approximately 95 percent.[201] No major complications, including pulmonary embolism or perioperative deaths, were encountered. Among patients who had venous reconstruction (including both the femorofemoral vein bypass and hybrid reconstruction) and patients receiving EVLA and/or stenting in two retrospective studies, there were no deaths, pulmonary emboli, or deep venous thromboses associated with the procedures.[203,207] In the retrospective analysis of catheter-directed thrombolysis at the time of stenting for May-Thurner syndrome,[206] technical failures to deploy stents after thrombolysis (including hematemesis in one case) resulted in stopping the use of thrombolytic agents in the treatment of these patients mid-study. Safety data for compression stockings in patients with venous obstruction are not available.

None of the RCTs reported on whether any harms varied by subgroup (age, sex, race, risk factors, comorbidities). Therefore, the SOE for safety concerns is insufficient.

Strength of Evidence

Table 37 summarizes the strength of evidence for the findings described above.

Table 37. KQ 3: Strength of evidence for major outcomes—treatments for LE chronic venous thrombosis/obstruction, including post-thrombotic syndrome

Outcomes rated as low, moderate, or high strength of evidence are shaded in gray.

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Changes on standardized symptom scores (Intermediate-term) Insufficient	2 RCTs, 1 Obs: 287	Low	Direct	Inconsistent	Imprecise	None	In a good-quality RCT, the addition of exercise training to patient education versus patient education alone resulted in no difference in post-thrombotic syndrome severity (Villalta score).[204] In a good-quality RCT, complex lymphedema therapy (including compression stockings) vs. compression stockings alone resulted in no significant between-group changes in post-thrombotic syndrome severity (Villalta score).[202] In a fair-quality observational study, change in Villalta score was assessed in a study of endovenous stenting vs compression stockings. The median change in Villalta score among patients receiving endovascular stenting was +13 (range: 2-24), compared to a median change of +9 for patients receiving compression therapy (range: 3-20) ($p<0.01$).[201]
Changes on standardized symptom scores (Long-term) Insufficient	1 Obs: 20	High	Direct	NA	Imprecise	None	One fair-quality observational study of stenting with thrombolysis vs. stenting alone resulted in fewer patients with improved pain and edema symptoms (38% vs. 75%), and more patients with worsened pain and edema symptoms (12% vs. 0%) post-procedure (scale: improved, stable/partially improved, or worsened symptoms).[206]
Improvement in LE venous hemodynamics / reflux severity (Long-term) Insufficient	3 Obs: 226	High	Direct	Inconsistent	Imprecise	None	In a fair-quality observational study, stenting with thrombolysis vs. stenting alone resulted in no difference in US-assessed patency of stented vein at follow-up.[206] In a good-quality observational study, femorofemoral vein bypass vs. hybrid reconstruction (endophlebectomy with patch angioplasty and stenting) had higher 5-year primary (70% vs 0%) and secondary patency (78% vs 30%) as measured by last imaging available (US, CTV, or MRV).[203] In a fair-quality observational study, EVLA plus stenting resulted in significantly improved superficial venous reflux disease from pre- to post-treatment (58% to 10%, $p<0.001$) but not deep venous reflux disease (51% vs. 35%, $p=0.254$) measured by Doppler US. EVLA alone did not have

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
							statistical significance for superficial (67% vs. 52%, p=0.099) or deep (33% vs 27%, p=0.218) venous reflux disease.[207]
Patient-Reported QOL (Intermediate-term) Insufficient	2 RCTs: 74	Low	Direct	Inconsistent	Imprecise	None	In a good-quality RCT, the addition of exercise training to patient education vs. patient education alone resulted in unadjusted improvement in VEINES-QOL scores (mean treatment effect +4.6; 95% CI, 0.54 to 8.7; p=0.03) and SF-36 physical component score (mean treatment effect +5.4; 95% CI, 0.5 to 10.4; p=0.03), but not SF-36 mental component score.[204] In a good-quality RCT, complex lymphedema therapy (including compression stockings) vs. compression stockings alone resulted in similar, non-significant between-group differences in VEINES-QOL scores.[202]
Patient-Reported QOL (Long-term) Insufficient	1 Obs: 169	Medium	Direct	NA	Imprecise	None	In a fair-quality observational study of stenting for superficial venous reflux disease at the time of EVLA, the CIVIQ components of pain (0-10 scale) and edema (0-3 scale) were assessed. There was a significant reduction in pain (4.92 to 1.12, p<0.001) and edema (2.17 to 0.6, p<0.001) with EVLA plus stenting, but not with EVLA alone (pain: 4.5 to 3.37, p=0.059; edema: 2.08 to 1.52, p=0.16).[207]
Qualitative reduction in LE edema (Intermediate-term) Insufficient	1 Obs: 216	Medium	Direct	NA	Imprecise	None	In a fair-quality observational study, endovenous stenting vs. compression stockings resulted in no difference in edema score (VAS, 0-3) (p=0.07).[201]
Qualitative reduction in LE pain (Intermediate-term) Insufficient	1 Obs: 216	Medium	Direct	NA	Imprecise	None	In a fair-quality observational study, endovenous stenting vs. compression stockings resulted in better pain scores (VAS, 0-10) (p=0.007).[201]
Recurrent ulceration (Intermediate-term) Insufficient	1 Obs: 216	Medium	Direct	NA	Imprecise	None	In a fair-quality observational study of endovenous stenting vs. compression stockings, recurrence-free ulcer healing rate was 87% in the stenting group compared to 71% in the compression group (p<0.01).[201]

Outcome (Timeframe)	Studies (N and Design)						
Strength of Evidence	**N Patients**	**Study Limitations**	**Directness**	**Consistency**	**Precision**	**Reporting Bias**	**Findings**
Recurrent ulceration (Long-term) Insufficient	1 Obs: 169	Medium	Direct	NA	Imprecise	None	In a fair-quality observational study of stenting at the time of EVLA versus EVLA alone, patients receiving combined treatment had significant reduction in venous ulcer from baseline (16%) to follow-up (2%), p=0.001, but not patients receiving EVLA alone (13% to 6%, p=0.151).[207]
Venous wound healing (Long-term) Insufficient	1 Obs: 188	High	Direct	NA	Imprecise	None	In a poor-quality observational study of endovenous stenting with and without EVLA (in which EVLA occurred if obstructive features were dominant) in a population of patients with venous ulcers at baseline, the prevalence of venous ulcers post-treatment was 78% in the combination therapy group (i.e., reflux plus obstruction at baseline) and 38% in the group receiving only stenting (i.e., no predominant obstructive symptoms at baseline requiring ablation).[208]

Abbreviations: CIVIQ=Chronic Venous Insufficiency Questionnaire; CTV=computed tomography venography; EVLA=endovenous laser ablation; KQ=key question; LE=lower extremity; MRV=magnetic resonance venography; N=number; NA=not applicable; Obs=observational; Pts=patients/study participants; QOL=quality of life; RCT(s)=randomized controlled trial(s); SF-36=Short Form 36-item Health Survey; US=ultrasound; VAS=visual analog scale; VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review, we reviewed 136 articles representing 111 studies of diagnostic and treatment choices for patients with lower extremity chronic venous disease (LECVD). We summarize the key findings in Table 38, followed by a brief description for each KQ.

