

# Technology Assessment



## Technology Assessment Program

***Prepared for:***

**Agency for Healthcare  
Research and Quality  
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# Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)

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Authors' Names [to be provided in Final Report]

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States.

The Centers for Medicare and Medicaid Services (CMS) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: (INSERT EPC NAME) Evidence-based Practice Center (Contract Number: (INSERT CONTRACT NUMBER)).

The report will be presented at the CMS public meeting – MEDCAC on July 20, 2016.

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Andrew Bindman M.D.  
Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman M.D., M.S.  
Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Aysegul Gozu MD, MPH  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Elise Berliner, PhD  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

# 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<sup>®</sup>, Embase<sup>®</sup>, and the Cochrane Database of Systematic Reviews for relevant English-language studies published since January 1, 2000.

**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 103 studies contributed evidence. Seven observational studies evaluated the comparative effectiveness of diagnostic testing modalities in a heterogeneous population of patients with LECVD. In addition to the history and physical, multiple physiologic and imaging modalities (plethysmography, duplex ultrasound [DUS], magnetic resonance venography, computed tomography venography, invasive venography, and phlebography) 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 DUS be used as the first-line diagnostic test for patients being evaluated for LECVD and/or who are planned for invasive treatment. Eighty-eight studies (84 randomized controlled trials [RCTs], 4 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 (LE) 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 when compared with high ligation plus stripping. Among patients undergoing endovenous interventions, those undergoing RFA, endovenous laser ablation (EVLA), and sclerotherapy demonstrated improvement in quality-of-life scores and standardized symptom scores. Patients treated with foam sclerotherapy had significantly less periprocedural pain but lower rates of vein occlusion and higher rates of repeat intervention when compared with patients treated with EVLA. Patients treated with RFA had significantly less periprocedural pain but less short-term improvement in venous chronic severity score when compared with patients treated with EVLA. When compared with placebo, patients who underwent foam sclerotherapy had statistically significant improvements in Venous Clinical Severity Score (VCSS), occlusion rates, and quality of life. Patients treated with compression therapy had significant improvements in standardized symptom scores and quality of life when compared with patients treated with placebo or no compression therapy. Eight studies (three RCTs, five observational) evaluated the

comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention in patients with LE chronic venous obstruction/thrombosis. In patients with post-thrombotic syndrome, exercise training plus patient education and monthly phone followup resulted in improved quality of life but not improved symptom severity when compared with patient education and monthly phone followup. In patients with both May-Thurner Syndrome and superficial venous reflux who were undergoing EVLA, stent placement at the time of EVLA resulted in less recurrent ulceration, improvement in reflux severity and symptoms, and improvement in quality of life in long-term followup. In patients with chronic proximal iliac vein obstruction, catheter-directed urokinase treatment at the time of endovenous stenting 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. Despite reporting of safety endpoints in many studies, the heterogeneity of definitions and timepoints precluded the quantitative analysis of safety endpoints in the majority of cases.

**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. Very limited comparative effectiveness data have been generated 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 contemporary literature. 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, 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup>

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.<sup>5</sup> 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 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 (Clinical, Etiologic, Anatomic, Pathophysiologic) classification, shown in Table 2.<sup>6,7</sup>

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

Clinical (C) <sup>a</sup>	Etiologic (E)	Anatomic (A)	Pathophysiologic (P)
C <sub>0</sub> No visible sign of venous disease	E <sub>c</sub> Congenital	A <sub>s</sub> Superficial	P <sub>r</sub> Reflux
C <sub>1</sub> Telangiectasia or reticular veins	E <sub>p</sub> Primary	A <sub>d</sub> Deep	P <sub>o</sub> Obstruction, thrombosis
C <sub>2</sub> Varicose veins	E <sub>s</sub> Secondary (e.g., post-thrombotic, trauma)	A <sub>p</sub> Perforator	P <sub>r,o</sub> Reflux and obstruction
C <sub>3</sub> Edema	E <sub>n</sub> No venous cause identified	A <sub>n</sub> No venous location identified	P <sub>n</sub> No venous pathophysiology identified
C <sub>4</sub> Changes in skin and subcutaneous tissue A Pigmentation or eczema B Lipodermatosclerosis or atrophie blanche	-	-	-
C <sub>5</sub> Healed ulcer	-	-	-
C <sub>6</sub> Active ulcer	-	-	-

<sup>a</sup>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 will consider all adult patients with LECVD (asymptomatic and symptomatic), all diagnostic tests, and all forms of treatment.

**Table 3. Available treatments for LECVD**

<b>Name of Treatment</b>	<b>Description of Treatment</b>
<b>Noninvasive Interventions</b>	
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
<b>Endovenous Interventions</b>	
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)
<b>Surgical Interventions</b>	
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'Insuffisance Veineuse en Ambulatoire (CHIVA)	Conservative and ambulatory treatment of varicose veins that preserves the architecture of the venous structure
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 Clinical, Etiologic, Anatomic, Pathophysiologic (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 duplex ultrasound (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 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 typically 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.

## **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, vascular surgeons often diagnosed and treated patients with LECVD; now, however, primary care physicians, cardiologists, vascular medicine specialists, and radiologists also diagnose and manage these patients in the United States. In addition to physician specialty, other reasons for therapeutic variation 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?

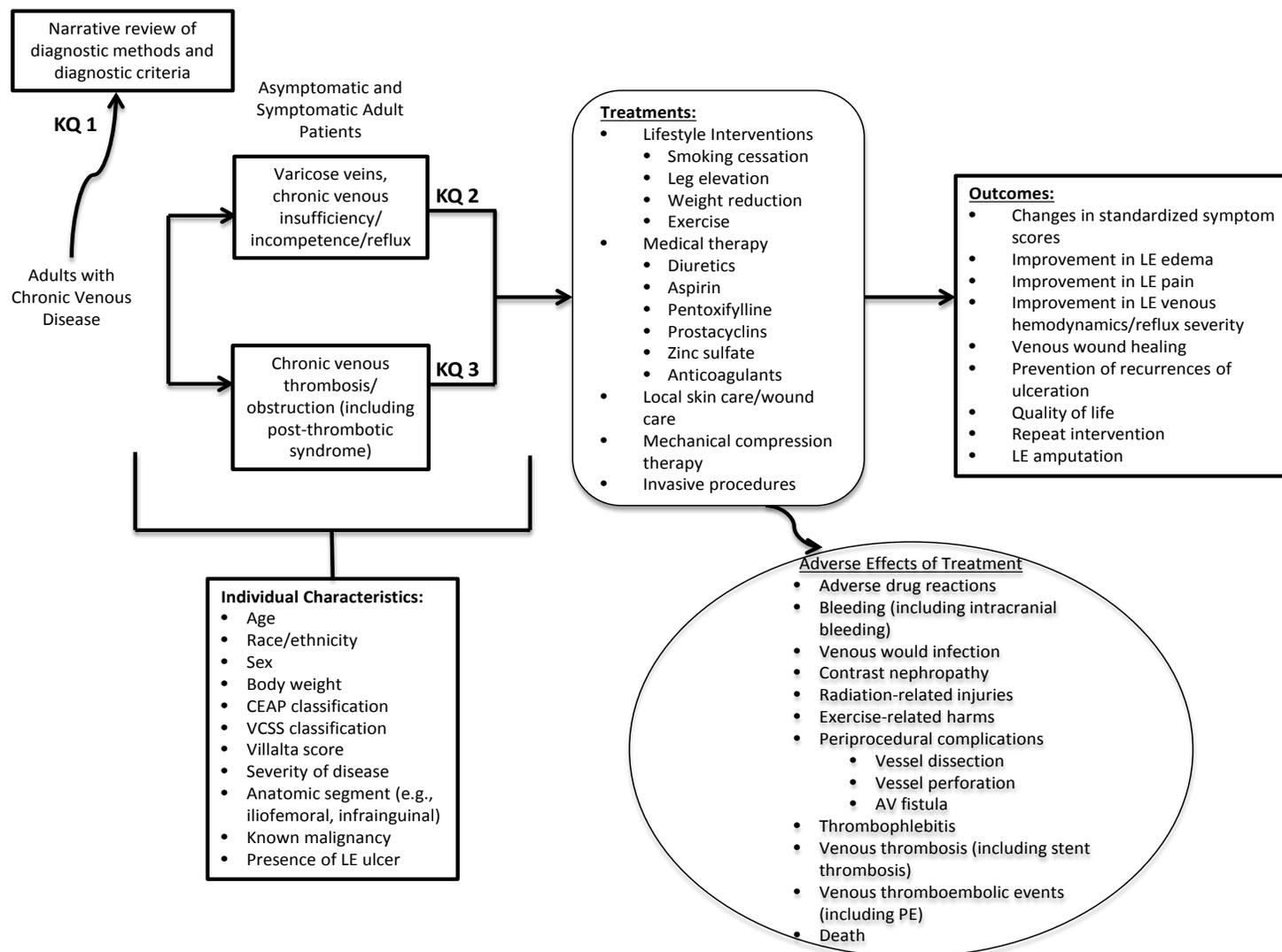
3c. How does the comparative effectiveness of treatment vary by patient characteristics, including age, sex, risk factors, comorbidities, characteristics of disease, anatomic segment affected, and characteristics of the therapy (e.g., exercise intensity, type of mechanical compression)?

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*<sup>8</sup> (hereafter referred to as the *Methods Guide*) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>9</sup> See the review protocol ([http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/lecvd\\_protocol.pdf](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). In collaboration with CMS and the AHRQ Task Order Officers, we drafted a protocol for the systematic review and recruited a technical expert panel (TEP) 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.<sup>10</sup> The PROSPERO registration is CRD42016035669.

### Literature Search Strategy

#### Search Strategy

To identify relevant published literature, we searched PubMed<sup>®</sup>, Embase<sup>®</sup>, and the Cochrane Database of Systematic Reviews, limiting the search to articles published from January 1, 2000, to January 6, 2016. This timeframe 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. The exact search strings used are given in Appendix A. While the draft report is under peer review, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.<sup>11-32</sup> 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<sup>®</sup> 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. Additional gray literature was solicited through the AHRQ Effective Health Care (EHC) website and a notice posted in the Federal Register. Given the timing of the posting of this latter solicitation, data from this gray literature will be included in the final report.

## 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	<p>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)</p> <p>KQ 2: Asymptomatic or symptomatic adults (over age 18) with the diagnosis of LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux</p> <p>KQ 3: Asymptomatic or symptomatic adults (over age 18) with the diagnosis of LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome)</p> <p>Subgroups of interest for KQs 2-3:</p> <ul style="list-style-type: none"> <li>• Age</li> <li>• Race/ethnicity</li> <li>• Sex</li> <li>• Body weight</li> <li>• CEAP classification</li> <li>• VCSS classification</li> <li>• Villalta score</li> <li>• Severity of disease</li> <li>• Anatomic segment affected (e.g., iliofemoral, infrainguinal)</li> <li>• Known malignancy</li> <li>• Presence of LE ulcer</li> </ul>	<p>Individuals younger than 18 years of age. Studies including both adults and patients under 18 will be excluded unless data for the adult population is reported separately.</p> <p>Individuals with acute venous disease (including acute DVT). Studies with mixed populations of both acute and chronic disease will be excluded unless data for the patients with chronic disease is reported separately.</p> <p>Pregnant women</p>
Interventions	<p>KQ 1: Any standard chronic venous disease diagnostic strategy, including: air plethysmography, LE DUS (with and without compression), invasive venography, MRV, computed tomographic venography, serum D-dimer testing, Villalta score</p> <p>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)</p> <ul style="list-style-type: none"> <li>• Medical therapies: diuretics, aspirin, pentoxifylline, prostacyclins, zinc sulfate</li> <li>• Invasive surgical/endovascular procedures: sclerotherapy (liquid, foam, glue), RFA, thermal ablation, chemical ablation, ambulatory phlebectomy, transilluminated powered phlebectomy, venous ligation, venous excision</li> </ul> <p>KQ 3: lifestyle interventions (e.g., smoking cessation, leg elevation, weight reduction, exercise), medical therapy, local</p>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	skin care/wound care, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) <ul style="list-style-type: none"> <li>• Medical therapies: anticoagulants including warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran; diuretics</li> <li>• Invasive surgical/endovascular procedures: endovenous angioplasty/stenting, ultrasound accelerated thrombolysis for chronic DVT (EkoSonic® endovascular system), surgical thromboembolectomy</li> </ul>	
Comparators	KQ 1: Specific diagnostic modalities listed above will be compared to one another  KQs 2-3: Specific treatments will be 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: <ul style="list-style-type: none"> <li>• Accuracy of diagnostic strategy, as measured by:               <ul style="list-style-type: none"> <li>○ Sensitivity</li> <li>○ Specificity</li> <li>○ Positive predictive value</li> <li>○ Negative predictive value</li> <li>○ Inter-rater reliability</li> <li>○ Internal consistency</li> <li>○ Test-retest reliability</li> <li>○ False positives</li> <li>○ False negatives</li> <li>○ Positive likelihood ratio</li> <li>○ Negative likelihood ratio</li> </ul> </li> </ul> KQs 2-3: <ul style="list-style-type: none"> <li>• Changes on standardized symptom scores (Villalta score, CEAP classification, and VCSS score)</li> <li>• Qualitative reduction in LE edema</li> <li>• Qualitative reduction in LE pain</li> <li>• Improvement in LE venous hemodynamics/reflux severity as measured by air plethysmography, DUS, or invasive venography</li> <li>• Venous wound healing</li> <li>• Recurrent ulceration</li> <li>• Patient-reported quality of life (including AVVQ)</li> <li>• Repeat intervention</li> <li>• LE amputation</li> <li>• Adverse effects of treatment, including:               <ul style="list-style-type: none"> <li>○ Adverse drug reactions</li> <li>○ Bleeding (including intracranial bleeding)</li> <li>○ Venous wound infection</li> <li>○ Contrast nephropathy</li> <li>○ Radiation-related injuries</li> </ul> </li> </ul>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> <li>○ Exercise-related harms</li> <li>○ Periprocedural complications (vessel dissection, vessel perforation, and AV fistula)</li> <li>○ Thrombophlebitis</li> <li>○ Venous thrombosis (including stent thrombosis),</li> <li>○ Venous thromboembolic events (including PE) <ul style="list-style-type: none"> <li>• Death</li> </ul> </li> </ul>	
Timing	Studies with all durations of followup will be included in the review, incorporating short-term ( $\leq 30$ 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	<ul style="list-style-type: none"> <li>• Original data</li> <li>• RCTs, prospective and retrospective observational studies with comparator</li> <li>• RCTs: sample size <math>\geq 20</math> subjects</li> <li>• Observational studies: sample size <math>\geq 20</math> subjects for KQs 1 and 3; for KQ2, sample size <math>\geq 500</math> subjects relevant to the KQ 2 population</li> </ul>	Editorials, nonsystematic reviews, letters, case series, case reports, abstract only, articles that have been retracted or withdrawn
Publications	<ul style="list-style-type: none"> <li>• English language only</li> <li>• Published January 1, 2000, to present</li> <li>• Relevant systematic reviews, meta-analyses, or methods articles (used for background only)</li> </ul>	Non-English language articles <sup>a</sup>

<sup>a</sup>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 Clinical, Etiologic, Anatomic, Pathophysiologic [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,<sup>33</sup> and the Newcastle-Ottawa Scale for observational studies.<sup>34</sup> 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
<b>Good (low risk of bias)</b>	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.
<b>Fair (moderate risk of bias)</b>	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.

Rating	Definition
<b>Poor (high risk of bias)</b>	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.<sup>35, 36</sup> 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
<b>Low risk of bias</b>	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.
<b>Medium risk of bias</b>	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.
<b>High risk of bias</b>	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<sup>2</sup> 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*.<sup>8, 37, 38</sup> 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.<sup>39</sup> 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 as shown in Table 7. 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 consisted of the definitions given in Table 7.

**Table 7. Definition of SOE ratings**

Rating	Definition
<b>High</b>	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.
<b>Moderate</b>	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.
<b>Low</b>	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.
<b>Insufficient</b>	We have no evidence, we are unable to estimate an effect, or we have no confidence in the

Rating	Definition
	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*.<sup>8,40</sup> 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 have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ website for 3 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the EHC website.

# 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.

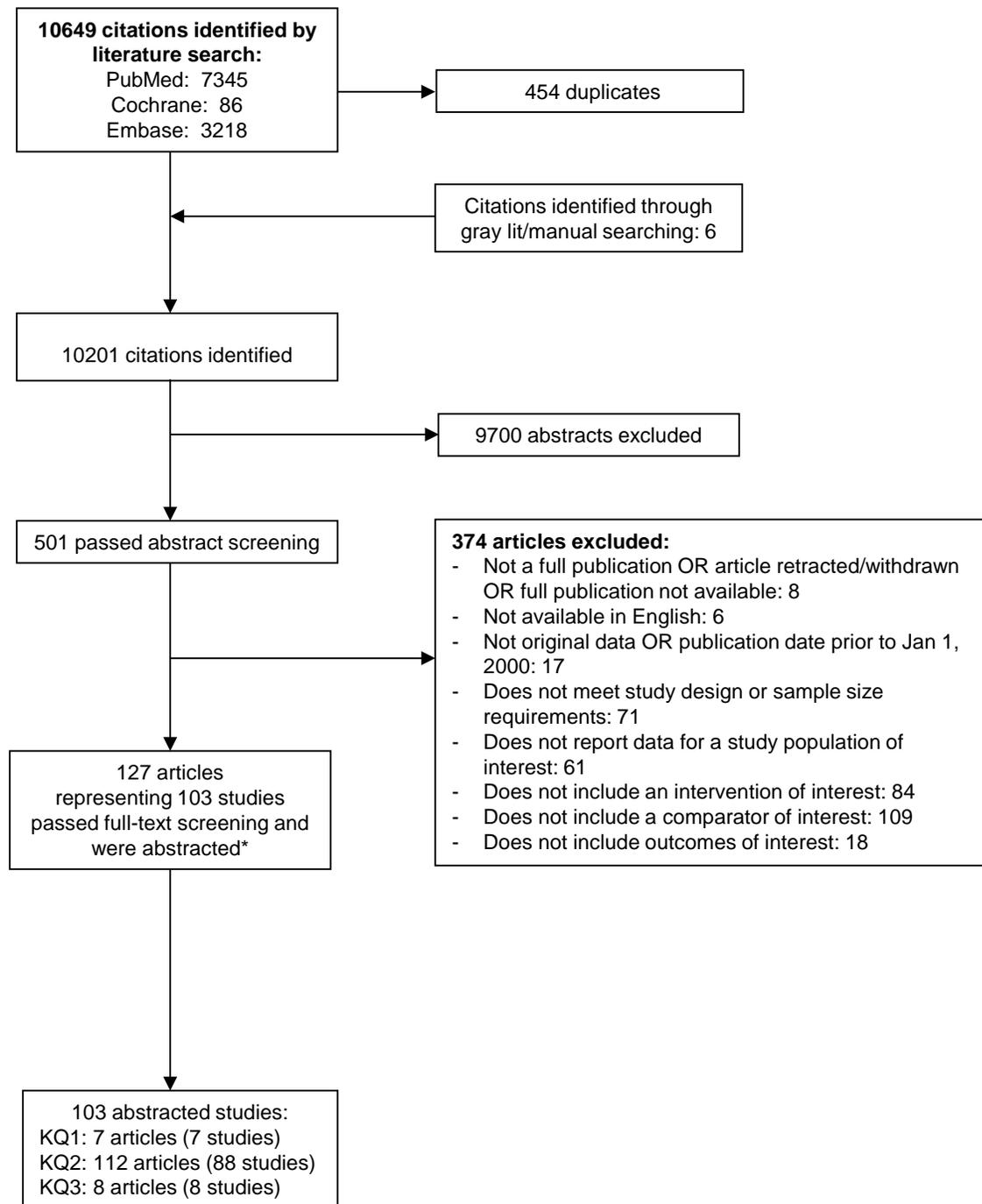
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

## Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed<sup>®</sup>, Embase<sup>®</sup>, and the Cochrane Database of Systematic Reviews yielded 10,195 unique citations. Manual searching of gray literature databases and bibliographies of key articles or referral by investigators identified 6 additional citations, for a total of 10,201 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 501 full-text articles were retrieved and screened. Of these, 374 were excluded at the full-text screening stage, leaving 127 articles for data abstraction. These 127 articles described 103 unique studies. The relationship of studies to the review questions is as follows: 7 studies relevant to KQ 1, 88 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 103 included studies.