Table 38. Key Findings

Key Question	N Studies and Patients	Findings
KQ 1 Narrative Review of Diagnostic Methods and Criteria for Adult Patients with LECVD	10 observational studies involving 769 patients	• Very few comparative studies of diagnostic testing methods for LECVD in the recent literature, with the majority of the comparative studies of diagnostic testing methods for LECVD published prior to 2000 (and therefore not included in this review). • Extreme heterogeneity of patients, comparisons, and outcomes reported in the included diagnostic studies. • Insufficient evidence for any specific diagnostic test method for any of the outcomes studied.
KQ 2 Treatments for Adult Patients with LE Varicose Veins and/or LE Chronic Venous Insufficiency/ Incompetence/Reflux	93 studies (87 RCTs, 6 observational) involving 127,011 patients	• For comparisons between surgical and endovascular interventions: o No long-term difference in effectiveness between RFA and high ligation plus stripping, but RFA was associated with better short-term outcomes (≤30 days), such as less periprocedural pain (SOE=low), faster improvement in symptom scores (SOE=low), and fewer adverse events when compared with high ligation plus stripping (SOE=low). o No difference in effectiveness between EVLA and surgery, though EVLA was associated with less periprocedural bleeding (SOE=moderate). o No other significant differences in adverse events (SOE=low). o No difference in effectiveness between sclerotherapy and surgery (SOE=low). • For comparisons between EVLA and foam sclerotherapy, groups receiving EVLA and foam sclerotherapy both demonstrated improvement in quality-of-life scores and the Venous Clinical Severity Score, however there were no statistically significant differences in improvement between groups (SOE=low for intermediate-term outcomes). • Insufficient evidence to support findings for comparisons between EVLA and EVLA plus

Key Question	N Studies and Patients	Findings
		phlebectomy. • For comparisons between EVLA and endovenous radiofrequency: o Groups receiving EVLA and endovenous radiofrequency both demonstrated improvement in quality-of-life scores; however, there were no statistically significant differences in improvement between groups (SOE=low). o Both groups demonstrated improvement in the Venous Clinical Severity Score. There was a significant between-group difference in favor of the EVLA group in the short term (SOE=low). o The RFA group had statistically significantly less periprocedural pain and fewer occurrences of superficial venous thrombosis (statistically significant p-value) and deep venous thrombosis (p-value NR), when compared with the EVLA group (SOE=low). • Insufficient evidence to support findings for comparisons between different surgical interventions. The comparative effectiveness of surgical and hybrid procedures is limited by a low number of studies, inconsistency in the procedures utilized, and outcomes assessed. • For comparisons between medical therapy and placebo, there is limited evidence published since 2000 to suggest that pentoxifylline is effective relative to placebo for reducing venous ulcers (SOE=low). • Insufficient evidence to support findings all other comparisons.
KQ 3 Treatments for Adult Patients with LE Chronic Venous Thrombosis/ Obstruction	8 studies (3 RCTs, 5 observational) involving 804 patients	• KQ 3a, Effectiveness of interventions: Given overall variable study quality, inconsistent selection of endpoints, and small sample sizes, insufficient strength of evidence limits ability to make any conclusions regarding effectiveness of any of the studied interventions. • KQ 3b, Diagnostic methods: Post-thrombotic syndrome is diagnosed for the purpose of clinical studies through a variety of ways including patient symptoms standardized to a vein-specific quality-of-life score, imaging (most commonly ultrasound), or a combination of the two assessments. • KQ 3c, Modifiers of effectiveness: There was insufficient evidence to make any conclusions about modifiers of effectiveness of the comparators in the clinical trials.

Key Question	N Studies and Patients	Findings
		• KQ 3d, Safety concerns: Study design limitations do not allow for any conclusive findings regarding the safety of endovenous stenting in patients with post-thrombotic syndrome.

KQ 1: Narrative Review of Diagnostic Methods and Criteria for Adult Patients with LECVD

Our review of diagnostic testing methods for LECVD demonstrated that very few comparative studies exist in the literature published since 2000. Based on our investigative team's clinical expertise and our nonsystematic review of the literature prior to 2000, it is clear that after a complete medical history and physical examination, the use of diagnostic imaging is particularly important to confirm the diagnosis, determine the etiology and anatomy of the LE venous abnormality, and plan endovenous and/or surgical interventions for LECVD. Over time, duplex ultrasound (DUS) has supplanted invasive imaging modalities (e.g., ascending and descending phlebography or venography) as the primary choice for diagnostic testing in all adult patients with LECVD. While DUS was considered the gold standard comparison in the majority of included studies of this review, invasive phlebography/venography and surgical confirmation were also used as gold standards.

The studies evaluating diagnostic methods in patients with LECVD were, in general, heterogeneous, of fair quality, and had small sample sizes. The patients in the studies included asymptomatic and symptomatic patients, patients with LE varicose veins, LE chronic venous insufficiency/incompetence/reflux, LE venous ulceration, and LE chronic venous obstruction/thrombosis. Finally, the outcomes assessed varied across studies based on the location of the disease (e.g., great saphenous vein [GSV], popliteal vein, site of prior venous ligation). Due to these factors, no meta-analyses were performed on this group of studies.

The diagnostic modalities assessed in this narrative review include medical history and clinical examination, ambulatory plethysmography, DUS, magnetic resonance venography (MRV), computed tomography venography (CTV), and invasive phlebography or venography. Ten observational studies assessed these diagnostic methods in the evaluation of patients with LECVD.

In one included study,[73] ambulatory plethysmography was compared to DUS alone, DUS plus MRV, and DUS plus CTV. Sensitivity ranged between 35 percent and 64 percent and specificity ranged between 47 percent and 88 percent; however, the gold standard was unclear for this study, thus lowering the quality of this evidence. Another study evaluated ambulatory plethysmography as compared with DUS.[68] The sensitivity of ambulatory strain-gauge plethysmography was very low (4 percent in femoral and saphenous veins; 5 percent in popliteal veins), while specificity was 100 percent in both venous systems. In the Society of Vascular Surgery (SVS)/American Venous Forum (AVF) consensus guidelines, the selective use of ambulatory plethysmography for diagnosis of simple varicose veins (Clinical, Etiologic, Anatomic, Pathophysiologic [CEAP] class C_2) is GRADE 2C (weak recommendation; benefits are closely balanced with risks and burden based on low quality evidence), while its use in patients with advanced LECVD (CEAP class C_3-C_6) is GRADE 1B.[75]

Eight studies evaluated the use of DUS with various other imaging modalities (described below) in the diagnosis of LECVD.[65-68,70-72,74] There was significant heterogeneity in the populations studied and clinical indication for diagnostic testing, and limited conclusions can be drawn from these studies. Although there is limited evidence that it is an effective firstline test, the SVS/AVF consensus guidelines recommend the use of DUS as a ubiquitous imaging test for the diagnosis of patients with suspected LECVD (GRADE 1A, strong evidence -- benefits clearly outweigh the risks, burden, and costs based on high quality evidence).

One study[69] evaluated MRV versus another diagnostic modality (invasive venography and intravascular ultrasound [IVUS]) in the diagnosis of LE chronic venous obstruction. MRV was 100 percent sensitive for the diagnosis of proximal venous obstruction, but specificity was only 22.8 percent and the false-positive rate was 41.5 percent.

One study[67] evaluated CTV versus another diagnostic modality (DUS) in the diagnosis of LECVD. The sensitivity of CTV for the diagnosis of GSV insufficiency was 98.2 percent and small saphenous vein (SSV) insufficiency was 53.3 percent, while the specificity for GSV insufficiency was 83.3 percent and for SSV insufficiency was 94.9 percent.

Seven studies evaluated the use of invasive phlebography or venography with another imaging modality in the diagnosis of LECVD.[65,66,68-70,72,74] There was significant heterogeneity in the populations studied and clinical indication for diagnostic testing, and limited conclusions can be drawn from these studies. The SVS/AVF consensus guidelines recommend the use of invasive venography or phlebography in patients who are undergoing invasive treatment of LECVD (GRADE 1B). Adjunctive use of IVUS during invasive venography is also recommended in patients with suspected proximal chronic venous obstruction or post-thrombotic syndrome (GRADE 1B).

KQ 2: Treatments for Adult Patients with LE Varicose Veins and/or LE Chronic Venous Insufficiency/Incompetence/Reflux

Ninety-three studies (87 RCTs, 6 observational; 127,011 patients) were identified that assessed the effectiveness of exercise training, medical therapy, weight reduction, compression therapy, skin/wound care, endovenous intervention, and/or surgical intervention on functional outcomes, quality of life, and safety events in patients with LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux/ulcers.

Table 39 summarizes the SOE by treatment comparison within KQ 2 that were graded as low, moderate, or high. The most frequently reported endpoints included quality-of-life scores, Venous Clinical Severity Score (VCSS) scores, periprocedural pain, and rates of recurrence and re-intervention. Adverse events were reported in most studies, however, there was dramatic variation in which adverse events were reported in individual studies, thus limiting the ability to perform meta-analysis on these outcomes. Seven studies (6 RCTs, 1 observational) reported variations in the treatment effectiveness by subgroup including CEAP classification, severity of disease, age, anatomic segment affected, and presence of ulcer. There were no studies reporting results by the following subgroups: Race/ethnicity, sex, body weight, Villalta score, VCSS classification, and known malignancy.

Table 39. KQ 2: Summary strength of evidence for major outcomes

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Findings
Venous stripping plus ligation vs. radiofrequency ablation (RFA)		
Clinical Symptom Scores (VCSS) (Short-, Intermediate-, and Long-term) Low	3 RCTs: 356	For one study, the mean decrease in Venous Clinical Severity Score (VCSS) at 50 days follow-up was 5.1 (standard deviation [SD] 1.5) for RFA and 4.4 (SD 1.1) for surgery (p=0.19).[91] One study[97] reported mean VCSS scores at several time points but only found a significant difference, with lower symptoms scores in the RFA compared to high ligation plus stripping, at 3 days and 1 week postintervention. However, this difference was not apparent at 2-year follow-up (RFA 0.48, standard error [SE] 0.293, 0.69 vs. high ligation plus stripping 0.76 SE 0.60,1.0; p=not statistically significant [NS]).[97] A separate study reported mean VCSS scores at 3 years and also found no difference between groups (RFA mean 0.44, SD 1.82 vs. high ligation plus stripping mean 0.3, SD 1.5; p=NS).[98]
Reduction in LE Pain (Short- and Intermediate-term) Low	1 RCT: 60 1 RCT: NR	Two RCTs[98,189] reported less pain on a visual analog scale (VAS) in the RFA arms vs. surgery arms. One study[98] reported that mean VAS scores were lower in the RFA arm than the surgery arm, indicating less pain in the RFA group at 10 days' follow-up (RFA mean=1.21, SD 1.72 vs. surgery mean=2.25, SD 2.23; no p-value reported). The other study reported significantly lower cumulative VAS scores over 6 weeks in the RFA arm vs. surgery arm but did not indicate the number of time points included in the cumulative score.[189]
Adverse Events (Surgical Site Infection) (Short- and Long-term) Low	2 RCTs, 1 Obs: 2,850	Surgical site infection rates were higher in the ligation plus stripping groups compared to the RFA groups in all studies reporting this outcome. In a multinational study (80 patients), 5.6% of patients in the ligation plus stripping group and 0% of the patients in the RFA group experienced surgical site infections at 3 days postoperation.[97] A larger (190 patients) but poor-quality study reported three out of 90 patients who underwent surgery had a periprocedural surgical site infection, whereas none of the patients who underwent RFA had any procedure-related infections.[153] A retrospective observational study compared patients who underwent RFA (1,188 patients) to those who underwent any type of surgical correction for venous incompetence/varicose veins (ligation, ligation plus stripping, phlebectomy, or ligation plus excision) (2,580 patients). Those undergoing a surgical intervention had a higher rate of surgical site infection (adjusted OR 2.56; 95% CI 1.19-5.50; p=0.016).[131]
Adverse Events (Thrombophlebitis) (Short-, Intermediate-, and Long-term) Low	3 RCTs: 695	Two RCTS reported lower rates of superficial thrombophlebitis in the surgery group compared with the RFA group; in a poor-quality study, 6.8% of patients randomized to RFA vs. 0% of patients in surgery were found to have superficial thrombophlebitis,[153] whereas a good-quality study reported 9.9% of the RFA group vs. 4.2% of the surgery group had superficial thrombophlebitis (Fisher exact test p=0.006 across the four arms; no p-value reported for arm-to-arm comparison).[98] One study[91] reported one out of 15 RFA patients vs. zero out of 13 surgery patients reported an incidence of superficial thrombophlebitis at 3 years' follow-up.
Venous ligation plus stripping vs. EVLA		
Vein recurrence[a] Repeat intervention (Long-term) Low	5 RCTs: 1,261	Five studies evaluated long-term superficial thrombophlebitis.[98,105,117,126,152] The findings of these studies were imprecise and inconsistent demonstrating no difference in superficial thrombophlebitis between the two strategies (OR = 1.009, 95% CI = 0.686 to 1.484) (Figure 6)