**Figure 2. Literature flow diagram**



## Description of Included Studies

Overall, we included 103 studies described in 127 publications: 7 studies were relevant to KQ 1, 88 studies to KQ 2, and 8 studies to KQ 3. Studies were conducted wholly or partly in continental Europe or the United Kingdom (UK; 69 studies – 67%), the United States or Canada (16 studies – 15%), the Middle East (3 studies – 3%), Asia (7 studies – 6%), 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 274 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 vs. no use (a pilot feasibility study enrolling patients already randomized to the PeriOperative ISchemic Evaluation-2 Trial),<sup>41</sup> a structured physical therapy program vs. control for management of chronic venous insufficiency/incompetence,<sup>42</sup> crosssectomy and avulsion vs. foam sclerotherapy for treatment of isolated varicosis of the anterior accessory great saphenous vein,<sup>43</sup> and use of a topical antisense compound vs. control for treatment of venous leg ulcers.<sup>44</sup> We did identify a conference abstract<sup>45</sup> 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 36,727 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 seven studies that examined diagnostic methods for all adult patients with LECVD.<sup>46-52</sup> All 7 were observational studies, representing a total of 384 patients. Two of the studies were conducted in the United States,<sup>47, 50</sup> three in the UK/Europe,<sup>46, 49, 51</sup> one in Asia,<sup>48</sup> and one in Latin America.<sup>52</sup> Four studies reported conducting the studies at a single center,<sup>47, 48, 50, 52</sup> and three studies did not report the number of study sites or this number was unclear.<sup>46, 49, 51</sup> Five studies did not report the funding source or the funding source was unclear.<sup>46, 47, 50-52</sup> One study reported funding from an industry source,<sup>49</sup> and one study reported funding from a nongovernment, nonindustry source.<sup>48</sup> Four studies were conducted in a specialty practice,<sup>47, 48,</sup>

<sup>50, 52</sup> 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. Six studies were rated as fair quality with a medium risk of bias,<sup>46-50, 52</sup> and the remaining study was rated as poor quality with a high risk of bias.<sup>51</sup> There were no studies rated as good quality with a low risk of bias in this group.

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) vs. invasive venography and intravascular ultrasound (IVUS) – one study<sup>50</sup>
- 3-dimensional computed tomography venography (CTV) vs. duplex ultrasound (DUS)– one study<sup>48</sup>
- Ascending and descending phlebography vs. DUS– two studies<sup>47, 49</sup>
- Ambulatory strain gauge plethysmography vs. DUS – one study<sup>49</sup>
- DUS vs. surgical evaluation/confirmation – three studies<sup>46, 51, 52</sup>
- Ascending phlebography vs. surgical evaluation/confirmation – two studies<sup>46, 51</sup>

## Key Points

- There are very few comparative studies of diagnostic testing methods for LECVD in the contemporary 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

### Systematic Review Results

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

The results from our systematic review are 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.<sup>53,54</sup> The recommendations made in these guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)).

## **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 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 the Clinical, Etiologic, Anatomic, Pathophysiologic (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).

Only one of the included studies evaluated ambulatory plethysmography as compared to triplex ultrasound,<sup>49</sup> 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<sub>2</sub>) is GRADE 2C, while its use in patients with advanced LECVD (CEAP class C<sub>3</sub>-C<sub>6</sub>) is GRADE 1B.<sup>53</sup>

## **Duplex Ultrasound**

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.<sup>53</sup> 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.<sup>53, 55</sup>

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.<sup>53</sup>

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.<sup>56</sup>

Six of the included studies evaluated the use of DUS with another imaging modality in the diagnosis of LECVD.<sup>46-49, 51, 52</sup> In two of the studies,<sup>48, 49</sup> DUS was used as the gold standard, while it was compared to another imaging modality or surgical evaluation in the remaining five studies.<sup>46, 47, 50-52</sup> 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<sup>50</sup> 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<sup>48</sup> 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.<sup>1</sup> 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 not 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.<sup>57</sup>

Five of the included studies evaluated the use of invasive phlebography or venography with another imaging modality in the diagnosis of LECVD.<sup>46, 47, 49-51</sup> In two of these studies,<sup>47, 50</sup> 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.<sup>46, 49, 51</sup> 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. 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 exist in the contemporary literature. 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 112 articles<sup>58-171</sup> describing 88 studies 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.<sup>95-97</sup> Twenty studies were described in more than one publication. 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 88 included studies, 4 were observational, representing a total of 20,245 enrolled patients.<sup>104, 110, 162, 163</sup> Eighty-three studies were randomized controlled trials (RCTs), representing a total of 16,482 enrolled patients, and one additional RCT represented a total of 130 legs enrolled.<sup>78</sup> One study was conducted in Africa,<sup>132</sup> 4 in Asia,<sup>118, 123, 126, 129</sup> 2 in Australia/New Zealand,<sup>137, 171</sup> 3 in Latin America,<sup>106, 140, 149</sup> 3 in the Middle East,<sup>109, 117, 165</sup> 65 in the UK/Europe,<sup>59, 61, 64, 66, 68, 71, 74, 75, 78, 80, 82, 84, 88, 90, 91, 94-97, 100, 102, 107, 111-116, 120-122, 124, 125, 127, 128, 131, 134-136, 138, 139, 141-148, 150-162, 164, 166-168, 170</sup> 8 studies in the United States,<sup>103, 104, 108, 110, 119, 130, 133, 163</sup> and 2 studies in both the UK/Europe and United States.<sup>74, 142</sup> Thirty-five studies were conducted in multiple centers,<sup>64, 66, 74, 75, 84, 88, 90, 94-97, 100, 103, 107-112, 119, 124, 126, 128, 130, 136, 142, 144, 150, 156, 158, 162-165, 167</sup> 46 were conducted in a single center,<sup>59, 71, 78, 80, 82, 91, 102, 104, 106, 113, 114, 116-118, 120, 122, 123, 125, 127, 129, 131-135, 137-141, 143, 145-149, 151, 153-155, 157, 161, 170, 171</sup> and 7 studies did not report the study site or it was unclear.<sup>115, 121, 152, 159, 160, 166, 168</sup> Nine studies reported government funding,<sup>66, 90, 95-97, 108, 118, 124, 154</sup> 12 studies reported industry funding,<sup>59, 74, 103, 119, 130, 136, 138, 142, 147, 150, 153</sup> and 19 studies reported non-government, non-industry funding.<sup>68, 84, 88, 100, 102, 104, 106, 109, 114, 116, 121, 122, 127, 131, 133, 139, 144, 151, 155</sup> Multiple studies reported a combination of funding sources; specifically, 4 studies reported a combination of industry and non-government funding,<sup>80, 82, 91, 134</sup> 3 studies reported a combination of government and industry funding,<sup>75, 126, 171</sup> 1 study reported a combination of funding from government, industry, and non-government sources,<sup>111</sup> and 1 study reported a combination of government and non-government funding.<sup>135</sup> Finally, there were 39 studies that did not report the funding source or it was unclear.<sup>61, 71, 78, 94, 107, 110, 112, 113, 115, 117, 120, 123, 125, 128, 129, 132, 137, 140, 141, 143, 145, 146, 148, 149, 152, 156-168, 170</sup> Of the 88 studies relating to KQ 2; 24 were rated as good quality,<sup>66, 71, 75, 82, 88, 97, 102, 103, 106, 113, 115, 116, 119, 120, 122, 126, 127, 135, 136, 138, 150, 156, 164, 168</sup> 47 studies were rated as fair quality,<sup>59, 61, 64, 68, 74, 78, 80, 84, 90, 91, 94-96, 100, 107, 108, 110-112, 114, 118, 121, 123-125, 128, 131, 133, 135, 137, 139-141, 143-146, 148, 149, 151, 152, 155, 158, 160, 161, 163, 167, 170</sup> and 17 studies were rated as poor quality.<sup>104, 109, 117, 129, 130, 132, 134, 142, 147, 153, 154, 157, 159, 162, 165, 166, 171</sup> These 88 studies included 10 studies in which patients were identified through clinical assessment,<sup>113, 120, 122, 125, 137, 150, 152, 157-159</sup> 40 that identified patients through duplex ultrasound,<sup>61, 64, 66, 68, 71, 74, 75, 78, 80, 84, 91, 94, 102-104, 106, 108, 111, 112, 116, 119, 123, 127-130, 132-134, 138, 139, 142, 143, 147, 149, 151, 153, 155, 160, 164</sup> 28 which noted a combination of clinical assessment and duplex ultrasound,<sup>88, 90, 95-97, 100, 114, 115, 118, 121, 124, 126, 135, 136, 141, 144, 145, 148, 154, 156, 161, 162, 165-168, 170, 171</sup> and 6 studies where the diagnostic criteria was uncertain.<sup>59, 82, 109, 117, 146, 163</sup>

## Key Points

### Comparisons Between Surgical and Endovenous Interventions

#### Comparisons between Surgical Interventions 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, such as less periprocedural pain (SOE = low), faster improvement in symptom scores (SOE = low) and quality of life (SOE = insufficient), 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 peri-procedural 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 Intervention Comparisons (Endovascular vs. Endovascular, Surgery vs. Surgery)**

### Comparisons between Endovascular Interventions and Endovascular Interventions

- Comparison between endovenous laser ablation (EVLA) versus foam sclerotherapy:
  - Groups receiving EVLA and foam sclerotherapy both demonstrated improvement in quality of life scores and the venous chronic severity score, however there were no statistically significant differences in improvement between groups. (SOE = low for intermediate term outcomes)
  - The foam sclerotherapy group had statistically significantly less peri-procedural pain but with lower rates of vein occlusion (i.e. lower rates of procedural success) and higher rates of repeated intervention, when compared with the EVLA group. (SOE = insufficient)

### Comparison between EVLA versus EVLA plus phlebectomy

- There was a statistically significant improvement in the VCSS and AVVQ QOL score in favor of the EVLA + phlebectomy group in the short/intermediate term. (SOE = insufficient)
- The EVLA + phlebectomy group reported less pain, which was statistically significant, than the EVLA group in the short term. (SOE = insufficient)
- There was a statistically significant difference in the rates of recurrence and repeated intervention in favor of the EVLA + phlebectomy group (statistically significant p-values). (SOE = insufficient)

### Comparison between EVLA versus endovenous radiofrequency:

- 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)
- Both groups demonstrated improvement in the venous chronic 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 peri-procedural 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 Surgical Interventions and Surgical Interventions

- There were no consistent differences in the comparative effectiveness of different surgical approaches (HL/stripping vs. HL/cryostripping, HL/stripping vs. CHIVA, ligation vs. stab avulsion) for available outcomes (peri-procedural complications, procedural pain, QoL, or hemodynamic outcomes). A possible exception is that CHIVA may have superior 5-year hemodynamic outcomes compared with HL/stripping, but there is limited data to support this. (SOE = insufficient)
- The comparative effectiveness of surgical and hybrid procedures is limited by a low number of studies, inconsistency in the procedures utilized, and outcomes assessed.

## **Comparisons of Interventions vs. Placebo or Usual Care**

### Comparisons between Compression Therapy and Placebo/No Compression Therapy

- Compression therapy is effective relative to no compression therapy (or placebo) for a variety of different clinical outcomes (SOE = insufficient)

### Comparisons between Medical Therapy and Placebo

- Pentoxifylline is not effective relative to placebo for treating venous ulcers (SOE = insufficient)

#### Comparisons between Endovascular Interventions Versus Placebo

- There was a statistically significant difference in favor of sclerotherapy for QOL/VCSS/Occlusion rates. (SOE = insufficient)

#### Comparisons between Endovascular Interventions Versus Medical Therapy:

- There is a statistically significant difference in favor of the sclerotherapy group for Venous ulcer healing/Recurrence of venous ulcer. (SOE = insufficient)

#### Comparisons between Surgical Interventions and Compression

- Although some studies favored surgical approaches over compression with regard to wound healing and QoL, there were no consistent differences in the comparative effectiveness of surgical approaches (HL/stripping, HL/stripping/SEPS, CHIVA) versus compression for most available outcomes (QoL, wound healing, hemodynamic outcomes). A meta-analysis of surgical approaches versus compression on intermediate-term wound healing showed a trend toward better outcomes with surgery, but this difference was not statistically significant. (SOE = insufficient)

## Detailed Synthesis

### Comparisons of Surgical Interventions versus Endovascular Interventions

#### Venous Stripping plus Ligation vs. Radiofrequency Ablation (RFA)

##### Overview

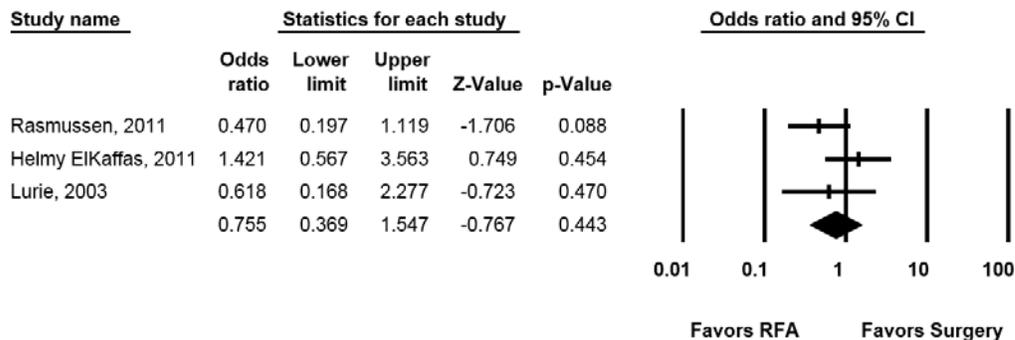
Six RCTs<sup>68, 74, 75, 132, 138, 168</sup> and one observational study<sup>110</sup> evaluated the effectiveness of venous stripping plus ligation vs. RFA in patients with venous reflux/incompetence/varicose veins. Of the RCTs, three were good-quality,<sup>75, 138, 168</sup> two were fair-quality,<sup>68, 74</sup> and one was poor-quality.<sup>132</sup> Note that the observational study<sup>110</sup> was not clear as to whether the ablation was with radiofrequency or laser but is included in the RFA findings.

##### Effect on Vein Recurrence/Recanalization and Repeat Intervention

Three RCTs reported long-term reflux recurrence rates at 1-2 years postintervention.<sup>74, 75, 132</sup> In one study,<sup>75</sup> 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% underwent re-intervention, whereas 15.5% of limbs randomized to ligation plus stripping were subject to repeat intervention (no p-value reported).<sup>75</sup> One smaller, fair-quality study<sup>68</sup> 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 recurrent (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.<sup>132</sup>

A meta-analysis of these three studies 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; odds ratio [OR]=0.75 (95% confidence interval [CI]=0.37 to 1.55) (Figure 3).

**Figure 3. Forest plot of reduction in vein recurrence/recanalization for RFA vs. 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 1 day postoperative and found no difference between groups (sclerotherapy: 19/20 patients successfully occluded; ligation plus stripping: 20/20 patients successfully occluded;  $p > 0.05$ ).<sup>168</sup>

### Effect on Clinical Symptoms

The mean decrease in Venous Clinical Severity Score (VCSS) at 50 days followup was 5.1 (standard deviation [SD] 1.5) for RFA and 4.4 (SD 1.1) for surgery ( $p = 0.19$ ).<sup>68</sup> One study<sup>74</sup> 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 followup (RFA 0.48, standard error [SE] 0.293, 0.69 vs. high ligation plus stripping 0.76 SE 0.60, 1.0;  $p = \text{not statistically significant [NS]}$ ).<sup>74</sup> 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;  $p = \text{NS}$ ).<sup>75</sup>

### Effect on Quality of Life

One fair-quality RCT<sup>74</sup> measured quality of life using the Chronic Venous Insufficiency Questionnaire-2 (CIVIQ-2) at baseline, 1-week followup, and 2-year followup. 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;  $p < 0.0001$ ).<sup>74</sup> At 2 years followup, the RFA arm also had lower CIVIQ-2 scores than the surgery arm, indicating a better quality of life (RFA mean 3.095, SE 2.838, 4.045 vs. high ligation plus stripping 7.067, SE 6.182, 9.388;  $p = \text{value NR}$ ).<sup>72</sup>

Two RCTs<sup>75, 138</sup> measured quality of life using the Aberdeen Varicose Vein Questionnaire (AVVQ). One study reported AVVQ in two articles<sup>75, 76</sup> and found no between-group differences at any followup time (3 day, 1 month, 1 year, or 3 year). One study<sup>138</sup> showed that the mean within-group change in score was -8.24 for surgery vs. -9.12 for RFA ( $p = 0.53$ ), indicating an improvement in quality of life for both groups at 5 weeks' followup.