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Findings
Improvement Hemodynamics Low	5 RCTs: 887	Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics.[84,94,117,126,152] The analysis suggested improvement in reflux/incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121) (Figure 7).
Clinical symptom scores (VCSS) Low	3 RCTs: 487	We synthesized three studies representing 487 patients for treatment effect on long-term VCSS score.[87,98,152] There was no significant difference between treatment strategies (standard difference in means = 0.021, 95% CI = -0.186 to 0.229) (Figure 8).
Clinical symptom scores (CEAP) Moderate	4 RCTs: 867	We also explored the CEAP after 12 months in 4 studies representing 867 patients.[101,117,121,139] No difference was found (standard difference in means = 0.061, 95% CI -0.096 to 0.219) (Figure 9).
Patient-Reported Quality of Life (EQ-5D) Low	4 RCTs: 1,436	Four studies[89,103,117,185] reported EuroQol 5D (EQ-5D) scores as an outcome at various time points postintervention. None of the studies reported a statistically significant difference between the surgery and EVLA groups at any time point.
Patient-Reported Quality of Life (AVVQ-Short-term) Low	4 RCTs: 583	We synthesized four studies representing 583 patients which evaluated short-term AVVQ effects.[103,105,139,185] These studies showed a -0.014 standardized difference in means (95% CI -0.340 to 0.311) showing no difference between strategies (Figure 10).
Patient-Reported Quality of Life (AVVQ-Intermediate-term) Low	4 RCTs: 426	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon.[105,139,168,185] Again there was no different in AVVQ scores (standard difference in means = -0.011, 95% CI 0-0.212 to 0.190) (Figure 11).
Patient-Reported Quality of Life (AVVQ-Long-term) Moderate	6 RCTs: 663	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ.[98,103,105,139,152,168] These studies also consistently found no difference between treatment strategies (standard difference in means = 0.063, 95% CI -0.122 to 0.247) (Figure 12).
Reduction in LE Pain Low	4 RCTs: 778	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale.[98,105,150,185] These studies demonstrated a -0.148 standardized difference in means (95% CI -0.531 to 0.236) showing no difference between treatment strategies (standard difference in means = -0.148, 95% CI -0.531 to 0.236) (Figure 13).
Adverse Events (Bleeding risk) Moderate	3 RCTs: 822	We were able to perform a meta-analysis on three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis).[120,121,152,186] This analysis demonstrated a statistically significant benefit of EVLA compared with surgery regarding reduction in bleeding risk (OR = 2.823, 95% CI = 1.324 to 6.022) (Figure 14).
Venous stripping plus ligation vs. sclerotherapy		
Vein recurrence[a] Low	3 RCTs: 395 1 RCT: 96 limbs	We synthesized evidence from 4 RCTs (3 RCTs with 395 patients, 1 RCT with 96 limbs) that explored long-term vein recurrence.[98,127,176,181] These studies did not demonstrate a difference between strategies (OR = 1.54, 95% CI 0.461 to 5.143) and were both inconsistent and imprecise (Figure 15).
Patient-Reported Quality of Life (AVVQ) Low	3 RCTs: 583	Three good-quality studies[88,89,98,127] reported AVVQ as an outcome at various time points ranging from baseline to three years follow-up. All studies showed decreased scores at follow-up, indicating an improvement in symptom scores but no difference between groups.

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Findings
Patient-Reported Quality of Life (EQ-5D) Moderate	3 RCTs: 900	We synthesized evidence from 3 RCTs (900 patients) that explored the long-term change quality of life as measured by EQ-5D.[88,89,117,118] These studies did not demonstrate a difference between strategies (difference in means = 0, 95% CI -0.028 to 0.029) (Figure 16).
Reduction of LE Pain Low	3 RCTs: 1,498 1 RCT: NR	Four RCTs[88,89,98,187,199] reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies[98,187,199] reported significantly lower pain scores in the sclerotherapy group when compared with the surgery group.
Adverse Events (Hematoma) Low	3 RCTs: 1,142 1 RCT: 96 limbs	We synthesized evidence from 4 RCTs (3 RCTs with 1,142 patients, 1 RCT with 96 limbs)[82,146,176,187] that explored hematomas as an outcome of interest. These inconsistent and imprecise studies did not demonstrate a difference between strategies (OR = 1.010, 95% CI 0.245 to 4.163) (Figure 17).
EVLA vs. sclerotherapy		
Changes on standardized symptom scores (Intermediate-term) Low	2 RCTs: 885	VCSS improved in both groups. No statistically difference between groups.[89,114]
Patient-Reported QOL (Intermediate-term) Low	2 RCTs: 885	There was a significant between-groups difference regarding effect size in adjusted data of AVVQ at 6 weeks (p=0.032). There was a significant between-groups difference regarding median within group change of AVVQ at 3 months (p=0.01) both demonstrating a benefit of EVLA.[89,114]
Patient-Reported QOL (Long-term) Low	2 RCTs: 580	QOL improved in both group. No statistically difference between groups.[98,114]
Qualitative reduction in LE pain (Short-term) Low	2 RCTs: 885	The foam sclerotherapy group reported less pain versus the EVLA group at 10 days (1.60 versus 2.58, respectively). There was a significant between-groups difference in pain in favor of foam sclerotherapy group at 07 days (p=0.005).[89,114]
EVLA vs. RFA		
Bleeding (Short-term) Low	2 RCTs: 249 1 Obs: 979 limbs	According to Shepherd et al., the number of patients with hematoma was 2 in EVLA group and was 0 in RFA group. According to the observational study (Obi) the number of patients with hematoma was 45 in EVLA group and 5 in RFA group. There was a significant between-groups difference regarding hematoma in favor of RFA group (p=<0.001).[122,123,125,154] Gale et al. reported the number of patients with bruising at 1 week. There was a significant more bruising in the EVLA group at 1 week (p=0.01).[154]
Changes on standardized symptom scores (Short-term) Low	2 RCTs: 205 1 Obs: 979 limbs	VCSS improved in both group. Demonstrating statistically difference in favor of EVLA group.[125,154,163]

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Findings
Changes on standardized symptom scores (Intermediate-term) Low	3 RCTs: 336	VCSS improved in both group. No statistically difference between groups.[122,123,154,163]
Changes on standardized symptom scores (Long-term) Low	2 RCTs: 249	VCSS improved in both group. No statistically difference between groups.[122,123,154]
Patient-Reported QOL (Short-term) Low	3 RCTs: 372	QOL improved in both group. No statistically difference between groups.[122,123,149,163]
Patient-Reported QOL (Intermediate-term) Low	4 RCTs: 490	QOL improved in both group. No statistically difference between groups[122,123,149,154,163]
Qualitative reduction in LE pain (Short-term) Low	2 RCTs: 285	Demonstrating statistically significance difference between groups in favor of RFA arm (p=0.001). At 7 days the median pain was 13,5 in the EVLA group and was 0 in the RFA group. RFA showed better improvement of pain score than the EVLA group at 10 days (-12.3 versus -6.3, respectively). There was a significant between-groups difference at 10 days (p=0.01).[122,123,149]
Endovascular treatment vs. placebo		
Changes on standardized symptom scores (Intermediate-term) Moderate	3 RCTs: 621	Two good-quality RCTs[124,141] demonstrated a statistically significance difference of VCSS in favor of 0.5% polidocanol endovenous group (p<0.0001) and 1% polidocanol endovenous group (p<0.0001) when compared with placebo group. Three good-quality studies[124,141,193] also reported Varicose Veins Symptoms Questionnaire (VVsymQ) or modified VEINES-Sym (m-VEINES-Sym) scores at 8 weeks. After converting to effect sizes, the summary effect of these studies demonstrated a statistically significant standardized difference in means of 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 18).
Improvement in LE venous hemodynamics/reflux severity (Intermediate-term) Moderate	3 RCTs: 465	Absence of reflux: In two RCTs, there was a significant between-groups difference in favor of 0.5% polidocanol endovenous group (p=0.00043) and 1% polidocanol endovenous group (p=0.0009) when compared with placebo group. In the second RCT, there was a significant between-groups difference in favor of pooled (0.5%, 1% and 2%) polidocanol endovenous group (p<0.001) when compared with of 0.125% polidocanol endovenous group. In a third RCT, in the foam sclerotherapy group the number of patients with occlusion was 11 at 4 weeks. In the placebo group the number of patients with occlusion was 0 at 4 weeks.[124,141,174]
Patient-Reported QOL (Intermediate-term) Moderate	3 RCTs: 621	The three good-quality RCTs[124,141,193] presented mean within-group changes for the modified or unmodified Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire (mVEINES-QOL and VEINES-QOL) scores at 8 weeks for each group. The summary effect of these studies was a statistically significant standardized difference in means of 0.81 (95% CI, 0.57 to 1.05) favoring 1% polidocanol (Figure 19).

Outcome (Timeframe) Strength of Evidence	Studies (N and Design) N Patients or Limbs	Findings
Invasive surgery vs. invasive surgery		
Qualitative reduction in LE pain (Short-term) Low	1 RCT: 40 1 RCT: NR	**High ligation/stripping vs. High ligation/cryostripping**[169]–No significant difference between procedures at 24 hours. **High ligation/stripping vs. High ligation/cryostripping**[172]**–**No significant difference between procedures at 7, 14, and 28 days.
Invasive surgery vs. compression		
Death (Long-term) Low	2 RCTs: 526 1 RCT: 196 limbs	**High ligation/stripping vs. compression**[108,111]–16 percent in the surgery group versus 19 percent in the compression group (p=0.245) at 3 years. **High ligation/stripping vs. compression**[191]–No deaths in either group over 6 months. **High ligation/stripping/SEPS vs. compression**[112,113]–A total of 23 patients died within 28 months; these patients contributed 8 limbs to the surgical group and 17 to the compression group (both legs were randomized for 2 patients), p=NR.
Improvement in LE venous hemodynamics/reflux severity (Intermediate-term) Low	2 RCTs: 258	**High ligation/stripping vs. compression**[108,111]–Number of legs with incompetent calf perforating veins dropped from 51 to 41 percent at 3 months among surgery patients (p<0.001), but increased from 42 to 46 percent among compression patients (p=0.144). No between-group comparison reported. **CHIVA vs. compression**[175,190]–By 6 months, venous volume, venous filling index, and residual volume fraction improved significantly in the CHIVA group (all p<0.001); no improvements observed in the compression group. No between-group statistical comparisons reported.
Recurrent Ulceration (Long-term) Low	2 RCTs: 127 1 RCT: 196 limbs	**High ligation/stripping vs. compression**[108,111]–Recurrence rate was 12 percent in the surgery group versus 28 percent with compression alone (p<0.0001). **High ligation/stripping/SEPS vs. compression**[112,113]–At long-term follow-up, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression (p=NR). **CHIVA vs. compression**[175,190]–A significantly higher number of patients in the compression arm (9 out of 24 patients) had recurrent ulcerations compared to 2 out of 27 surgery patients (p≤0.005).