## Effect on Pain

Two RCTs<sup>75, 168</sup> reported less pain on a visual analog scale (VAS) in the RFA arms vs. surgery arms. One study<sup>75</sup> 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' followup (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.<sup>168</sup>

## Adverse Events

Adverse events were reported in all but one study. Variability of followup 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% 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.<sup>74</sup> 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.<sup>132</sup> 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 to 5.50; p=0.016).<sup>110</sup>

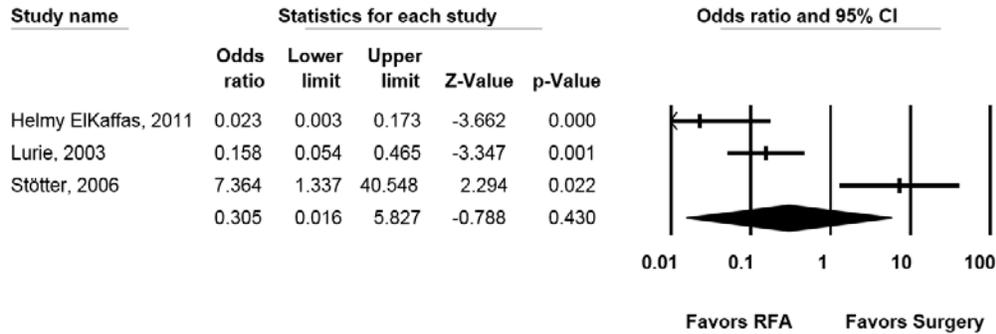
Several blood-related adverse outcomes were reported in various studies, including DVT, pulmonary embolism (PE), thrombophlebitis, hematoma, hemorrhage, and ecchymosis. A large observational study reported that after adjustment for age, gender, race, body mass index, surgeon specialty, and presence of 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).<sup>110</sup> 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; no p-value reported for one study;<sup>132</sup> 0/121 for RFA, 1/119 surgery; no p-value reported for the other<sup>75</sup>).

Additionally, the same two RCTs reported lower rates of 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 thrombophlebitis,<sup>132</sup> whereas a good-quality study reported 9.9% of the RFA group vs. 4.2% of the surgery group had thrombophlebitis (Fisher exact test p=0.006 across the four arms; no p-value reported for arm-to-arm comparison).<sup>75</sup> 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 followup time period.<sup>75</sup> One study<sup>68</sup> reported one out of 15 RFA patients vs. zero out of 13 surgery patients reported an incidence of thrombophlebitis at 3 years' followup.

One study<sup>74</sup> 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 vs. three cases in the RFA group (no p-value reported).<sup>74</sup> The three RCTs reporting hematoma outcomes have inconsistent findings. The fair-quality, multinational study reported one incident of periprocedural hematoma in each of the RFA and surgery arms (2.3% event rate in the RFA, 2.8% in surgery).<sup>74</sup> 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; no p-value reported).<sup>168</sup> 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; no p-value reported).<sup>132</sup> 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 vs. venous stripping plus ligation**



Abbreviations: CI=confidence interval; RFA=radiofrequency ablation

One study reported postprocedural ecchymosis at three time points.<sup>74</sup> Significantly fewer patients in the RFA arm compared with the surgery arm experienced ecchymosis at three postoperative time points (3 days, 1 week, and 3 weeks).

### Strength of Evidence

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

**Table 8. Strength of evidence for major outcomes—KQ 2—venous stripping plus ligation vs. RFA**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Vein recurrence/ Repeat intervention	3 RCTs: 597 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	A meta-analysis of three RCTs <sup>74, 75, 132</sup> 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; odds ratio [OR] = 0.75 (95% confidence interval [CI] = 0.37 to 1.55)
Insufficient							
Reflux	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). <sup>168</sup>
Insufficient							
Clinical Symptom Scores (VCSS)	3 RCTs: 356 pts.	Medium	Direct	Consistent	Imprecise	Suspected	For one study, the mean decrease in Venous Clinical Severity Score (VCSS) at 50 days followup was 5.1 (standard deviation [SD] 1.5) for RFA and 4.4 (SD 1.1) for surgery (p=0.19). <sup>68</sup> One study <sup>74</sup> 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 followup (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]). <sup>74</sup> 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). <sup>75</sup>
Low							
Patient-reported Quality of Life	3 RCTs: 416 pts.	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). <sup>74</sup> At 2 years followup, the RFA arm also had lower CIVIQ-2 scores than the surgery arm, indicating a better quality of life (RFA mean 3.095, SE 2.838, 4.045 vs. high ligation plus stripping 7.067, SE 6.182, 9.388; p not reported). <sup>72</sup> One study reported AVVQ in two articles <sup>75, 76</sup> and found no between-group differences at any followup time (3 day, 1 month, 1 year, or 3 year). One study <sup>138</sup> showed that the mean within-group change in score was -8.24 for surgery vs. -9.12 for RFA (p=0.53), indicating an improvement in quality of life for both groups at 5 weeks' followup.
Insufficient							
Reduction in	1 RCT:	Low	Direct	Consistent	Imprecise	None	Two RCTs <sup>75, 168</sup> reported less pain on a visual analog scale (VAS) in the

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
LE Pain	60 pts. 1 RCT: NR	Low						RFA arms vs. surgery arms. One study <sup>75</sup> 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' followup (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. <sup>168</sup>
Adverse Events (Surgical Site Infection)	2 RCTs, 1 Obs.: 2,850 pts.	Low	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. <sup>74</sup> 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. <sup>132</sup> 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). <sup>110</sup>
Adverse Events (Blood-related)	2 RCTs, 1 Obs.: 5,033 pts.	Insufficient	Medium	Direct	Inconsistent	Imprecise	Suspected	Several blood-related adverse outcomes were reported in various studies, including DVT, pulmonary embolism (PE), 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 0.28-0.97). <sup>110</sup> 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; no p-value reported for one study, <sup>132</sup> 0/121 for RFA, 1/119 surgery; no p-value reported for the other <sup>75</sup> ).
Adverse Events (Thrombophlebitis)	3 RCTs 695 pts.	Low	Medium	Direct	Consistent	Imprecise	Suspected	Two RCTs reported lower rates of 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 thrombophlebitis, <sup>132</sup> whereas a good-quality study reported 9.9% of the RFA group vs. 4.2% of the surgery group had thrombophlebitis (Fisher exact test p=0.006 across the four arms; no p-value reported for arm-to-arm comparison). <sup>75</sup> One study <sup>68</sup> reported one out of 15 RFA patients vs.

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Adverse Events (Hematoma)	3 RCTs 318 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	zero out of 13 surgery patients reported an incidence of thrombophlebitis at 3 years' followup.
Insufficient							The three RCTs reporting hematoma outcomes have inconsistent findings. The fair-quality, multinational study reported one incident of periprocedural hematoma in each of the RFA and surgery arms (2.3% event rate in the RFA, 2.8% in surgery). <sup>74</sup> 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; no p-value reported). <sup>168</sup> 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; no p-value reported). <sup>132</sup> A meta-analysis of these three inconsistent and imprecise findings did not show a difference between strategies (Figure 4).

## Venous Stripping plus Ligation vs. EVLA

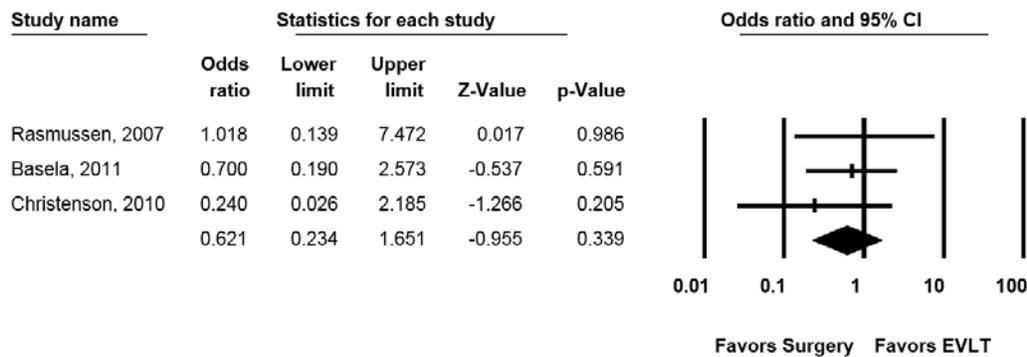
### Overview

Fifteen RCTs<sup>61, 64-66, 71, 75, 78, 80-82, 93, 94, 99, 100, 105, 117, 128, 131, 147, 164, 165</sup> were included in the evaluation of venous stripping plus ligation vs. EVLA. One study<sup>71</sup> compared cryostripping vs. EVLA, one study<sup>78</sup> compared high ligation plus stripping plus foam sclerotherapy vs. EVLA plus foam sclerotherapy, two studies<sup>80, 131</sup> compared high ligation plus stripping plus phlebectomy vs. EVLA plus phlebectomy, and one study<sup>99, 100</sup> compared high ligation plus stripping vs. EVLA plus ligation.

### Effect on Vein Recurrence/Recanalization and Repeat Intervention

We were able to perform a meta-analysis on 3 studies representing 491 patients that evaluated short-term thrombophlebitis.<sup>64, 131, 165</sup> This analysis did not demonstrate a statistically significant difference in thrombophlebitis and was both imprecise and inconsistent across the three studies (Figure 5).

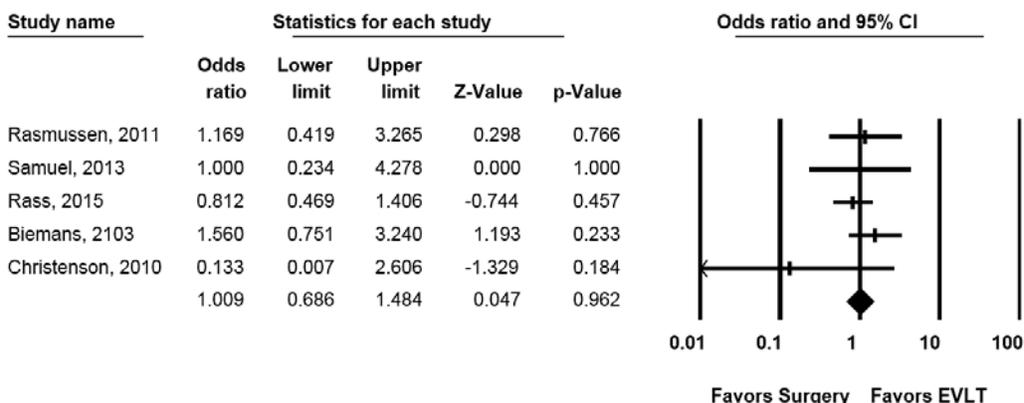
**Figure 5. Forest plot of short-term thrombophlebitis for venous stripping plus ligation vs. EVLA**



Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation

Five studies evaluated long-term thrombophlebitis.<sup>75, 82, 94, 105, 131</sup> The findings of these studies were imprecise and inconsistent demonstrating no difference in thrombophlebitis between the two strategies (OR 1.009; 95% CI, 0.686 to 1.484) (Figure 6).

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



Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation

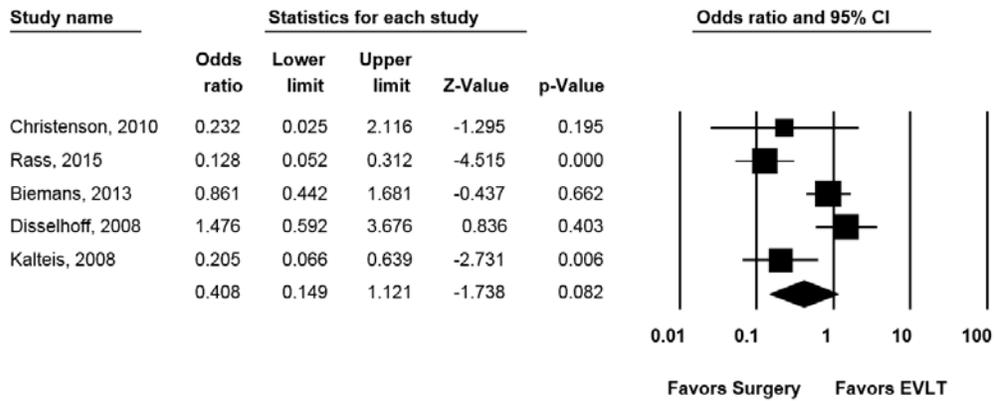
One additional study reported no recurrence as an outcome at 26 weeks, 1 year, and 2 years.<sup>81</sup> Significantly more EVLA patients had no recurrence at any time point (26 weeks, 38/52 surgery patients vs. 51/51 EVLA;  $p < 0.001$ ; 1 year, 38/51 surgery patients vs. 45/48 EVLA;  $p$ -value NR; 2 years, 29/44 surgery patients vs. 36/44 EVLA patients;  $p = 0.0020$ <sup>81</sup>).

### Effect on Reflux/Incompetence

At 2 years, 77% (95% CI, 72% to 78%) of the EVLA patients and 66% (95% CI, 60% to 67%) of cryostripping patients were free of duplex-defined varicose vein recurrence ( $p = 0.253$ ).<sup>71</sup> The same study measured freedom from venous incompetence at 5 years and found a lower rate in the surgery group (51%; 95% CI, 39 to 66) than the EVLA group (62%; 95% CI, 50 to 76) but the substantial loss to followup for these 5-year findings lower the quality of the study for this specific outcome to fair.<sup>71</sup> 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;  $p = 1.00$ ).<sup>131</sup> One study<sup>147</sup> reported abolishment of reflux as an outcome in a three-arm study comparing two different powers of lasers vs. surgery. At 3 months' followup, 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 ( $p = 0.227$ ).<sup>147</sup> Abolishment of reflux was also reported at 12 months; however, >40% patient attrition detracts from the power of these results.<sup>147</sup>

Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics over long-term time period.<sup>61, 71, 94, 105, 131</sup> The analysis suggested a trend towards 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).

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

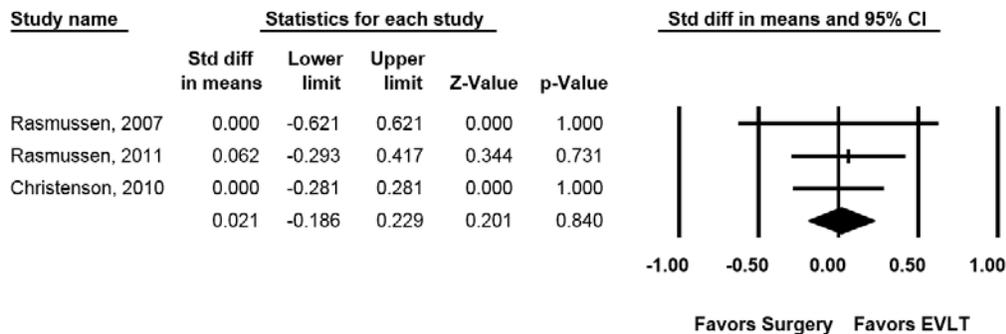


Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation

### Effect on Clinical Symptom Scores

We synthesized three studies representing 487 patients for treatment effect on long-term VCSS score.<sup>64, 75, 131</sup> There was no significant difference between treatment strategies (Figure 8).

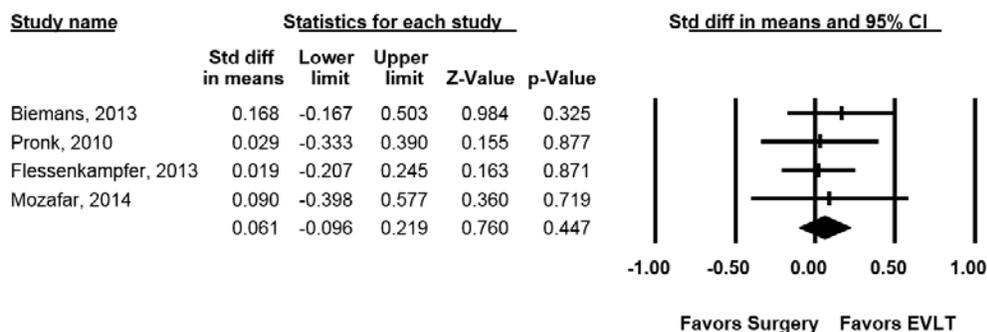
**Figure 8. Forest plot of long-term VCSS effects for venous stripping plus ligation vs. EVLA**



Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation; Std diff=standardized difference

We also explored the CEAP after 12 months in 4 studies representing 867 patients.<sup>78, 94, 100, 117</sup> No difference was found (Figure 9).

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



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

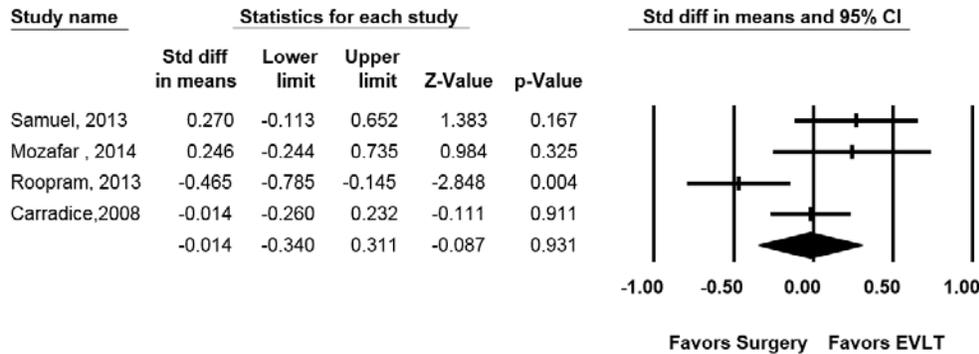
### Effect on Quality of Life

Four studies<sup>66, 80, 94, 164</sup> 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. In the study with the largest population measuring this outcome<sup>66</sup> the mean change within groups was 0.111 for EVLA and 0.097 for surgery (p-value NR). Two fair quality studies<sup>80, 94</sup> reported similar scores at baseline and 1 year. In one study,<sup>80</sup> the median score at baseline was 0.79 then 1.0 at one year for the EVLA group and the median score at baseline was 0.80 at baseline then 1.0 at one year followup 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 one year versus surgery at baseline was 0.85 then 0.87 at one year (p-value NR).<sup>94</sup> 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).<sup>164</sup>

Two RCTs<sup>94, 105, 128</sup> reported CIVIQ-2 scores as an outcome at various time points that were not conducive for meta-analysis. Neither study reported a significant difference between EVLA versus 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<sup>94</sup> study reported scores at baseline, 3 months, and 12 months. Mean scores in both groups decreased at both 3 month and 12-month followup 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<sup>128</sup> only collected CIVIQ-2 data on the last 100 patients to enroll out of 346 patients in the entire study at 3-months, 12-months, and 60-months followup. 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=11.8, surgery=11.0, p=0.813).<sup>128</sup>

We synthesized four studies representing 583 patients which evaluated short-term AVVQ effects.<sup>80, 82, 117, 164</sup> These studies showed a -0.014 standardized difference in means (95% CI, -0.340 to 0.311) showing no difference between strategies (Figure 10).