[a] Vein recurrence refers to the establishment of patency of the venous system; such recurrence often requires repeat intervention.
Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CEAP=Clinical, Etiologic, Anatomic, Pathophysiologic; CHIVA= Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; CI=confidence interval; CIVIQ-2=Chronic Venous Insufficiency Questionnaire-2; DVT=deep vein thrombosis; EQ-5D=EuroQol 5D; EVLA=endovenous laser ablation; GSV=great saphenous vein; KQ=key question; LE=lower extremity; N=number; OR=odds ratio; QOL=quality of life; RCTs=randomized controlled trials; RFA=radiofrequency ablation; SD=standard deviation; SEPS= subfascial endoscopic perforating vein surgery; SF-36=Short-Form 36-item survey; SOE=strength of evidence; VAS=visual analog scale; VCSS=Venous Clinical Severity Score; VEINES-QOL=Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire

KQ 3: Treatments for Adult Patients with LE Chronic Venous Thrombosis/Obstruction

Eight studies (3 RCTs, 5 observational; 804 patients) were identified that assessed the effectiveness of exercise training, medical therapy, weight reduction, compression therapy, skin/wound care, endovenous intervention, and/or surgical intervention on functional outcomes, quality of life, and safety events in patients with LE chronic venous obstruction/thrombosis. Studies that assessed individual treatment modalities or combinations of treatment modalities were analyzed, however differences in the treatment comparisons, outcome measures, and follow-up time points eliminated the possibility that study results could be pooled for analysis of direct comparisons. There were no studies reporting results by the following subgroups: Age, race/ethnicity, sex, body weight, CEAP classification, VCSS classification, severity of disease, anatomic segment affected, presence of ulcer, and known malignancy.

Unfortunately given the small number of studies, heterogeneity in outcomes and interventions assessed, diverse populations evaluated, and inconsistency in findings, the evidence was insufficient to support any findings.

Findings in Relationship to What is Already Known

The SVS/AVF have published a comprehensive set of consensus guidelines on LECVD,[75] and venous ulcers,[77] and the United Kingdom's (UK's) National Institute for Health and Care Excellence (NICE) has published a clinical guideline on varicose veins.[78]

For KQ 1, which addresses the diagnostic modalities used in patients with LECVD, our findings offer little in addition to the SVS/AVF guidelines as very few comparative studies exist in the published literature since 2000. There was insufficient evidence to confirm or refute the recommendation to perform DUS for confirmation of LECVD or to plan invasive intervention.

For KQ 2, which addresses treatment strategies for patients with LE varicose veins and LE chronic venous insufficiency/incompetence/reflux, our findings are consistent with the SVS/AVF and NICE guidelines. For surgical intervention (ligation plus stripping) versus endovenous intervention (radiofrequency ablation [RFA], endovenous laser ablation [EVLA], endovenous steam ablation [EVSA], or sclerotherapy), our findings were similar to findings in the NICE systematic review showing no significant differences between treatment modalities for the following outcomes: quality of life, VCSS score, and rates of recurrence and re-intervention.

For KQ 3, which addresses treatment strategies for patients with LE chronic venous thrombosis/obstruction, no clinical guidelines exist in the literature and very few topic reviews exist. With only 8 relevant studies included in this systematic review, there is insufficient evidence to make clear recommendations regarding treatment options. With low SOE (due to a single RCT with small sample size), patients with post-thrombotic syndrome appear to benefit from an exercise training program based on a statistically significant improvement in quality of life and a non-statistically significant improvement in Villalta symptom score.[204]

Challenges in Evaluating the Existing Literature in LECVD Patients

Comparing diagnostic and treatment choices in patients with LECVD has the following challenges:

- *Population differences*: Inclusion and exclusion criteria have varied among studies, and stratification based on symptom status (specifically LE varicose veins, LE chronic venous insufficiency, both) is important but lacking. Furthermore, very few studies evaluated a cohort of patients with LE chronic venous obstruction/thrombosis, and most studies established a cohort of patients with acute DVT and followed these patients long-term. These studies were excluded from the current systematic review.
- *Evolution in interventional techniques:* Improvements specifically in endovenous techniques have made comparisons between treatment strategies more challenging. We were unable to account for these differences.
- *Endpoint differences*: These differences include variable reporting of functional and quality of life endpoints and adverse events in the evaluation of patients with LECVD. This prohibited the quantitative analysis of study results for multiple treatment comparisons.
- *Descriptive characteristics of included patients:* Very few studies included descriptive characteristics of diagnostic testing or disease severity (e.g., CEAP classification) to guide inclusion of patients or determine modifiers of effectiveness of various treatments.
- *Length of follow-up*: Study follow-up was heavily weighted towards short-term follow-up, and there was variable reporting of duration of follow-up. While study outcomes were grouped into short-, intermediate-, and long-term follow-up, this prohibited the quantitative analysis of study results for multiple treatment comparisons and multiple timepoints.
- *Study design*: While a significant number of RCTs exist in LECVD, many did not properly document/ensure allocation concealment and blinding of outcomes assessors. Additionally, especially among studies of surgical and endovenous interventions, few studies employed patient blinding (sham procedures). This resulted in an overall increase in the likelihood of bias within the literature.

Applicability

We used 2000 as the start date for the literature search to improve the applicability of the findings to current clinical practice. In doing so, we acknowledge that earlier comparative studies of diagnostic modalities and treatment choices were not included in this review. Including older studies with outdated gold standards for diagnostic methods (e.g., ascending and descending phlebography) may have biased the results against an accepted standard (DUS). Including older studies with suboptimal background therapy (e.g., compression therapy) may have biased the results of endovenous and/or surgical intervention to favor active treatment over suboptimal usual care treatment.

In the analysis of all patients with LECVD, the majority of studies were single-center studies conducted outside of the United States. There were no studies that specifically evaluated the role of new or novel diagnostic tests in patients with LECVD. There were also no studies that specifically evaluated the role of long-term medical therapy (e.g., oral anticoagulants) in patients with LE chronic venous obstruction/thrombosis.

Table 40 shows the potential issues with applicability in included studies of patients with LECVD.

Table 40. Potential issues with applicability of included studies

Issues	KQ 1 N=10	KQ 2 N=93	KQ 3 N=8	Total N=111
Population (P)				
Narrow eligibility criteria and exclusion of those with comorbidities	0	4	1	5
More complex patients than typical of the community	0	1	1	2
Run-in period with high exclusion rate for non-adherence or side effects	0	2	0	2
Narrow or unrepresentative severity, stage of illness, or comorbidities	0	4	0	4
Intervention (I)				
Diagnostic tools used differently than as recommended or commonly used in practice	0	1	0	1
Dosing not reflective of current practice	0	2	0	2
Co-interventions that are likely to modify the effectiveness of therapy	0	12	2	14
Highly selected intervention team or level of training/proficiency not widely available	0	5	1	6
Follow-up not reflective of current practice	0	4	1	5
Comparator (C)				
Diagnostic tools used differently than as recommended or commonly used in practice	0	1	0	1
Comparator unclear	0	2	1	3
Inadequate comparison therapy or use of a substandard alternative therapy	0	1	1	2
Outcomes (O)				
Composite outcomes that mix outcomes of different significance	0	3	0	3
Short-term follow-up	0	25	0	25
Surrogate outcomes	0	8	0	8
Timing (T)				
Duration of participant follow-up was inadequate	0	15	1	16
Setting (S)				
Study conducted solely outside the United States	6	85	4	95
Study was conducted only at a single site	7	50	7	64

Abbreviation: KQ=key question

Implications for Clinical and Policy Decisionmaking

LECVD is an increasingly prevalent condition in the United States due to an aging and obese population. There is a significant need for comparative safety and effectiveness studies due to the increasing prevalence, multiple potential treatment options, and high costs to the healthcare system. The current analysis provides an important evidence review that must be put in context with current clinical practice so that it may inform both future research and clinical and policy decisionmaking.

The findings for diagnostic testing in LECVD add little to the argument that noninvasive imaging costs are substantial and continue to rise for patients with this condition. However, given the low sensitivity of ambulatory plethysmography and the general acceptance of DUS as the gold standard, it seems reasonable to concede that DUS is an acceptable first diagnostic test for LECVD. An unanswered research question for diagnostic testing remains, Which patients

warrant testing? The answer to this question (and multiplier for cost analyses) will drive overall costs to the healthcare system.

Regarding the treatment of patients with LE varicose veins and LE chronic venous insufficiency/incompetence/reflux, this review found that several therapies—surgical intervention, endovenous intervention, and compression therapy—were effective at improving functional measures and quality-of-life measures. In patients with symptomatic LE chronic venous insufficiency/incompetence/reflux, the current findings that endovenous intervention is associated with less periprocedural pain and complications when compared with surgical intervention (e.g., high ligation plus stripping) reinforces that this should be first line therapy. A major concern is the lack of data to support guidelines' recommendations for the treatment of patients with lower CEAP scores (C_1 and C_2), as the prevalence of asymptomatic disease drives costs. Additionally, with increasing innovation of endovenous intervention, more contemporary, well-performed multicenter RCTs and registry analyses of actual utilization are needed to determine efficacy and effectiveness. Finally, whether the treatments studied are cost effective was beyond the scope of this review.

Regarding treatment of patients with chronic obstruction/thrombosis, this review highlights the lack of evidence the guide long-term oral anticoagulant use in these patients. Many such patients are being under-treated (3 months) while other patients are being treated with lifelong anticoagulants. With novel oral anticoagulants, particularly the patients in the lifelong treatment group has huge implications for payers. Additionally, the diagnostic testing strategy for these patients is extremely varied and needs to be understood before treatment is begun. Patients with iliofemoral DVT should be treated differently if the patient has proximal venous obstruction versus not. Finally, since endovenous intervention for iliofemoral DVT is becoming more common and the use of thrombolytics in this group has increased, there is a need for effectiveness data (but more importantly safety data) for this approach.

Limitations of the Systematic Review Process

The current review was limited to English-language–only studies and focused on those that compared two treatment modalities. After full-text review, we noted that there were 86 RCTs in KQ 2 (assessment of LE chronic venous insufficiency/incompetence/reflux), and after discussion with our Agency for Healthcare Research and Quality (AHRQ) Task Order Officer, we then abstracted data from large observational studies (N=4) for this KQ that reported outcomes in >500 patients. As such, the findings for KQ 2 are biased towards randomized comparisons, and it is possible that information from observational studies would have provided additional information for this population. Note that the update of the final report added nine additional studies (three to KQ 1 and six to KQ 2).

There are several other limitations to the available evidence for the treatment of LECVD. First, many treatment comparisons are within similar treatment modalities (i.e., endovenous therapy with compound A versus compound B, surgery with technique A versus technique B). While these comparisons may be meaningful, there is a significant need for treatment strategy studies (i.e., study of compression therapy prior to endovenous and/or surgical intervention). Specifically, we were not able to assess the effectiveness of treatment strategies that were delivered if another modality had a suboptimal result or failed. Many studies did not designate whether subjects were asymptomatic or symptomatic (especially those studies including patients undergoing treatment for varicose veins where the patients may have perceived symptoms despite not having classic symptoms such as pain, paresthesia, or heaviness). Furthermore, the

literature did not fully address whether patients with varicose veins only (i.e., no reflux) should be treated differently than patients with more severe forms of venous insufficiency/incompetence/reflux. The literature was also insufficient to allow complete evaluation of patients with multiple venous issues (e.g., varicose veins, venous insufficiency, and venous obstruction/thrombosis) as many patients have multiple components of this disease.

Regarding endpoints, there are numerous and heterogeneous measures reported, often with no clearly agreed upon definitions for patients with LECVD. The time points for follow-up are variable and often the ascertainment is not standardized. Finally, there are little data on important subgroups of harms.

Research Recommendations

The current literature search for LECVD revealed many single-center studies that were conducted outside of the United States. Very few multicenter, multinational studies were found during this systematic review. From the studies that were included, there was a notable variation in (1) outcome measures used to assess procedural success, symptom status, and quality life, (2) follow-up assessment time points, and (3) type of outcomes reported (i.e., surrogate and hard clinical endpoints). Therefore, there are numerous areas of evidence gaps and areas for potential future research in LECVD. An improvement in the methodology of upcoming trials in these areas will increase the strength of evidence of the findings. Specifically, measuring outcomes that are (1) important to patients (e.g. quality of life, patient perception) and (2) able to be collected within the context of clinical care (e.g. office practice) will be imperative to improve the clinical care of these patients. We note that there are a number of trials planned, ongoing, or pending publication investigating diagnostic imaging and/or treatment modalities for LECVD, which upon completion may provide valuable data to address some of the identified gaps.

KQ 1 Research Gaps

For KQ 1, the primary limitation of the available evidence was the low number of studies that directly compared diagnostic treatment modalities. While clinical practice has shifted in favor of using DUS as the gold standard for diagnosis of LECVD, assessment of severity and location of disease, and preparation for invasive treatment, the study of existing diagnostic technology and novel technology needs further investment and investigation. Furthermore, as endovenous intervention is performed more frequently, the study of periprocedural noninvasive imaging and invasive imaging to establish appropriate use criteria and best clinical practices for which patients should be imaged/studied and how they should be imaged/studied is needed.