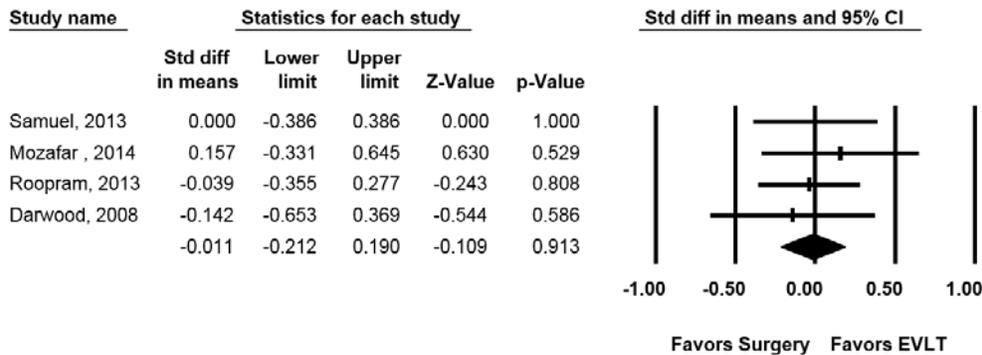
**Figure 10. Forest plot of short-term AVVQ effects for venous stripping plus ligation vs. EVLA**



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

Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon.<sup>82, 117, 147, 164</sup> Again there was no difference in AVVQ scores (Figure 11).

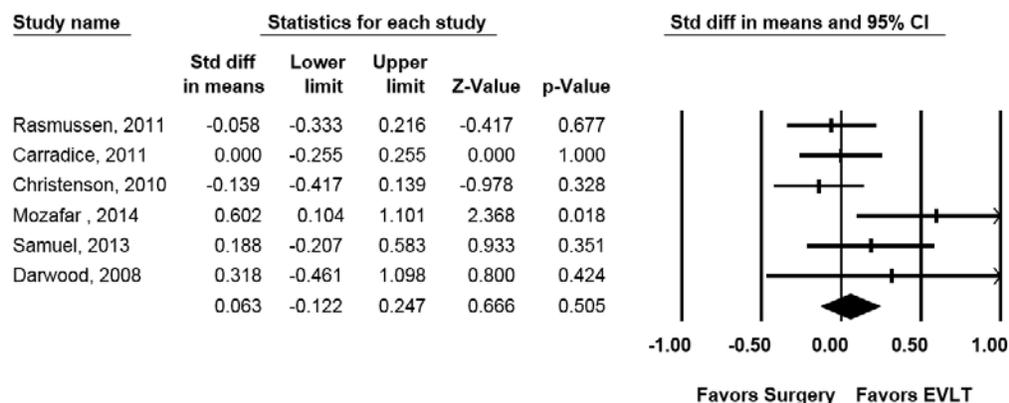
**Figure 11. Forest plot of intermediate-term AVVQ effects for venous stripping plus ligation vs. EVLA**



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

Finally we synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ.<sup>75, 80, 82, 117, 131, 147</sup> 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 vs. EVLA**

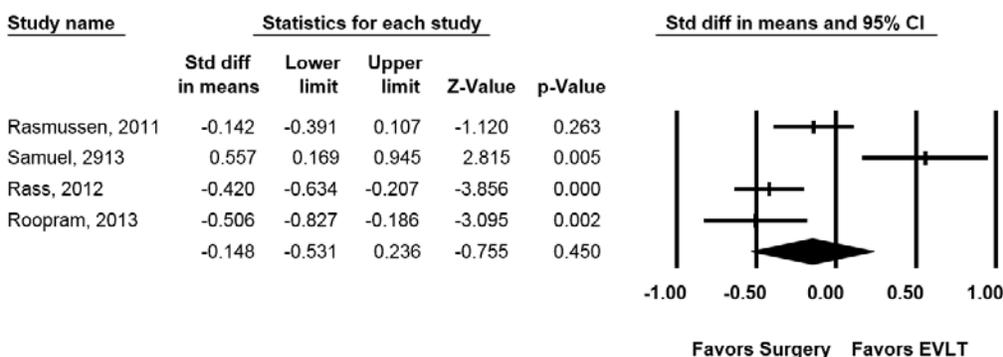


Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CI=confidence interval; EVLA=endovenous laser ablation; Std diff=standardized difference

### Effect on Pain

Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale.<sup>75, 82, 128, 164</sup> 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).

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



Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation; Std diff=standardized difference

### Adverse Events

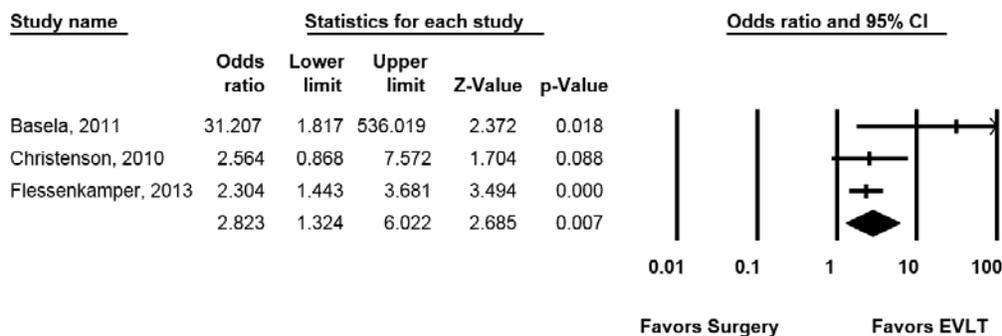
Six RCTs<sup>71, 78, 94, 100, 128, 131</sup> reported DVT as an outcome at various time points that precluded meta-analysis. None of the studies reported a significant difference between EVLA and surgery patients. Four studies<sup>71, 78, 94, 131</sup> reported zero cases of DVT in either EVLA or surgery arms, whereas two other studies<sup>100, 128</sup> reported one case of DVT in both arms.

Infection was reported as an outcome in six RCTs<sup>80, 94, 128, 131, 147, 165</sup> at various time points that precluded meta-analysis. Five studies<sup>80, 94, 131, 147, 165</sup> reported higher incidence of infection in the surgery arm but the difference was statistically significant in two studies.<sup>80, 94</sup> In the EVLA arm of one fair-quality study, 0 out of 78 patients had infections at 3 months followup versus 3 out of 68

surgery patients had infections ( $p=0.03$ ).<sup>94</sup> Another fair-quality reported infections in 2 out of 137 EVLA patients and 8 out of 133 surgery patients ( $p=0.048$ ).<sup>80</sup> The followup time was not described for this study.<sup>80</sup> Three studies<sup>131, 147, 165</sup> reported infections in the short-term, postoperative period. One poor-quality study<sup>147</sup> reported groin infections requiring antibiotics and found the occurrence in 2 out of 32 surgery patients versus 0 out of 71 EVLA patients (no p-value reported). 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,  $p=0.147$ ).<sup>165</sup> A fair-quality study reported no incidence of infection in either arm at 12 days postintervention.<sup>131</sup> Only one study reported a higher incidence of infection in EVLA patients when compared with surgery patients at 12-months followup, 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 three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis).<sup>99, 100, 131, 165</sup> 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).

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



Abbreviations: CI=confidence interval; EVLA=endovenous laser ablation

Two studies<sup>131, 165</sup> reported skin burns occurring immediately postoperatively as an outcome. Both studies had one instance of skin burn in the EVLA group and none in the surgery group.<sup>131, 165</sup> Two studies<sup>131, 165</sup> reported postoperative paresthesia and found different event rates. One study found that one patient out of 99 in the EVLA group vs. one patient out of 100 in the surgery group experienced parasthesias,<sup>131</sup> whereas a different study<sup>80</sup> 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 measured paresthesia as an outcome at 12 months postoperative and reported the outcome in one of 68 surgery patients vs. zero of 78 EVLA patients ( $p=NS$ ).<sup>94</sup>

One study<sup>80</sup> 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 out of 68 surgery patients vs. 3 out of 78 EVLA patients ( $p=0.85$ ).<sup>94</sup> Two studies<sup>75, 131</sup> stated there was no significant difference in phlebitis for patients who underwent EVLA vs. surgery (4/125 EVLA vs. 5/119 surgery;  $p=NS$ ),<sup>75</sup> (4/99 EVLA vs. 1/100 surgery,  $p=0.369$ ).<sup>131</sup> The same study<sup>75</sup> and another study<sup>94</sup> found zero instances of PE in either group, suggesting PE is a rare side effect for either treatment.

## **Strength of Evidence**

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

**Table 9. Strength of evidence for major outcomes—KQ 2—venous stripping plus ligation vs. EVLA**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Vein recurrence/ Repeat intervention (Short Term)	3 RCTs: 491 pts.	High	Direct	Inconsistent	Imprecise	None	We were able to perform a meta-analysis on 3 studies representing 491 patients that evaluated short-term thrombophlebitis. <sup>64, 131, 165</sup> This analysis did not demonstrate a statistically significant difference in thrombophlebitis and was both imprecise and inconsistent across the three studies (Figure 5).
Insufficient							
Vein recurrence/ Repeat intervention (Long Term)	5 RCTs: 1,261 pts.	Low	Direct	Consistent	Imprecise	None	Five studies evaluated long-term thrombophlebitis. <sup>75, 82, 94, 105, 131</sup> The findings of these studies were imprecise and inconsistent demonstrating no difference in thrombophlebitis between the two strategies (OR = 1.009, 95% CI = 0.686 to 1.484) (Figure 6)
Low							
Improvement hemodynamics	5 RCTs: 887 pts.	Low	Direct	Consistent	Imprecise	None	Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics. <sup>61, 71, 94, 105, 131</sup> The analysis suggested a trend towards improvement in reflux/incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121) (Figure 7)
Low							
Clinical symptom scores (VCSS)	3 RCTs: 487 pts.	Medium	Direct	Consistent	Imprecise	None	We synthesized three studies representing 487 patients for treatment effect on long-term VCSS score. <sup>64, 75, 131</sup> There was no significant difference between treatment strategies (standard difference of means = 0.021, 95% CI = -0.186 to 0.229) (Figure 8).
Low							
Clinical symptom scores (CEAP)	4 RCTs: 867 pts.	Medium	Direct	Consistent	Precise	Unclear	We also explored the CEAP after 12 months in 4 studies representing 867 patients. <sup>78, 94, 100, 117</sup> No difference was found (standard difference of means = 0.061, 95% CI -0.096 to 0.219)(Figure 9).
Moderate							
Patient-reported Quality of Life (EQ-5D)	4 RCTs: 1,436 pts.	Medium	Direct	Consistent	Imprecise	None	Four studies <sup>66, 80, 94, 164</sup> 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.
Low							
Patient-reported Quality of Life (CIVIQ-2)	2 RCTs: 297 pts.	Medium	Direct	Consistent	Imprecise	None	Two RCTs <sup>94, 105, 128</sup> reported CIVIQ-2 scores as an outcome at various time points that were not conducive for meta-analysis. Neither study reported a significant difference between EVLA versus surgery at any time point but the mean within group change was negative for all arms,

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
							all time points, and both studies.
Insufficient							
Patient-reported Quality of Life (AVVQ-Short Term)	4 RCTs: 583 pts.	Medium	Direct	Inconsistent	Imprecise	Unclear	We synthesized four studies representing 583 patients which evaluated short-term AVVQ effects. <sup>80, 82, 117, 164</sup> These studies showed a -0.014 standardized difference in means (95% CI -0.340 to 0.311) showing no difference between strategies (Figure 10).
Low							
Patient-reported Quality of Life (AVVQ-Intermediate Term)	4 RCTs: 426 pts.	Medium	Direct	Consistent	Imprecise	Suspected	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon. <sup>82, 117, 147, 164</sup> Again there was no difference in AVVQ scores (standard difference of means = -0.011, 95% CI 0-0.212 to 0.190) (Figure 11).
Low							
Patient-reported Quality of Life (AVVQ-Long Term)	6 RCTs: 663 pts.	Medium	Direct	Consistent	Imprecise	Suspected	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ. <sup>75, 80, 82, 117, 131, 147</sup> These studies also consistently found no difference between treatment strategies (standard difference of means = 0.063, 95% CI -0.122 to 0.247) (Figure 12).
Moderate							
Reduction in LE Pain	4 RCTs: 778 pts.	Low	Direct	Inconsistent	Imprecise	None	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale. <sup>75, 82, 128, 164</sup> 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 of means = -0.148, 95% CI -0.531 to 0.236) (Figure 13).
Low							
Adverse Events (Presence of DVT)	6 RCTs: 822 pts.	Medium	Direct	Consistent	Imprecise	None	Six RCTs <sup>71, 78, 94, 100, 128, 131</sup> 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 <sup>71, 78, 94, 131</sup> reported zero cases of DVT in either EVLA or surgery arms, whereas two other studies <sup>100, 128</sup> reported one case of DVT in both arms.
Insufficient							
Adverse Events (Venous)	6 RCTs: 822 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	Infection was reported as an outcome in six RCTs <sup>80, 94, 128, 131, 147, 165</sup> at various time points that precluded meta-analysis. Five studies <sup>80, 94, 131, 147, 165</sup> reported higher incidence of infection in the surgery arm but the difference

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Infection)							was statistically significant in two studies.
Insufficient							
Adverse Events (Bleeding risk)	3 RCTs: 822 pts.	Medium	Direct	Consistent	Precise	Suspected	We were able to perform a meta-analysis on three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis). <sup>99, 100, 131, 165</sup> 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).
Moderate							

## Venous Stripping plus Ligation vs. Sclerotherapy

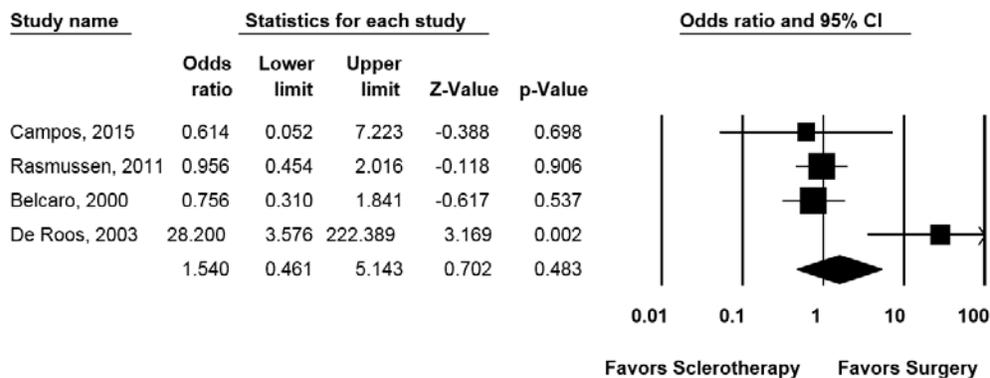
### Overview

Twelve RCTs compared venous stripping plus ligation surgery vs. foam sclerotherapy.<sup>58, 59, 65, 66, 75, 84, 93-95, 106, 124, 129, 140, 145, 166</sup> Four studies compared surgery vs. liquid sclerotherapy.<sup>96, 155, 160, 166</sup> One study compared venous stripping plus ligation to venous stripping plus ligation plus foam sclerotherapy.<sup>84</sup> Another study compared venous stripping plus ligation to ligation plus sclerotherapy.<sup>145</sup>

### Effect on Recurrence and Repeat Intervention

We synthesized evidence from 4 RCTs (3 RCTs with 395 patients, 1 RCT with 96 limbs) which 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).

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



Abbreviation: CI=confidence interval

Four studies<sup>75, 93, 94, 96, 155</sup> reported repeat intervention rates at 3 months, 1 year, and 3 years. Three studies<sup>75, 93, 94, 155</sup> reported higher incidence of repeat intervention in the sclerotherapy arms but significance was only reported in one study.<sup>75</sup> One good quality study<sup>75</sup> with four treatment arms (EVLA, RFA, foam sclerotherapy, and high ligation plus stripping) compared rates of repeat intervention at 3 years followup. A significantly higher percent of sclerotherapy patients underwent repeat interventions when compared with surgery patients (sclerotherapy=31.6% vs. surgery=15.5%,  $p<0.0001$ ).<sup>75</sup> Within the 28 days of the intervention, a European study reported 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).<sup>155</sup> 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 (sclerotherapy repeat intervention in 1/38 patients, surgery repeat intervention in 1/34 patients, statistical significance NR).<sup>96</sup> In a fair quality study, at 3 months followup, 15 out of 77 sclerotherapy patients and 11 out of 68 surgery patients underwent repeat intervention.<sup>93, 94</sup> Alternatively, this study<sup>93</sup> also reported freedom

from repeat intervention rates at 5-years' followup and found no significant difference between arms (22/77 foam sclerotherapy patients vs. 22/69 ligation plus stripping patients;  $p=0.546$ ).

### **Effect on Reflux**

Only one poor-quality European study reported elimination of reflux as an outcome.<sup>166</sup> At 3 months postintervention, there was no significant difference in the percent of patients with elimination of reflux between the groups (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).<sup>166</sup> A fair-quality study reported changes in ambulatory venous pressure (AVP) from baseline to 10 years.<sup>84</sup> 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).<sup>84</sup>

### **Effect on Clinical Symptoms**

Five studies<sup>59, 65, 66, 75, 106, 124</sup> 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 followup for both sclerotherapy and surgery but there was no significant difference between groups (baseline: sclerotherapy= $12.26 \pm 3.05$ , surgery= $12.5 \pm 1.64$ ; 12 months: sclerotherapy= $4.26 \pm 3.14$ , surgery= $3.39 \pm 1.57$ ; intragroup change  $p<0.001$ , between group  $p=NS$ ).<sup>106</sup> One study reported baseline and 6-month VCSS scores and there was an improvement in mean scores for both treatment groups (baseline: sclerotherapy= $4.9 \pm 2.6$ , surgery= $5.1 \pm 2.5$ ; 12 months: sclerotherapy= $1.6 \pm 1.7$ , surgery= $1.4 \pm 1.7$ ;  $p$ -value NR).<sup>65, 66</sup> One good-quality study only reported 3 year followup VCSS scores and not baseline scores.<sup>75</sup> The mean score for sclerotherapy was 0.15 (SD 0.4) versus 0.3 (SD 0.5) for surgery ( $p>0.05$ ).<sup>75</sup> Two studies reported improvement in VCSS scores at different time points.<sup>59, 124</sup> 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 NR).<sup>59</sup> A 3-year followup 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).<sup>58</sup> One fair-quality study of 393 patients reported improvement in VCSS scores at 2 years' followup, but there was no statistically significant difference between groups (foam sclerotherapy mean change -1.49, surgery mean change -1.75;  $p=0.232$ ).<sup>124</sup>

Two studies reported changes in CEAP classification at 3 months' followup.<sup>59, 129</sup> 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.<sup>129</sup> 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).<sup>59</sup>

### **Effect on Quality of Life**

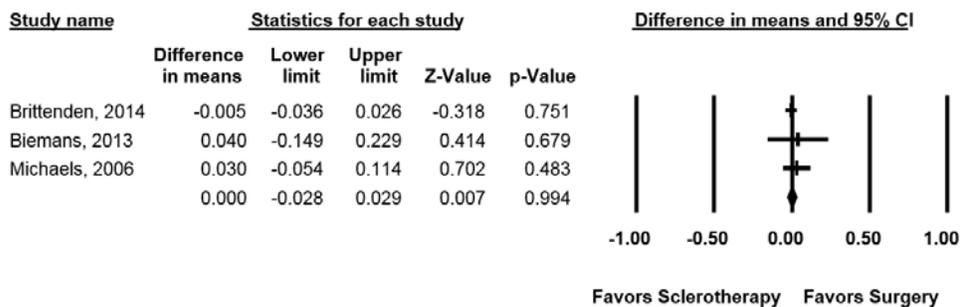
Three good-quality studies<sup>65, 66, 75, 106</sup> reported AVVQ as an outcome at various time points ranging from baseline to three years followup. All studies showed decreased scores at followup,

indicating an improvement in symptom scores. One study reported mean AVVQ scores at 3 days, 1 month, 1 year, and 3 years followup.<sup>75</sup> Mean scores decreased at successive followups, indicating an improvement in PVD-related symptoms, however no between group difference was noted at any followup 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).<sup>75</sup> One study reported baseline and 6 month followup and mean change in scores showed improvement for both groups, however statistical significance wasn't 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).<sup>65, 66</sup> Similarly, one study reported baseline and 1 year followup for 51 patients randomized to either foam sclerotherapy or high ligation plus stripping surgery.<sup>106</sup> The baseline and 1 year scores were higher in comparison to the previous study described,<sup>65, 66</sup> 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).<sup>106</sup>

One poor-quality study reported median within-group change in AVVQ scores at 3 months' followup. The surgical group had a median within-group improvement score of 7 points, whereas the sclerotherapy group had a 6-point improvement (no p-value reported).<sup>129</sup> 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).<sup>58</sup>

We synthesized evidence from 3 RCTs (900 patients) which explored the long-term change quality of life as measured by EQ-5D. These studies did not demonstrate a difference between strategies (Figure 16).

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



Abbreviation: CI=confidence interval

One fair-quality study reported the mean change in EQ-5D scores at 2 years' followup and found no difference between the groups (foam sclerotherapy mean change 0.064, surgery mean change 0.061; p=0.889).<sup>124</sup>

## Effect on Pain

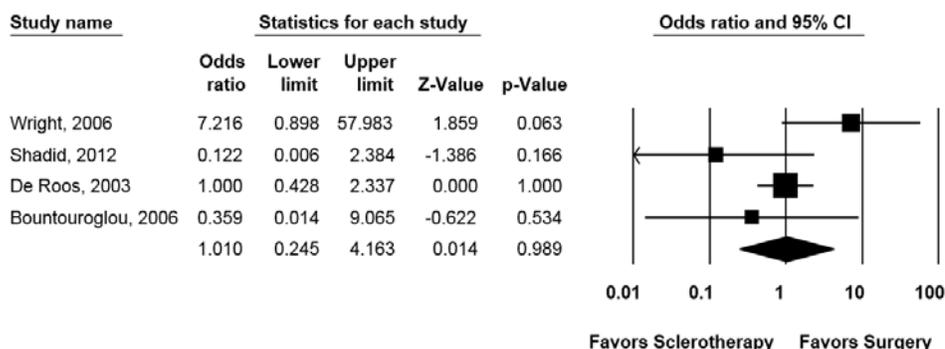
Four RCTs<sup>65, 66, 75, 96, 166</sup> reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies<sup>75, 96, 166</sup> reported significantly lower pain scores in the sclerotherapy group when compared with the surgery group. At 10 days followup, a good-quality study found that patients in the sclerotherapy arm had a mean VAS score of 1.6+/-2.04) versus those in the surgery arm had a mean score of 2.25 ± 2.23 (p<0.0001).<sup>75</sup> One poor-quality study of 217 patients used a VAS scale that ranged from 0-100.<sup>166</sup> 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).<sup>166</sup> A fair-quality study of 49 patients reported that the difference in mean pain scores was significant at 1 year followup (sclerotherapy, mean=0.77, SD=0.18; surgery, mean=0.83, SD=0.14; p<0.05).<sup>96</sup> One study<sup>65, 66</sup> reported baseline and 6 months followup 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 years' followup following ultrasound-guided foam sclerotherapy or surgical stripping with high ligation.<sup>124</sup> 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).<sup>124</sup>

## Adverse Events

One study<sup>94</sup> reported no DVTs or PEs in any of three arms (EVLA, sclerotherapy, or surgery) within 3 months of intervention. Another study<sup>75</sup> 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=NS). This study also reported PE in one of 124 patients in the foam sclerotherapy arm and zero of 119 in the surgery arm.<sup>75</sup> 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=NS).<sup>124</sup> 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 NR).<sup>166</sup> 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).<sup>59</sup>

We synthesized evidence from 4 RCTs (3 RCTs with 1,142 patients, 1 RCT with 96 limbs) which 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).

**Figure 17. Forest plot of hematoma effects for sclerotherapy vs. 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 followup timeframe, did not report the total number of patients in either arm.<sup>129</sup> In another fair-quality study, one of 29 surgery patients and three of 27 sclerotherapy patients experienced hematoma within an undefined timeframe postintervention (p-value NR).<sup>140</sup>

Four studies<sup>59, 124, 129, 155</sup> reported thrombophlebitis as an adverse event outcome; however, the various followup times precluded meta-analysis. In one study, the rate of thrombophlebitis was high for both groups but the difference was not statistically significant (sclerotherapy, 27.1% event rate; phlebectomy, 12.5% event rate; p=0.07).<sup>155</sup> A second study reported significantly higher 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).<sup>124</sup> A poor-quality study reported one case of 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.<sup>129</sup> Similarly, a fair-quality study reported that zero out of 23 surgery patients and three out of 28 sclerotherapy patients experienced thrombophlebitis at 3 months (p-value NR).<sup>59</sup> A 5-year followup 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 thrombophlebitis (p-value NR).<sup>58</sup>

Six studies<sup>59, 94, 96, 124, 129, 140</sup> 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 NR)<sup>96</sup> (sclerotherapy, 0/77 patients; ligation plus stripping, 3/68; p-value NR)<sup>94</sup> (sclerotherapy, 0/unknown patients; ligation plus stripping, 1/unknown patients; p-value NR)<sup>129</sup> (sclerotherapy, 0/27 patients; surgery, 1/29 patients; p-value NR).<sup>140</sup> A fair-quality study of 73 patients (82 limbs) compared sclerotherapy to surgery with additional mechanical compression therapy for both arms.<sup>59</sup> Two out of 30 sclerotherapy patients and two out of 28 surgery patients reported periprocedural infection (p-value NR).<sup>59</sup> At 5 years' followup, groin infections were reported in two out of 39 limbs treated with foam sclerotherapy and two out of 43 limbs treated with surgery.<sup>59</sup> The fifth study reported a marginally statistically significant difference between groups with zero out of 230 sclerotherapy patients and four out of 200 surgery patients having wound infections within 1 week of intervention (p=0.031).<sup>124</sup>

## **Strength of Evidence**

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

**Table 10. Strength of evidence for major outcomes—KQ 2—venous stripping plus ligation vs. sclerotherapy**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Vein recurrence/	3 RCTs: 395 pts. 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) which 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).
Low							
Repeat intervention	3 RCTs 567 pts.	Medium	Direct	Consistent	Imprecise	None	Three studies <sup>75, 93, 94, 155</sup> reported higher incidence of repeat intervention in the sclerotherapy arms but significance was only reported in one study. <sup>75</sup>
Insufficient							
Reflux	1 RCT: 654 pts.	High	Direct	Inconsistent	Imprecise	Suspected	Only one poor-quality European study reported elimination of reflux as an outcome. <sup>166</sup> At 3 months postintervention, there was no significant difference in the percent of patients with elimination of reflux between the groups (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). <sup>166</sup> A fair-quality study reported changes in ambulatory venous pressure (AVP) from baseline to 10 years. <sup>84</sup> 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 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). <sup>84</sup>
Insufficient	1 RCT: NR						
Clinical Symptom Scores (VCSS)	5 RCTs 1,372 pts.	Low	Direct	Inconsistent	Imprecise	Suspected	Five studies <sup>59, 65, 66, 75, 106, 124</sup> 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 followup 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). <sup>106</sup> 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). <sup>65, 66</sup> One good-quality study only reported 3 year followup VCSS scores and not baseline scores. <sup>75</sup> The mean score for sclerotherapy was 0.15 (SD 0.4) versus 0.3 (SD 0.5) for surgery
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	N Pts	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
									(p>0.05). <sup>75</sup> Two studies reported improvement in VCSS scores at different time points. <sup>59, 124</sup> 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). <sup>59</sup> A 3-year followup 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). <sup>58</sup> One fair-quality study of 393 patients reported improvement in VCSS scores at 2 years' followup, but there was no statistically significant difference between groups (foam sclerotherapy mean change -1.49, surgery mean change -1.75; p=0.232). <sup>124</sup>
Clinical Symptom Scores (CEAP)	2 RCTs: 129 pts.	High		High	Direct	Inconsistent	Imprecise	None	Two studies reported changes in CEAP classification at 3 months' followup. <sup>59, 129</sup> 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. <sup>129</sup> 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). <sup>59</sup>
		Insufficient							
Patient-reported Quality of Life (AVVQ)	3 RCTs: 583 pts.	Low		Low	Direct	Consistent	Imprecise	Suspected	Three good-quality studies <sup>65, 66, 75, 106</sup> reported AVVQ as an outcome at various time points ranging from baseline to three years followup. All studies showed decreased scores at followup, indicating an improvement in symptom scores but no difference between groups.
		Low							
Patient-reported Quality of Life (EQ-5D)	3 RCTs: 900 pts.	Medium		Medium	Direct	Consistent	Precise	None	We synthesized evidence from 3 RCTs (900 patients) which explored the long-term change quality of life as measured by EQ-5D. These studies did not demonstrate a difference between strategies (difference in means = 0, 95% CI -0.028 to 0.029) (Figure 16).
		High							
Reduction of LE Pain	3 RCTs: 1,498 pts. 1 RCT: NR	Medium		Medium	Direct	Consistent	Imprecise	Suspected	Four RCTs <sup>65, 66, 75, 96, 166</sup> reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies <sup>75, 96, 166</sup> reported significantly lower pain scores in the sclerotherapy group when compared with the surgery group.
		Low							
Adverse Events (Presence of DVT)	4 RCTs: 1,796 pts. 1 RCT: 82 limbs	Medium		Medium	Direct	Inconsistent	Imprecise	Suspected	One study <sup>94</sup> reported no DVTs or PEs in any of three arms (EVLA, sclerotherapy, or surgery) within 3 months of intervention. Another study <sup>75</sup> 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

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
		Insufficient						also reported PE in one of 124 patients in the foam sclerotherapy arm and zero of 119 in the surgery arm. <sup>75</sup> 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). <sup>124</sup> 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). <sup>166</sup> 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). <sup>59</sup>
Adverse Events (Hematoma)	3 RCTs: 1,142 pts. 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) <sup>59, 124, 155, 166</sup> which 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).
Low								
Adverse Events (Thrombophlebitis)	2 RCTs: 1,084 pts. 2 RCTs: 178 limbs	Medium	Direct	Inconsistent	Imprecise	None		Four studies <sup>59, 124, 129, 155</sup> reported thrombophlebitis as an adverse event outcome; however, the various followup times precluded meta-analysis. In one study, the rate of 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). <sup>155</sup> A second study reported significantly higher 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). <sup>124</sup> A poor-quality study reported one case of 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. <sup>129</sup> Similarly, a fair-quality study reported that zero out of 23 surgery patients and three out of 28 sclerotherapy patients experienced thrombophlebitis at 3 months (p-value not reported). <sup>59</sup> A 5-year followup 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 thrombophlebitis (p-value not reported). <sup>58</sup>
Insufficient								
Adverse Events (Wound)	6 RCTs: 889 pts.	Medium	Direct	Consistent	Imprecise	Suspected		Six studies <sup>59, 94, 96, 124, 129, 140</sup> reported wound infections at various time points that were not conducive for meta-analysis. Four studies found zero

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Infections)							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) <sup>96</sup> (sclerotherapy, 0/77 patients; ligation plus stripping, 3/68; p-value not reported) <sup>94</sup> (sclerotherapy, 0/unknown patients; ligation plus stripping, 1/unknown patients; p-value not reported) <sup>129</sup> (sclerotherapy, 0/27 patients; surgery, 1/29 patients; p-value not reported). <sup>140</sup>
Insufficient							

## **Venous Stripping plus Ligation vs. Thermal Ablation**

### **Overview**

There was one study comparing venous stripping plus ligation vs. steam thermal ablation with a total of 102 patients.<sup>107</sup> 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.<sup>107</sup>

### **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, neither group reported any instances of DVT or PE.<sup>107</sup>

### **Strength of Evidence**

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

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

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Recurrence	1 RCT: 102 pts.	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. <sup>107</sup>
insufficient							
Clinical Symptom Scores (VCSS)	1 RCT: 102 pts.	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	1 RCT: 102 pts.	Medium	Direct	NA	Imprecise	None	After 1 week, neither group reported any instances of DVT or PE. <sup>107</sup>
insufficient							

## Comparisons of Endovascular Interventions versus Endovascular Interventions

### EVLA vs. Sclerotherapy

Three RCTs,<sup>65, 66, 75, 91</sup> two of good quality<sup>65, 66, 75</sup> and one of fair quality,<sup>91</sup> reported comparisons of EVLA vs. endovenous foam sclerotherapy. One of these studies was shared in two publications.<sup>65, 66</sup> 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 followup periods ranged from 7 days to 3 years. Three RCTs were conducted in the UK/Europe: one study was conducted at 11 sites,<sup>65, 66</sup> one was conducted at 2 sites,<sup>75</sup> and the third was conducted in a single center.<sup>91</sup> One study reported government and industry funding sources,<sup>75</sup> another reported only government funding<sup>65, 66</sup> and one reported both an industry and non-government funding source.<sup>91</sup> 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<sup>65, 66, 75</sup> and in the remaining study the majority of patients had a baseline CEAP class of C2-C4.<sup>91</sup>

### Effect on Quality of Life

Two good-quality RCTs<sup>65, 66, 75</sup> and one fair-quality RCT<sup>91</sup> reported information on quality of life following EVLA versus endovenous foam sclerotherapy. The studies presented AVVQ scores at 6 weeks,<sup>65</sup> 3 months,<sup>91</sup> 6 months,<sup>65, 66</sup> 15 months<sup>91</sup> and at 3 years<sup>75</sup> 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 ( $p=0.032$ ).<sup>65</sup> 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 ( $p=0.01$ ).<sup>91</sup> AVVQ scores improved within each group by 6 months.<sup>66</sup> 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.<sup>66</sup> 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.<sup>91</sup> 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.<sup>75</sup> 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.<sup>75</sup> One study reported the EuroQol 5D 3L (EQ-5D-3L). The EQ-5D-3L score improved within each group at 6 months.<sup>66</sup> 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.<sup>66</sup> The majority of studies presented Short Form 36-item Health Survey (SF-36) data for each group.<sup>65, 66, 75</sup> 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 ( $p=0.908$ ).<sup>91</sup>

### **Effect on Other Standardized Symptom Scores**

Two good-quality RCTs<sup>66, 75</sup> and one fair-quality RCT<sup>91</sup> 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 ( $p=0.796$ ).<sup>91</sup> VCSS improved within each group at 6 months,<sup>66</sup> 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.<sup>66</sup> 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 ( $p=0.902$ ).<sup>91</sup> At 3 years, the mean VCSS in the EVLA group was 0.34 compared with 0.15 in the foam sclerotherapy group.<sup>75</sup> One study also reported information on the effect on VCSS in a subgroup of patients having great saphenous veins  $\geq 8$  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 ( $p=0.897$ ).<sup>91</sup> 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.<sup>91</sup> There was no statistically significant between-group difference at 3 months ( $p=0.148$ ) or at 15 months ( $p=0.866$ ).<sup>91</sup> This study also presented information on the effect on STS in a subgroup of patients having great saphenous veins  $\geq 8$  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.<sup>91</sup> There was a statistically significant between-group difference in favor of foam sclerotherapy at 3 months ( $p=0.014$ ).<sup>91</sup>

### **Effect on LE Pain**

One study reported 0-10 VAS pain scores for residual varicosities. VAS improved within each group at 6 months.<sup>66</sup> 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.<sup>66</sup> 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).<sup>75</sup> 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 ( $p=0.005$ ).<sup>91</sup>