KQ 2 Research Gaps

Due to conceptual heterogeneity in design of the available studies (compression therapies utilized, surgical and endovenous interventions utilized, outcomes selected, outcome definitions, outcome timing, and analytic/statistical approaches) and a general paucity of studies pertaining to most comparisons, there is a general need for high-quality, adequately powered comparative effectiveness studies of “best practice” procedures using standardized consensus outcomes at clinically-relevant timepoints. Additionally, there is a paucity of studies investigating efficacy and safety in clinical and socioeconomically important subgroups such as anatomic subclasses, CEAP subclasses, and women. As a result, future studies will also need to incorporate subanalyses of these important subgroups.

In terms of the heterogeneity of the studies, the primary limitation of the available evidence for treatment of patients with LE chronic venous insufficiency/incompetence/reflux was the heterogeneity of outcomes assessing functional and quality of life measures for this KQ. Furthermore, while mechanical compression therapies are routinely used postoperatively as an adjunct to invasive interventions for the treatment of LE chronic venous insufficiency/incompetence/reflux and for treatment of venous ulceration, there is little evidence to inform decisions about which of the many types of compression therapies to prescribe or the optimal dosing and duration of compression therapy for chronic venous insufficiency with or without venous ulcers.

Lastly, with the profusion of available treatment strategies (surgery, endovascular intervention, hybrid intervention, compression therapy, and medical therapy) future studies of the comparative effectiveness of these treatment strategies will be necessary to guide clinicians and patients.

KQ 3 Research Gaps

For KQ 3, the primary limitation of the available evidence was the low number of studies that directly compared treatment options in patients with LE venous obstruction/thrombosis. Few high-quality studies exist comparing the available treatment options that are routinely used in clinical practice in the United States (e.g., long-term oral anticoagulation, iliac and inferior vena cava angioplasty and stenting, thrombolysis) making the evidence base insufficient for the comparative effectiveness of these interventions and highlighting the need for future studies. Additionally, the literature on patients being treated for LE chronic venous thrombosis is extremely sparse, as most cohorts have been established at the time of acute deep vein thrombosis (DVT) and have not studied patients at intermediate- or long-term timepoints. More RCTs or prospective cohort studies with assessment of functional capacity, quality of life, and additional venous outcomes (e.g., severity of edema, severity of reflux, wound healing) are needed.

Underreporting of Subgroup Results across All KQs

Across all KQs, the underreporting of results for subgroups that may modify the comparative effectiveness was common. Given the limited space in publications, it would be helpful to have online, supplementary appendices that report the outcomes by age, race, sex, venous symptom severity, and comorbidities. The representation of women and the reporting of race/ethnicity were also low in these studies. Future studies that oversample for women and minority populations are needed to address subpopulation questions.

Conclusions

The available evidence for treatment of patients with LECVD is limited by heterogeneous studies that provide comparisons of multiple treatment options, varied outcomes measured, and disparate timepoints of outcome assessment. In addition, surrogate outcomes are often reported and patient-reported outcomes are infrequently measured despite the fact that the American Venous Forum guidelines give measurement of patient-reported outcomes a Class 1B recommendation. Very little comparative effectiveness data has been identified to study new and existing diagnostic testing modalities for patients with LECVD. Several advances in care in endovenous interventional therapy have not been rigorously tested, and very few studies on

conservative measures (e.g., lifestyle modification, compression therapy, exercise training) exist in the recent literature published since 2000. Additionally, the potential additive effects of many of these therapies are unknown. The presence of significant clinical heterogeneity of these results makes conclusions for clinical outcomes uncertain and provides an impetus for further research to improve the care of patients with LECVD.

Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AV	Arteriovenous
AVF	American Venous Forum
AVP	ambulatory venous pressure
AVVQ	Aberdeen Varicose Vein Questionnaire
AVVSS	Aberdeen Varicose Vein Severity Score
CA	Cyanoacrylate
CCVUQ	Charing Cross Venous Ulcer Questionnaire
CEAP	Clinical, Etiologic, Anatomic, Pathophysiologic
CHIVA	Cure conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire
CI	confidence interval
CIVIQ	Chronic Venous Insufficiency Questionnaire
CIVIQ-2	Chronic Venous Insufficiency Questionnaire-2
CIVIQ-20	Chronic Venous Insufficiency Questionnaire-20
CMS	Centers for Medicare and Medicaid Services
CTV	computed tomography venography
DUS	duplex ultrasound
DVT	deep vein thrombosis
EHC	Effective Health Care
EHIT	endovascular heat-induced thrombosis
EMA	endovenous microwave ablation
EQ-5D	EuroQol 5D
EQ-5D-3L	EuroQol 5D 3L
EQ VAS	EuroQol Visual Analogue Scale
EVLA	endovenous laser ablation
EVLA ABK	endovenous laser ablation above and below the knee
EVLA AK	endovenous laser ablation above the knee
EVSA	endovenous steam ablation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSV	great saphenous vein
HR	hazard ratio
ICTRP	International Clinical Trials Registry Platform
IQR	interquartile range
IVUS	Intravascular ultrasound
KQ(s)	key question(s)
LE	lower extremity
LECVD	lower extremity chronic venous disease
MOCA	mechanochemical endogenous ablation
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
MVO	maximum venous outflow
Nd:YAG	neodymium-doped yttrium aluminum garnet

NR	not reported
NS	not statistically significant
OR	odds ratio
PAD	peripheral artery disease
PE(s)	pulmonary embolism(s)
PEM	polidocanol endovenous microfoam
PICOTS	populations, interventions, comparators, outcomes, timing, settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT(s)	Randomized controlled trial(s)
RFA	radiofrequency ablation
SD	standard deviation
SE	standard error
SEPS	subfascial endoscopic perforating vein surgery
SF-12	Short Form 12-item Health Survey
SF-36	Short Form 36-item Health Survey
SOE	strength of evidence
SSV	small saphenous vein
STS	Saphenous Treatment Score
SVS	Society of Vascular Surgery
TEP	technical expert panel
UK	United Kingdom
VAS	visual analog scale
VCSS	Venous Clinical Severity Score
VDS	Venous Disability Score
VEINES-QOL	Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire
VRT	venous refilling time
VSDS	Venous Segmental Disease Score
VTE	chronic venous insufficiency/incompetence
VVSymQ	Varicose Veins Symptoms Questionnaire
WHO	World Health Organization

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