### **Effect on Perioperative/Postoperative Complications**

Two studies reported the number of patients with venous thrombosis and venous thromboembolic events for each group.<sup>75,91</sup> In one study,<sup>75</sup> 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,<sup>91</sup> 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 thrombophlebitis at 1 month for EVLA and foam sclerotherapy groups, with each group having one patient with hemorrhage.<sup>75</sup> A total of four patients in the EVLA group had thrombophlebitis versus 17 in the foam sclerotherapy group.<sup>75</sup> The other study reported the presence of hematoma and dermal thermal injury in the EVLA group during the postoperative period.<sup>91</sup> Two patients had hematoma and two had dermal thermal injury.<sup>91</sup>

### **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.<sup>66</sup> 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.<sup>75</sup> 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 ( $p=0.001$ ).<sup>91</sup> According to one study, three patients in the EVLA group repeated intervention compared with 28 in the foam sclerotherapy group.<sup>91</sup> In the other study, the percentage of patients that repeated intervention at 3 years was 12.5% in the EVLA group, and was 31.6% in the foam sclerotherapy group.<sup>75</sup> 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.<sup>91</sup>

### **Strength of Evidence**

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

**Table 12. Strength of evidence for major outcomes—KQ 2—EVLA vs. sclerotherapy**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Bleeding (Short-term)	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	2 bleeding events in EVLA arm and none in foam sclerotherapy arm. <sup>91</sup>
Insufficient							
Bleeding (Intermediate-term)	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. <sup>75</sup>
Insufficient							
Changes on standardized symptom scores (Short-term)	1 RCT 785	Low	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups. <sup>66</sup>
Insufficient							
Changes on standardized symptom scores (Intermediate-term)	2 RCTs: 885	Low	Direct	Consistent	Precise	Suspected	VCSS improved in both groups. No statistically difference between groups. <sup>66, 91</sup>
Low							
Changes on standardized symptom scores (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	VCSS improved in both groups. No statistically difference between groups. <sup>75</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	3 RCTs: 1,374	Low	Direct	Consistent	Imprecise	Suspected	In 3 different RCTs, there was no statistically significant difference in presence of reflux, <sup>66</sup> recurrence of varicoses, <sup>75</sup> or change of venous filling index/VFI. <sup>91</sup>
<b>Insufficient</b>							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	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). <sup>91</sup>
<b>Insufficient</b>							
Patient-reported QOL (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups. <sup>75</sup>
<b>Insufficient</b>							
Patient-reported QOL (Intermediate-term)	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. <sup>66,91</sup>
<b>Low</b>							
Patient-reported QOL (Long-term)	2 RCTs: 580	Medium	Direct	Consistent	Imprecise	Suspected	QOL improved in both group. No statistically difference between groups. <sup>75,91</sup>
<b>Low</b>							
Periprocedural complications (Short-term)	1 RCT 100	Medium	Direct	NA	Imprecise	Suspected	The number of patients with dermal thermal injury in post operative period was 2 in EVLA group. <sup>91</sup>
<b>Insufficient</b>							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Qualitative reduction in LE pain (Short-term)	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). <sup>66, 91</sup>
Low							
Qualitative reduction in LE pain (Intermediate-term)	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. <sup>66</sup>
Insufficient							
Repeat Intervention (Intermediate-term)	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. <sup>91</sup>
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 group, and was 31.6% in foam sclerotherapy group. <sup>75</sup>
Insufficient							
Thrombophlebitis (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The number of patients with thrombophlebitis at 1 month was 4 in EVLA group and was 17 in foam sclerotherapy group. <sup>75</sup>
Insufficient							
Venous thrombo-embolic events (Intermediate-term)	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. <sup>75, 91</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
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. <sup>75, 91</sup>
Insufficient							
Abbreviations: [To be added in final draft]							

## **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.<sup>116</sup> This study included 320 patients with symptomatic varicose veins. Followup 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 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% at 3 months, 1.16% at 2 years, and 0.77% at 3 years. The percentage of complications in the foam sclerotherapy group was 6.3% at 3 months, and was 0 at 3 years (no data presented for 2-year followup). 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. Strength of evidence for major outcomes—KQ 2—Nd:YAG laser ablation vs. sclerotherapy**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Improvement in LE venous hemodynamics/reflux severity (Long-term)	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. <sup>116</sup>
Insufficient							
Patient-reported QOL (Intermediate-term)	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. <sup>116</sup>
Insufficient							
Patient-reported QOL (Long-term)	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. <sup>116</sup>
Insufficient							
Periprocedural complications (Intermediate-term)	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. <sup>116</sup>
Insufficient							
Periprocedural complications (Long-term)	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. <sup>116</sup>
Insufficient							
Qualitative reduction in LE pain (Short-term)	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. <sup>116</sup>
Insufficient							

Abbreviations: [To be added in final report]

## **EVLA versus RFA**

Five RCTs, two of good quality,<sup>101, 102, 127</sup> one of fair quality<sup>133</sup> and 2 of poor quality,<sup>134, 142</sup> reported comparisons of EVLA versus endovenous RFA, associated with compression in all groups. One of these studies was shared in two publications.<sup>101, 102</sup> 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.<sup>127</sup> Individual study sample sizes ranged from 66 to 131. Study followup periods ranged from 2 days to 1 year. One RCT was conducted in a single U.S. center,<sup>133</sup> three were conducted in a single center in the UK/Europe,<sup>101, 102, 127, 134</sup> and the remaining study was conducted at 6 sites in the United States and the UK/Europe.<sup>142</sup> Two studies reported an industry funding source,<sup>134, 142</sup> while three reported non-government/non-industry funding.<sup>101, 102, 127, 133</sup> 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<sup>127, 142</sup> and in two other studies the majority of patients had a baseline CEAP class of C3-C4.<sup>101, 102, 133</sup> The CEAP class was not reported in the final RCT.<sup>134</sup>

One fair quality observational study<sup>104</sup> reported comparisons of EVLA versus RFA. This study involved 979 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Study followup 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 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.

## **Effect on Quality of Life**

Two studies of good quality presented AVVQ scores for each group.<sup>101, 102, 127</sup> At 6 weeks the mean between-group change of AVVQ was 0.2 in the EVLA group and -0.3 in the RFA group.<sup>102</sup> 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 ( $p=0.12$ ).<sup>127</sup> 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.<sup>101, 102</sup> One fair-quality study<sup>133</sup> and one poor-quality study<sup>142</sup> 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.<sup>133</sup> The poor-quality study 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.<sup>142</sup> One study presented the mean improvement of EQ5-D for each group. The mean improvement of EQ5-D was 0.22 in the EVLA group and 0.16

in the RFA group. There was no statistically significant between-group difference ( $p=0.66$ )<sup>127</sup> One study also reported SF-36 data for each group.<sup>101, 102</sup>

### **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 ( $p=0.0009$ ).<sup>142</sup> 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 ( $p=0.0006$ ).<sup>133</sup> One study of good quality presented VCSS scores at 6 weeks and 6 months for each group.<sup>101, 102</sup> 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.<sup>101, 102</sup> 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 ( $p=0.019$ ).<sup>104</sup> One fair-quality study reported the number of patients with clinical class of CEAP  $\geq 3$  at 1 year. Before treatment, 21 RFA patients and 24 EVLA patients had a clinical class of CEAP score  $\geq 3$ . 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 followup.<sup>133</sup>

### **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 ( $p=0.001$ ).<sup>127</sup> 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 ( $p=0.01$ ).<sup>101, 102</sup>

### **Effect on Perioperative/Postoperative Complications**

Three RCTs reported the number of patients with venous thromboembolic events<sup>127, 133, 142</sup> 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.<sup>101, 102</sup> A fair-quality observational study reported venous thromboembolic events for each group.<sup>104</sup> 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.<sup>104</sup> 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 ( $p=0.106$ ).<sup>104</sup> 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).<sup>104</sup> One good-quality RCT<sup>101, 102</sup> and one fair-quality observational study.<sup>104</sup> 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.<sup>101, 102</sup> 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).<sup>104</sup> 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.<sup>133</sup> Two good-quality RCTs reported on the incidence of thrombophlebitis at 1 week<sup>127</sup> and 1 month<sup>101, 102</sup> and one poor-quality RCT<sup>142</sup> reported on thrombophlebitis at 2 days and 1 month for each group. In one of the high-quality RCTs, the percentage of patients with thrombophlebitis at 1 week was 2.6% in the EVLA group and 1.3% in the RFA group (between-group difference NS).<sup>127</sup> The other good-quality RCT reported 5/67 patients with thrombophlebitis in the RFA group and 3/64 in the EVLA group.<sup>101, 102</sup> In the poor-quality RCT, the number of patients with 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 thrombophlebitis.<sup>142</sup>

### **Effect on Improvement in Venous Hemodynamics**

One good-quality study,<sup>127</sup> one fair-quality study<sup>133</sup> and one poor-quality study<sup>134</sup> reported postprocedure occlusion rates for each group at intervals including 1 week,<sup>133</sup> 30 days,<sup>134</sup> and 3 months.<sup>127</sup> In the fair-quality study, at 1 week, 46 patients (100%) in the EVLA group and 48 (100%) in the RFA group had venous occlusion.<sup>133</sup> In the poor-quality study, at 30 days, 37 patients in the EVLA group had occlusion versus 38 in the RFA group (difference NS).<sup>134</sup> 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).<sup>127</sup> The fair-quality study also reported mean number of microphlebectomies at short-term followup: 6.5 in the EVLA group; 5.5 in RFA.<sup>133</sup> The same study<sup>133</sup> 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. Strength of evidence for major outcomes—KQ 2—EVLA vs. RFA**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short-term)	2 RCTs 249 1 Obs	Medium	Direct	Consistent	Imprecise	None	According to <i>Shepherd et al</i> , 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 ( $p < 0.001$ ). <sup>101, 102, 104, 133</sup>
Low	979 limbs						<i>Gale et al</i> reported the number of patients with bruising at 1 week. There was a significant more bruising in the EVLA group at 1 week ( $p = 0.01$ ). <sup>133</sup>
Bleeding (Intermediate-term)	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. <sup>133</sup>
Insufficient							
Changes on standardized symptom scores (Short-term)	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. <sup>104, 133, 142</sup>
Low							
Changes on standardized symptom scores (Intermediate-term)	3 RCTs 336	Medium	Direct	Consistent	Imprecise	None	VCSS improved in both group. No statistically difference between groups. <sup>101, 102, 133, 142</sup>
Low							
Changes on standardized symptom scores (Long-term)	2 RCTs 249	Medium	Direct	Consistent	Imprecise	None	VCSS improved in both group. No statistically difference between groups. <sup>101, 102, 133</sup>
Low							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Improvement in LE venous hemodynamics /reflux severity (Short-term)	1 RCT 118	Medium	Direct	NA	Imprecise	None	Occlusion rate: No statistically difference between groups <sup>133</sup>
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	2 RCTs 259	Medium	Direct	Inconsistent	Imprecise	Suspected	Occlusion rate: No statistically difference between groups. <sup>127, 134</sup>
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long-term)	1 RCT 118	Medium	Direct	NA	Imprecise	None	Recanalization: Demonstrating a statistically significance in favor of EVLA group (p=0.002). <sup>133</sup>
Insufficient							
Patient-reported QOL (Short-term)	3 RCTs 372	Low	Direct	Consistent	Imprecise	None	QOL improved in both group. No statistically difference between groups <sup>101, 102, 127, 142</sup>
Low							
Patient-reported QOL (Intermediate-term)	4 RCTs 490	Medium	Direct	Consistent	Imprecise	None	QOL improved in both group. No statistically difference between groups SOE= high <sup>101, 102, 127, 133, 142</sup>
Low							
Patient-reported QOL (Long-term)	1 RCT 118	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups <sup>133</sup>
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Qualitative reduction in LE pain (Short-term)	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). <sup>101, 102, 127</sup>
Repeat Intervention (Short-term)	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. <sup>133</sup>
Insufficient							
Thrombophlebitis (Short-term)	3 RCTs 372	Low	Direct	Inconsistent	Imprecise	None	The number of patients with thrombophlebitis at 2 days was 5 in EVLA group. No one patient had thrombophlebitis in RFA group. Demonstrating a significant between-groups difference regarding thrombophlebitis in favor of RFA group at 2 days (p=0.020). At 1 month, no one patient had thrombophlebitis in both group. At 1 week the percentage of patients with 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 thrombophlebitis in each group: 6 in RFA group and 3 in EVLA group. <sup>101, 102, 127, 142</sup>
Insufficient							
Venous thrombo-embolic events (Short-term)	1 RCT 154	Low	Direct	NA	Imprecise	None	At 1 week, no patient presented pulmonary embolism in both groups. <sup>127</sup>
Insufficient							
Venous thrombo-embolic events (Intermediate-term)	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. <sup>101, 102, 104, 142</sup>
Insufficient							
Venous thrombosis (Short-term)	2 RCTs 272	1 Fair, 1 Good	Direct	Consistent	Imprecise	None	<i>Nordon et al</i> reported that no patient presented deep venous thrombosis in both groups at 1 week. <sup>127</sup> <i>Gale et al</i> reported that one patient presented deep venous thrombosis in EVLA group and no patient presented DVT in RFA group at 1 week. <sup>133</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Venous thrombosis (Intermediate-term)	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. <sup>104</sup>
							Insufficient
Venous Wound Infection (Short-term)	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. <sup>101, 102, 104</sup>
							Insufficient

Abbreviations: [To be included in final draft]

## **EVLA plus Phlebectomy versus RFA plus Phlebectomy**

One good-quality RCT<sup>75</sup> (N=762) and 1 fair-quality observational study<sup>163</sup> (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 followup 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.<sup>75</sup> 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.<sup>75</sup>

### **Effect on 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.<sup>75</sup> The same study also reported median AVSS 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.<sup>75</sup>

### **Effect on Other Standardized Symptom Scores**

The RCT also presented VCSS data at 3 years' followup. At 3 years, the mean VCSS in the EVLA plus phlebectomy group was 0.34 versus 0.44 in the RFA plus phlebectomy group.<sup>75</sup>

### **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).<sup>75</sup>

### **Effect on Perioperative/Postoperative Complications**

Both studies reported the number of patients with venous thromboembolic events<sup>75, 163</sup> 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.<sup>163</sup> The RCT reported rates of hemorrhage and 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 thrombophlebitis versus 12 in the RFA plus phlebectomy group.<sup>75</sup>

### **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.<sup>75</sup>

**Strength of Evidence**

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

**Table 15. Strength of evidence for major outcomes—KQ 2—EVLA plus phlebectomy vs. RFA plus phlebectomy**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
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. <sup>75</sup>
Insufficient							
Changes on standardized symptom scores (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups. <sup>75</sup>
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. <sup>75</sup>
Insufficient							
Patient-reported QOL (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups. <sup>75</sup>
Insufficient							
Patient-reported QOL (Long-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	No statistically difference between groups. <sup>75</sup>
Insufficient							
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). <sup>75</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
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. <sup>75</sup>
Insufficient							
Thrombophlebitis (Short-term)	1 RCT 489	Low	Direct	NA	Imprecise	None	The number of patients with thrombophlebitis at 1 month was 4 in EVLA+P group and was 12 in RFA+P group. <sup>75</sup>
Insufficient							
Venous thromboembolic 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. <sup>163</sup>
Insufficient							
Venous thromboembolic 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. <sup>75</sup>
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 EVLAP group and in RFAP group. <sup>75</sup>
Insufficient							

Abbreviations: [To be added in final report]

## **EVLA versus EVLA plus Phlebectomy**

Two RCTS, both of fair quality, compared EVLA versus EVLA plus phlebectomy.<sup>123, 143</sup> In all, the studies included a total of 184 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Study followup periods ranged from 1 week to 1 year. One study was conducted in a single-center in the UK/Europe;<sup>143</sup> the other was conducted in a single center in Asia.<sup>123</sup> 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<sup>123</sup> and in the other study the baseline CEAP class was not reported.

### **Effect on 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) ( $p=0.015$ ).<sup>143</sup>

### **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 ( $p=0.433$ ).<sup>143</sup>

### **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.<sup>123</sup>

### **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 ( $p=0.018$ ).<sup>123</sup> The same study reported the presence of skin burn, ecchymosis, 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 ( $p=0.011$ ).<sup>123</sup> 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 ( $p<0.001$ ).<sup>143</sup>

### **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 ( $p=0.022$ ).<sup>123</sup>

## **Strength of Evidence**

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

**Table 16. Strength of evidence for major outcomes—KQ 2—EVLA vs. EVLA plus phlebectomy**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Bleeding (Short-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	Demonstrating statistically significance in less bleeding in EVLA arm (p=0.018). <sup>123</sup>
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 + phlebectomy group. <sup>123</sup>
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. <sup>143</sup>
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) <sup>123</sup>
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 + phlebectomy group at 6 weeks (p<0.001) and 3 months (p=0.015). <sup>143</sup>
Insufficient							
Patient-reported QOL (Long-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups <sup>123</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Periprocedural complications (Short-term)	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). <sup>143</sup>
Insufficient							
Qualitative reduction in LE edema (Short-term)	1 RCT 134	Medium	Direct	NA	Imprecise	None	Both groups had a similar number of patients with a non-significant between-groups difference. <sup>123</sup>
Insufficient							
Qualitative reduction in LE pain (Short-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	The EVLA group reported less patients with pain versus the EVLTAP 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. <sup>123</sup>
Insufficient							
Venous wound infection (Short-term)	1 RCT 132	Medium	Direct	NA	Imprecise	None	Similar number of patients with wound infection. No significant difference between groups. <sup>123</sup>
Insufficient							

## **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,<sup>100</sup> while longer term followup (mean 3.6 years [max 6 years]) was reported in a second publication.<sup>99</sup> 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% 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.<sup>100</sup>

### **Effect on Improvement in Venous Hemodynamics**

Inguinal recurrence on ultrasound was the primary outcome of the short-term followup study. In the high ligation/stripping arm, 0/159 patients had inguinal recurrence, versus 10/148 (6.7%) in the high ligation/EVLA arm ( $p < 0.0009$ ).<sup>100</sup> The long-term followup study evaluated reflux into the great saphenous vein (GSV) as measured on ultrasound.<sup>99</sup> In the ligation/stripping group, reflux was present in zero patients at 2 years, five patients (6.6%) at 3 years, two patients (3.6%) at 4 years, five patients (9.5%) at 5 years, and five patients (11.7%) at 6 years. In the ligation/EVLA group, reflux was present in 12 (11.7%) patients at 2 years, nine patients (13.3%) at 3 years, 11 patients (18.4%) at 4 years, eight patients (12.8%) at 5 years, and four (7.0%) 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% of patients reported pain at 1 day versus 50.0% in the high ligation/EVLA arm ( $p = 0.0069$ ).<sup>100</sup> At 2 months, 7.8 percent of patients in the high ligation/stripping arm reported persistent pain versus 13.5 percent in the high ligation/EVLA arm ( $p = \text{NS}$ ).<sup>100</sup>

### **Effect on Other Standardized Symptom Scores**

The RCT presented Venous Disability Score (VDS) and CEAP data at baseline and at 2 months.<sup>100</sup> VDS scores were similar in both groups at baseline (between-group p-value NR); at 2 months, approximately 85% of high ligation/stripping and high ligation/EVLA patients were asymptomatic by VDS (between-group p-value NR). In both groups, >70% of the population was CEAP C2 at baseline; by 2 months, approximately 90% of high ligation/stripping and high ligation/EVLA patients were CEAP C0-1 ( $p = \text{NS}$  for between-group difference at baseline and 2 months). CEAP distributions remained similar between the ligation/stripping and ligation/EVLA arms during long-term followup.<sup>99</sup> At 12 months, approximately 85% of the ligation/stripping group remained at CEAP class C0-1 versus approximately 90% of the ligation/EVLA group (between-group p-value NR); these percentages decreased over time in each group, and at 6 years of followup, approximately 60% of the ligation/stripping group had a CEAP class of C0-1 versus approximately 75% 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).<sup>146</sup> This study included 65 patients with LE chronic venous insufficiency/reflux and varicose veins; however, the study did not report the presence of symptoms. Followup 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 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. Strength of evidence for major outcomes—KQ 2—EVLA vs. EVLA plus sclerotherapy**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
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. <sup>146</sup> )
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. <sup>146</sup>
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). <sup>146</sup>
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 EVLTAP 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 EVLTAP. <sup>143</sup>

Abbreviations: [To be added in final draft]

## Cyanoacrylate (CA) Embolization versus RFA

One fair-quality RCT reported a comparison of CA embolization versus RFA.<sup>108</sup> This study included 242 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Followup 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 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% in the RFA group ( $p<0.01$ ). In addition, 22 patients in the CA embolization group had 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. Strength of evidence for major outcomes—KQ 2—CA embolization vs. RFA**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting	
						Bias	Findings
Bleeding (Short-term)	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 ( $p<0.01$ ). <sup>108</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Changes on standardized symptom scores (Short-term)	1 RCT 226	Medium	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups. <sup>108</sup>
Insufficient							
Changes on standardized symptom scores (Intermediate-term)	1 RCT 226	Medium	Direct	NA	Imprecise	None	VCSS improved in both group. No statistically difference between groups. <sup>108</sup>
Insufficient							
Patient-reported QOL (Short-term)	1 RCT 226	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups. <sup>108</sup>
Insufficient							
Patient-reported QOL (Intermediate-term)	1 RCT 226	Medium	Direct	NA	Imprecise	None	QOL improved in both group. No statistically difference between groups. <sup>108</sup>
Insufficient							
Qualitative reduction in LE pain (Short-term)	1 RCT 226	Medium	Direct	NA	Imprecise	None	No significant difference between procedures (p=0.36). <sup>108</sup>
Insufficient							
Thrombophlebitis (Intermediate-term)	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 thrombophlebitis was 16. There was not a significant between-groups difference at 3 months (p=0.36). <sup>108</sup>
Insufficient							

Abbreviations: [To be added in final draft]

## **Mechanochemical Endogenous Ablation (MOCA) versus RFA**

One fair-quality RCT reported a comparison of mechanochemical endogenous ablation versus RFA.<sup>111</sup> This study included 117 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. The followup period was 1 month. The study was conducted in two centers in the UK/Europe and reported government, industry, non-government, and non-industry funding sources. The mean age of the study participants was 51.4 years, and 59 percent of participants were female. Baseline CEAP class was not reported, nor was racial/ethnic composition of the study population.

## Effect on Quality of Life

The study presented mean AVVQ scores at 1 month for each group following MOCA or RFA. At one month, AVVQ scores were improved in the MOCA group from a baseline of 22.6 to 12.7, while AVVQ improved from a baseline of 22.7 to 15.5 in the RFA group (p=0.410). The study also evaluated EuroQol Visual Analogue Scale (EQ VAS) and EQ-5D-3L. In the MOCA group, mean EV QAS improved from 79.1 at baseline to 86 at 1 month, while in the RFA group, AVVQ improved from a 77.1 at baseline to 81 at 1 month (p-value for comparison=0.158). Mean EQ-5D-3L scores improved from 0.692 at baseline to 0.842 at 1 month in the MOCA group, while scores improved from 0.744 to 0.782 at 1 month (p-value for comparison=0.259).

## Effect on Other Standardized Symptom Scores

The study presented VCSS data at baseline and at 1 month postprocedure. In the MOCA group, VCSS improved from a baseline of 6.5 to 2.12 at 1 month, while in the RFA group, VCSS improved from 5.6 to 2.96 at 1 month (p-value for comparison=0.220). The study also presented VDS data at baseline and 1 month postprocedure. In the MOCA group, mean VDS was 1.44 at baseline, improving to 0.53 at 1 month, while in the RFA group, mean VDS was 1.24 at baseline, improving to 0.69 at 1 month (p for comparison=0.451).

## Effect on LE Pain

The study presented mean VAS pain scores at 1 month for MOCA group and RFA group. The MOCA group reported statistically significantly less pain at 1 month compared with the RFA group (utility 19.3 versus 34.5; p<0.001).

## Effect on Perioperative/Postoperative Complications

The study reported no instances of thrombophlebitis in the MOCA group at 1 month postprocedure, versus 2 in the RFA group. In addition, there were no instances of venous thrombosis in the MOCA group at 1 month, versus 1 in the RFA group.

## Strength of Evidence

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

**Table 19. Strength of evidence for major outcomes—KQ 2—MOCA vs. RFA**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting	
						Bias	Findings
Bleeding (Short-term)	1 RCT 117	Medium	Direct	NA	Imprecise	Suspected	4.5 events in MOCA arm and 1 event in RFA arm. <sup>111</sup>
Insufficient							
Changes on standardized symptom scores (Intermediate-term)	1 RCT 117	Medium	Direct	NA	Imprecise	Suspected	VCSS improved in both group. No statistically difference between groups. <sup>111</sup>
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	N Pts	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-reported QOL (Intermediate-term)	1 RCT	117	Medium	Direct	NA	Imprecise	Suspected	QOL improved in both group. No statistically difference between groups. <sup>111</sup>	
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 1 month (utility 19.3 versus 34.5, p<0.001). <sup>111</sup>	
Insufficient									
Thrombophlebitis (Short-term)	1 RCT	117	Medium	Direct	NA	Imprecise	Suspected	The number of patients with thrombophlebitis at 1 month was 0 in the MOCA group and 2 in RFA group. <sup>111</sup>	
Insufficient									

Abbreviations: [To be added in final draft]

## EVLA versus Thermal Ablation

One fair-quality RCT reported a comparison of EVLA versus endovenous steam ablation (EVSA)<sup>112</sup> in 237 patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins. Followup 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% 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 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 in 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 thrombophlebitis at 2 weeks, while zero patients in the EVLA group and three patients in the EVSA group experienced 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<sup>2</sup> at 2 weeks versus 1 cm<sup>2</sup> in the EVSA group. At 12 weeks, both groups had mean surface area of ecchymosis of 0 cm<sup>2</sup>. 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% in the EVLA group and was 93.9% in EVSA group (p=0.251). At 1 year, the occlusion rate was 96% in the EVLA group and was 86.9% 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. Strength of evidence for major outcomes—KQ 2—EVLA vs. thermal ablation**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
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. <sup>112</sup>
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). <sup>112</sup>
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). <sup>112</sup>
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. <sup>112</sup>
Insufficient							
Thrombophlebitis (Short-term)	1 RCT 218	Medium	Direct	NA	Imprecise	None	The number of patients with thrombophlebitis at 2 weeks was 10 in the EVLA group and 10 in EVSA group. <sup>112</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Thrombophlebitis (Intermediate-term)	1 RCT 218	Medium	Direct	NA	Imprecise	None	At 12 weeks, there was 0 patients with thrombophlebitis in EVLA group and there were 3 patients with thrombophlebitis in EVSA group. <sup>112</sup>
Insufficient							
Abbreviations: [To be added in final draft]							

## Comparisons of Endovascular Interventions vs. Other Therapies

### Endovascular Treatment vs. Placebo

Two good-quality RCTs<sup>103, 119</sup> and one fair-quality RCT<sup>153</sup> reported a comparison of different doses of polidocanol endovenous microfoam (PEM) versus placebo. In all, the studies included 544 patients; two studies<sup>103, 119</sup> included patients with symptomatic LE chronic venous insufficiency/reflux and varicose veins, while one study did not relate the presence of symptoms.<sup>153</sup> Individual study sample sizes ranged from 25 to 284. Followup periods ranged from 4 to 12 weeks. The two good-quality studies were conducted in the United States: one comprised 19 sites,<sup>103</sup> the other 14 sites.<sup>119</sup> The fair-quality study was conducted at a single center in the UK/Europe.<sup>153</sup> All studies reported an industry funding source.<sup>103, 119, 153</sup> The mean age of study participants ranged from 48.9 to 55.5 years, and the proportion of female patients ranged from 72 to 74.6 percent. The two U.S. studies reported that approximately 93% of study participants were white.<sup>103, 119</sup> In all studies, the majority of patients had a baseline CEAP class of C2-C4.

### Effect on Quality of Life

The two good-quality RCTs presented mean within-group changes for the Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire (VEINES-QOL) scores at 8 weeks for each group. One study compared doses of 0.5% PEM versus 1% PEM versus placebo. The mean within-group change of VEINES-QOL scores in the 0.5% group was 22.79 in the 0.5% group, 20.42 in the 1% group, and 7.42 in the placebo group.<sup>119</sup> There was a statistically significant between-group difference in favor of the 0.5% group ( $p < 0.0001$ ) and 1% group ( $p < 0.0001$ ) when compared with the placebo group.<sup>119</sup> The other study compared pooled doses (0.5%, 1% and 2%) of PEM, 0.125% PEM, and placebo. The mean within-group change of VEINES-QOL score in the pooled (0.5%, 1% and 2%) PEM group was 21.26, versus 16.28 in the 0.125% PEM group, versus 7.67 in the placebo group. There were statistically significant between-group differences in favor of the pooled (0.5%, 1% and 2%) PEM group ( $p < 0.0001$ ) and 0.125% PEM group ( $p = 0.0001$ ) when compared with the placebo group.<sup>103</sup>

### Effect on Other Standardized Symptom Scores

Both good-quality RCTs presented mean within-group change of VCSS at 8 weeks for each group. The study comparing doses of 0.5% and 1% PEM versus placebo reported a mean within-group change of VCSS of -5.15 in the 0.5% PEM group compared with -5.05 in the 1% PEM group and -1.52 in the placebo group.<sup>119</sup> There were statistically significant between-group differences in favor of the 0.5% PEM group ( $p < 0.0001$ ) and 1% PEM group ( $p < 0.0001$ ) when compared with placebo.<sup>119</sup> The other study compared pooled doses (0.5%, 1% and 2%) of PEM versus 0.125% PEM versus placebo. The mean within-group change of VCSS was -3.96 in the pooled PEM group, -2.97 in the 0.125% 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% PEM group ( $p < 0.0001$ ) compared with placebo.<sup>103</sup> Both good-quality studies also reported Varicose Veins Symptoms Questionnaire (VVsymQ) scores at 8 weeks. In the first study, the 0.5% PEM group had a mean VVsymQ score of 83.1%; the 1% PEM group had a mean score of 77.8%; and the placebo group had a mean score of 21.2%.<sup>119</sup> There were statistically significant between-group differences in favor of the 0.5% PEM group ( $p < 0.0001$ ) and 1% PEM group ( $p < 0.0001$ ) when compared with placebo group.<sup>119</sup> The other 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% PEM group was -5.44 versus -4.63 in the 1% PEM group and in the placebo group. There were statistically significant between-group differences in favor of 0.5% PEM group ( $p < 0.0001$ ) and 1% PEM group ( $p < 0.0001$ ) when compared with placebo group.<sup>103</sup>

### **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% and 1% PEM versus placebo. In the study comparing 0.5% and 1% PEM with placebo study, the percentages of patients without reflux were 60%, 58%, and 1.8%, respectively.<sup>119</sup> There were statistically significant between-group differences in favor of the 0.5% PEM group ( $p = 0.00043$ ) and the 1% PEM group ( $p = 0.0009$ ) when compared with placebo group.<sup>119</sup> In the other study, 123 patient in the pooled (0.5%, 1% and 2%) PEM group showed absence of reflux, compared with 24 in the 0.125% 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% PEM group.<sup>103</sup> 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.<sup>153</sup> 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  $< 0.05$ ).<sup>153</sup>

### **Strength of Evidence**

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

**Table 21. Strength of evidence for major outcomes—KQ 2—endovascular treatment vs. placebo**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes on standardized symptom scores (Intermediate-term)	2 RCTs 440	Low	Direct	Consistent	Precise	Suspected	<p><sup>103, 119</sup> Two good-quality RCTs demonstrated a statistically significance difference of VCSS in favor of 0.5% polidocanol endovenous group (p&lt;0.0001) and 1% polidocanol endovenous group (p&lt;0.0001) when compared with placebo group.</p> <p>The percentage of patient that changed VSSymQ at 8 weeks in the 0.5% polidocanol endovenous group was 83.1% in the 1% polidocanol endovenous group was 77.8% and in the placebo group was 21.2%. Demonstrating a statistically significant difference in favor of 0.5% polidocanol endovenous group (p&lt;0.0001) and 1% polidocanol endovenous group (p&lt;0.0001) when compared with placebo group.</p>
Moderate							
Improvement in LE venous hemodynamics /reflux severity (Short-term)	1 RCT 25	High	Direct	NA	Imprecise	Suspected	<p><sup>153</sup> 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</p> <p>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&lt;0.05)</p>
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Intermediate-term)	3 RCTs 465	Medium	Direct	Consistent	Precise	Suspected	<p><sup>103, 119, 153</sup> 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&lt;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</p>
Moderate							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Patient-reported QOL (Intermediate-term)	2 RCTs 443	Low	Direct	Consistent	Precise	Suspected	<sup>103, 119</sup> The mean within group change of VEINES-QOL in the 0.5% polidocanol endovenous group was 22.79, in the 1% polidocanol endovenous group was 20.42 and in the placebo group was 7.42. Demonstrating a statistically significant difference in favor of 0.5% polidocanol endovenous group (p<0.0001) and 1% polidocanol endovenous group (p<0.0001) when compared with placebo group.
Moderate							
Abbreviations: [To be added in final draft]							

## **Endovascular Treatment vs. Compression**

One fair-quality<sup>139</sup> and one poor-quality RCT<sup>130</sup> compared foam sclerotherapy versus mechanical compression with stockings, and one fair-quality RCT<sup>149</sup> compared EVLA versus mechanical compression with stockings. In total, all three studies comprised 150 patients with LE chronic venous insufficiency/reflux varicose veins and active ulcers. Individual study sample sizes ranged from 40 to 58, and study followup ranged from 1 day to 1 year. One study was conducted at 3 U.S. centers,<sup>130</sup> one at a single center in the UK/Europe<sup>139</sup> and one at a single center in Latin America.<sup>149</sup> One study reported non-government and non-industry funding sources,<sup>139</sup> one reported only industry funding,<sup>130</sup> and one did not report a funding source.<sup>149</sup> The mean/median age of study participants ranged from 45.5 to 69 years. The proportion of female patients ranged from 75 to 100 percent, although study did not report the proportion of females participants.<sup>139</sup> In two studies, the majority of patients had a baseline CEAP class of C6, while one study did not report baseline CEAP class.<sup>130</sup>

### **Effect on Quality of Life**

One poor-quality RCT comparing foam sclerotherapy with compression assessed AVVQ scores in both groups; however, there was a high rate of crossover of patients from the compression group to the foam sclerotherapy group, with 49 out of 58 patients ultimately received sclerotherapy. The AVVQ overall score was not reported.<sup>130</sup>

### **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.<sup>149</sup>

### **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.<sup>139, 149</sup> In one study<sup>139</sup> one patient presented with DVT in the foam sclerotherapy group at 22 weeks. In the other study,<sup>149</sup> neither group reported instances of venous thrombosis, thrombophlebitis, or wound infection in the postintervention period.<sup>149</sup>

### **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.<sup>139</sup> 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.<sup>139</sup>

### **Effect on Venous Ulcers**

Two studies reported on venous wound healing in the foam sclerotherapy or EVLA groups versus the respective mechanical compression groups.<sup>139, 149</sup> The study of foam sclerotherapy versus compression presented the number of patients with venous wound healing for each group at 12 and 24 weeks.<sup>139</sup> 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.<sup>149</sup> In the EVLA group, the percentage of patients with venous wound healing was 62.9% at 3 months, 81.5% at 6 months, 81.5% at 9 months, and 81.5% at 12 months. In the compression group, the percentage of patients with venous wound healing was 12% at 3 months, 20% at 6 months, 16% at 9 months, and 24% 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% in the compression group and 0% in the EVLA group. Additionally, this study represented the mean ulcer area for each group. At 12 months' followup, the mean ulcer area was 2.70 cm<sup>2</sup> in the EVLA group and 12.76 cm<sup>2</sup> in the compression group (p-value for comparison=0.0037).<sup>149</sup>

### **Strength of Evidence**

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

**Table 22. Strength of evidence for major outcomes—KQ 2—endovascular treatment vs. compression**

Outcome (Timeframe)	Studies (N and Design)	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 <sup>139</sup> 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 <sup>139</sup> 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. <sup>149</sup>
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. <sup>149</sup>
Insufficient							
Recurrent Ulceration (Intermediate-term)	1 RCT 52	Medium	Direct	NA	Imprecise	Suspected	At 90 days, the percentage of patients with recurrence of varicoses veins was 44.4% in the mechanical compression group and was 0 in the endovenous laser ablation group. <sup>149</sup>
Insufficient							
Thrombophlebitis (Short-term)	1 RCT 52	Medium	Direct	NA	Precise	Suspected	None of groups had patients with thrombophlebitis in either strategy of compression or EVLA. <sup>149</sup>
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Venous thrombo-embolic events (Intermediate-term)	2 RCTs 86	Medium	Direct	Consistent	Imprecise	Suspected	In two RCTs, one targeting foam sclerotherapy vs. placebo <sup>139</sup> 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, <sup>149</sup> no patients with venous thromboembolic events in either group.
Insufficient							
Venous thrombosis (Short-term)	1 RCT 216	Medium	Direct	NA	Precise	Suspected	None of groups had patients with venous thrombosis the post-intervention period for each group. <sup>149</sup>
Insufficient							
Venous Wound Healing (Intermediate-term)	2 RCTs 86	Medium	Direct	Inconsistent	Imprecise	Suspected	In one fair-quality RCT comparing foam sclerotherapy vs. placebo <sup>139</sup> there was no difference in venous wound healing at 12 weeks. In a second fair-quality RCT which compared EVLA vs. placebo, <sup>149</sup> 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)
Insufficient							
Venous Wound Healing (Long-term)	2 RCTs 86	Medium	Direct	Inconsistent	Imprecise	Suspected	In one-fair quality RCT of foam sclerotherapy vs. placebo <sup>139</sup> there was a non significant between-group difference at 24 weeks (p=0.72). In a second fair-quality RCT of EVLA vs. placebo, <sup>149</sup> there was a significant between-group difference at 6 months benefiting EVLA (p=0.0001).
Insufficient							

Abbreviations: [To be added in final draft]

## Comparisons of Invasive Surgical Approaches versus Alternative Invasive Surgical Approaches

### High Ligation plus Stripping ± Phlebectomy vs. High Ligation plus Cryostripping ± Phlebectomy

#### Description of Included Studies

Four RCTs, one of good quality<sup>168</sup> and three of fair quality,<sup>144, 148, 151</sup> 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,<sup>144, 148, 168</sup> while 1 study included patients with LE chronic venous insufficiency/reflux but did not report the presence of varicose veins or presence of symptoms.<sup>151</sup> Individual study sample sizes ranged from 40 to 536. Study followup periods ranged from 4 weeks to 9 months. All four RCTs were conducted in the UK/Europe; one was conducted at three sites,<sup>144</sup> two were single-site studies,<sup>148, 151</sup> and one did not report the number of sites.<sup>168</sup> Three studies did not report a funding source,<sup>144, 148, 168</sup> while one reported nongovernment/nonindustry funding.<sup>151</sup>

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;<sup>144, 148</sup> in two studies, baseline CEAP class was not reported.<sup>151, 168</sup>

#### Effect on Perioperative/Postoperative Complications

One fair-quality RCT reported rates of procedural complications with high ligation plus conventional stripping or cryostripping;<sup>144</sup> 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,<sup>168</sup> and two fair quality<sup>148, 151</sup>). 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,<sup>151</sup> and the other fair-quality study reported a 2.6 percent hematoma rate with conventional stripping versus a 1.5 percent rate for cryostripping.<sup>148</sup> 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,<sup>144</sup> while the other reported no DVT with either procedure (no statistical comparison provided).<sup>148</sup> One fair-quality study reported that thrombophlebitis occurred in one patient after conventional stripping and in two patients after cryostripping ( $p = \text{NS}$ ).<sup>151</sup>

#### Effect on Postoperative Pain

Three RCTs reported information on postoperative pain following high ligation plus conventional stripping or cryostripping (one good quality,<sup>168</sup> two fair quality<sup>148, 151</sup>). 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.<sup>148, 151</sup> 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.<sup>151</sup> 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).<sup>168</sup>

### **Effect on Quality Of Life**

Two fair-quality RCTs reported information on quality of life following high ligation and conventional stripping or cryostripping.<sup>144, 148</sup> 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;<sup>144</sup> 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.<sup>144, 148</sup> In one study,<sup>144</sup> 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,<sup>148</sup> 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,<sup>168</sup> one fair quality<sup>144</sup>). 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,  $p = \text{NS}$ ). 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 vs. CHIVA**

### **Description of Included Studies**

Two studies, one good-quality RCT<sup>135</sup> and one poor-quality retrospective cohort study,<sup>162</sup> 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 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 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. Both studies were conducted in the UK/Europe, the RCT at a single site and the cohort study at three sites. The RCT was government-funded and the cohort study did not report a funding source.

For the RCT, the mean age of study participants was 50 years; 71 percent of the population was female, and the study population's racial/ethnic composition was 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. Neither study reported CEAP class at baseline.

### **Effect on Perioperative/Postoperative Complications**

The good-quality RCT<sup>135</sup> reported rates of procedural complications with high ligation and stripping versus CHIVA. In the stripping with clinical marking arm, 6 patients (3.8 percent) had subcutaneous hemorrhage, versus 7 (4.4 percent) in the stripping with duplex marking arm and 6 (3.8 percent) in the CHIVA arm ( $p=0.950$ ). In the stripping with clinical marking arm, 1 patient (0.6 percent) had 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.

### **Effect on Mortality**

The good-quality RCT<sup>135</sup> reported that no deaths occurred with high ligation and stripping or CHIVA.

### **Effect on Improvement in Venous Hemodynamics**

The good-quality RCT<sup>135</sup> 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 followup, 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 poor-quality cohort study<sup>162</sup> 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 followup 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<sup>162</sup> reported the number and percentage of patients reporting LE pain during the 9-year followup, 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 followup, 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 followup, 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.

## **Ligation of Incompetent Veins (without Stripping) vs. Stab Avulsion**

### **Description of Included Studies**

One fair-quality RCT reported comparisons of six varicose vein treatments, including surgical ligation versus stab avulsion.<sup>84</sup> 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. Strength of evidence for major outcomes—KQ 2—invasive surgery vs. invasive surgery**

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	N Pts	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short Term)	3 RCTs: 601 pts. 1 RCT: NR	Insufficient		Medium	Direct	Inconsistent	Imprecise	Suspected	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>148, 151, 168</sup> - hematoma rates differed substantially between studies, suggesting heterogeneity in definitions, no between-group statistical comparisons <b>High ligation/stripping vs. CHIVA</b> <sup>135</sup> - 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).
Death	1 RCT: 501 pts.	Insufficient		Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. CHIVA</b> <sup>135</sup> - No death in any arm.
Improvement in LE venous hemodynamics /reflux severity (Short Term)	1 RCT: 60 pts.	Insufficient		Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>168</sup> - 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)
Improvement in LE venous hemodynamics /reflux severity (Long Term)	3 RCTs, 1 Obs.: 11,627 pts. 1 RCT: NR	Insufficient		Medium	Direct	Inconsistent	Imprecise	None	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>168</sup> - at 1 year, 0/19 conventional stripping patients had evidence for groin neovascularization with versus 1/19 cryostripping patients. <b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>144</sup> - 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 <b>High ligation/stripping vs. CHIVA</b> <sup>135</sup> - 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). <b>High ligation/stripping vs. CHIVA</b> <sup>162</sup> - 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 <b>Ligation vs. stab avulsion</b> <sup>84</sup> - 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

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
							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.
Patient-reported QOL (Short Term)	1 RCT: 494 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>144</sup> - no significant between-group difference in improvement in AVVQ or SF-36 domains at 6 weeks
Insufficient							
Patient-reported QOL (Intermediate Term)	2 RCTs: 640 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>144</sup> - 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 <b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>148</sup> - six SF-36 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
Insufficient							
Periprocedural complications (Short Term)	1 RCT: 494 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>144</sup> - 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)
Insufficient							
Qualitative reduction in LE edema (Long Term)	1 Obs.: 11,206 pts.	High	Direct	NA	Precise	None	<b>High ligation/stripping vs. CHIVA</b> <sup>162</sup> - 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.
Insufficient							
Qualitative reduction in LE pain (Short Term)	1 RCT: 40 pts. 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>148</sup> - no significant difference between procedures at 24 hours <b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>151</sup> - no significant difference between procedures at 7, 14, and 28 days
Low							
Qualitative	1 RCT: 60	Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>168</sup> - median

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
reduction in LE pts. pain (Intermediate Term)							cumulative pain scores from 0 to 60 days 7.5 for standard stripping and 10.6 for cryostripping (p=NR for pairwise comparison)
Insufficient							
Qualitative reduction in LE pain (Long Term)	1 Obs.: 11,206 pts.	High	Direct	NA	Precise	None	<b>High ligation/stripping vs. CHIVA<sup>162</sup></b> - 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.
Insufficient							
Thrombo-phlebitis (Short Term)	1 RCT: 541 pts. 1 RCT: NR	Medium	Direct	Consistent	Imprecise	Suspected	<b>High ligation/stripping vs. High ligation/cryostripping<sup>148</sup></b> - thrombophlebitis in one patient after conventional stripping and in two patients after cryostripping <b>High ligation/stripping vs. CHIVA<sup>135</sup></b> - 1 patient (0.6 percent) in the stripping with clinical marking arm had 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).
Insufficient							
Venous thrombo-embolic events (Short Term)	2 RCTs: 501 pts. 1 RCT: NR	Mediu	Direct	Consistent	Imprecise	Suspected	<b>High ligation/stripping vs. High ligation/cryostripping<sup>144</sup></b> - no DVT with conventional stripping versus one with cryostripping <b>High ligation/stripping vs. High ligation/cryostripping<sup>148</sup></b> - no DVT with conventional stripping or with cryostripping <b>High ligation/stripping vs. CHIVA<sup>135</sup></b> - No DVT/PE in any arm.
Insufficient							

## **Invasive Surgical Approaches vs. Hybrid Surgical/Endovenous Approaches**

### **High Ligation plus Stripping ± Phlebectomy vs. High Ligation plus EVLA**

#### **Description of Included Studies**

One fair-quality RCT compared high ligation plus stripping (with or without phlebectomy) to a hybrid procedure, high ligation plus EVLA. For this study, one publication reported short-term (2-month) results,<sup>100</sup> while a second publication presented longer-term followup (up to 6 years, mean 3.6 years).<sup>99</sup> The 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). This multicenter study was conducted in the UK/Europe at three sites, and reported nongovernment, nonindustry funding. The mean age of study participants in the arms of interest was approximately 48 (73 percent female); no data on the racial/ethnic composition of the population were reported. The majority of patients were CEAP C2.

#### **Effect on Perioperative/Postoperative Complications**

This RCT reported rates of postprocedural DVT. In the high ligation/stripping arm, 1/159 patients had DVT versus 0/148 in the high ligation/EVLA arm.<sup>100</sup>

#### **Effect on Improvement in Venous Hemodynamics**

Inguinal recurrence on ultrasound was the primary outcome of the short-term followup 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 ( $p < 0.0009$ ).<sup>100</sup> The long-term followup study evaluated reflux into the GSV on ultrasound.<sup>99</sup> 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).

#### **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 ( $p = 0.0069$ ).<sup>100</sup> 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 ( $p = \text{NS}$ ).<sup>100</sup>

#### **Effect on Other Standardized Symptom Scores**

This study presented VDS and CEAP data at baseline and 2 months.<sup>100</sup> 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 ( $p = \text{NS}$  between-group difference at baseline and 2

months). CEAP distributions remained similar between the ligation/stripping and ligation/EVLA arms during long-term followup.<sup>99</sup> 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 followup, 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).

## **High Ligation/Stripping ± Phlebectomy vs. 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,<sup>145</sup> 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<sup>145</sup> 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).

## **Ligation of Incompetent Veins (without Stripping) vs. 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.<sup>84, 160</sup> One study randomized 887 patients with symptomatic LE varicose veins to 6 treatment arms (numbers for the ligation and ligation/sclerotherapy arms NR),<sup>84</sup> 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).<sup>160</sup> 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,<sup>84</sup> while the other did not report funding.<sup>160</sup>

In one RCT,<sup>84</sup> mean age of study participants in the ligation and ligation/sclerotherapy arms was approximately 43 (68 percent female); in the other,<sup>160</sup> 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;<sup>84</sup> 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.<sup>160</sup> 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).<sup>84</sup> 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).<sup>160</sup> Finally, one RCT reported the mean number of sites of venous incompetence on duplex assessment at baseline and 10 years;<sup>84</sup> 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 vs. 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).<sup>118</sup> 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<sup>118</sup> 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 Quality Of Life**

AVVQ scores during 2-year followup were reported.<sup>118</sup> 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  $p = \text{NS}$ ).

### **Effect on Other Standardized Symptom Scores**

VCSS scores during 2-year followup were reported.<sup>118</sup> 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  $p = \text{NS}$ ).

### **Strength of Evidence**

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

**Table 24. Strength of evidence for major outcomes—KQ 2—invasive surgery vs. hybrid approaches**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short Term)	1 RCT: 449 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/foam sclerotherapy</b> <sup>99,100</sup> - the 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).
Insufficient							
Changes on standardized symptom scores (Short Term)	1 RCT: 449 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99,100</sup> - 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).
Insufficient							
Changes on standardized symptom scores (Long Term)	2 RCTs: 637 pts.	Medium	Direct	Unclear	Imprecise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99,100</sup> - 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 followup, 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). <b>High ligation/stripping vs. High ligation/microwave ablation</b> <sup>118</sup> - 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).
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Short Term)	1 RCT: 449 pts.	Medium	Direct	NA	Precise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99,100</sup> - 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).
Insufficient							
Improvement in LE venous hemodynamics /reflux severity (Long Term)	3 RCTs: 496 limbs 1 RCT: NR	Medium	Direct	Unclear	Imprecise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99,100</sup> - 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). <b>High ligation vs. High ligation/foam sclerotherapy</b> <sup>84</sup> - mean AVP
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Strength of Evidence	N Pts						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). <b>High ligation vs. High ligation/foam sclerotherapy</b> <sup>160</sup> - 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). <b>High ligation/stripping vs. High ligation/microwave ablation</b> <sup>118</sup> - 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).
Patient-reported QOL (Long Term)	1 RCT: 188 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/microwave ablation</b> <sup>118</sup> - 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).
Insufficient							
Qualitative reduction in LE pain (Short Term)	1 RCT: 412 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99, 100</sup> - 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).
Insufficient							
Venous thrombo-embolic events (Short Term)	1 RCT: 449 pts.	Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. High ligation/EVLA</b> <sup>99, 100</sup> - In the high ligation/stripping arm, 1/159 patients had DVT versus 0/148 in the high ligation/EVLA arm.
Insufficient							

## **Invasive Surgical Approaches versus Compression**

### **High Ligation/Stripping ± Phlebectomy vs. Compression**

#### **Description of Included Studies**

Five RCTs, 2 of good quality<sup>85, 88, 97</sup> and 3 of fair quality,<sup>114, 167, 170</sup> 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.<sup>85, 88</sup> 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 followup periods ranged from 7 weeks to 3 years. All five RCTs were conducted in the UK/Europe; two were conducted at two sites,<sup>97, 167</sup> one was multicenter but did not report the number of sites,<sup>85, 88</sup> and two were single-site studies.<sup>114, 170</sup> Two studies reported nongovernment/nonindustry funding,<sup>85, 88, 114</sup> one reported government funding,<sup>97</sup> and two did not report a funding source.<sup>167, 170</sup>

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,<sup>167, 170</sup> in one study, the majority of patients had a baseline CEAP class of C3;<sup>114</sup> and in two studies, baseline CEAP class was NR.<sup>85, 88, 97</sup>

#### **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 thrombophlebitis.<sup>85, 88</sup>

#### **Effect on Venous Wound Healing and Ulcer Recurrence**

Three RCTs reported venous wound healing rates with surgery versus compression (one good-quality study,<sup>85, 88</sup> one fair-quality study<sup>167, 170</sup>). 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,<sup>167</sup> 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,<sup>170</sup> 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,<sup>97</sup> one fair quality<sup>170</sup>). 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,<sup>85, 88</sup> one fair quality<sup>170</sup>). 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 Quality Of Life**

Three RCTs reported information on quality of life after high ligation and stripping or compression (one good-quality,<sup>97</sup> two fair-quality<sup>114, 170</sup>); because each study utilized different instruments and measurement time points, meta-analysis was not attempted. The good-quality study<sup>97</sup> 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<sup>114</sup> 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<sup>170</sup> 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 ( $\pm$  calf varicosity avulsion) versus compression,<sup>85, 88</sup> 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;<sup>97</sup> 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.<sup>114</sup> 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 ( $p = \text{NS}$ ). 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 ( $p = \text{NS}$ ). 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 followup, 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 ( $p = \text{NR}$ ).

## **High Ligation plus Stripping plus Subfascial Endoscopic Perforating Vein Surgery (SEPS) vs. Compression**

### **Description of Included Studies**

One fair-quality RCT<sup>89, 90</sup> reported a comparison of a combination surgery strategy (high ligation plus stripping plus SEPS) versus compression. An initial report<sup>90</sup> provided data with a mean followup of 28 months, and a subsequent report provided 97-month followup of this population.<sup>89</sup> 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 followup report (80 limbs). This RCT was conducted at 12 sites in the UK/Europe. The original study utilized government funding, and the followup 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 ( $p = \text{NS}$ );<sup>90</sup> at long-term followup, all but 4.4 percent of surgery patients' limbs achieved some degree of ulcer healing versus 2.9 percent with compression ( $p = \text{NS}$ ).<sup>89</sup> By the end of the initial study,<sup>90</sup> 72 percent of surgery patients' limbs were deemed ulcer-free, versus 53 percent with compression ( $p = 0.11$ ); at long-term followup,<sup>89</sup> 48.9 percent of surgery patients' limbs were ulcer-free, versus 2.9 percent for compression patients ( $p = \text{NR}$ ). At long-term followup, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression ( $p = \text{NR}$ ).

### **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;<sup>90</sup> these patients contributed 8 limbs to the surgical group and 17 to the compression group (both legs were randomized for 2 patients),  $p = \text{NR}$ . No deaths were felt to relate to the allocated treatment or venous ulcers.

## **CHIVA vs. Compression**

### **Description of Included Studies**

One poor-quality RCT<sup>169, Zamboni, 2003 #6669</sup> 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,<sup>169</sup> and 3 years in the second.<sup>154</sup> 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.<sup>169</sup> 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.<sup>169</sup> 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 followup, 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 Quality of Life**

In the poor-quality study’s CHIVA group,<sup>169</sup> 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.<sup>154</sup> 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 ( $p\leq 0.005$ ).

### **Effect on Repeat Intervention**

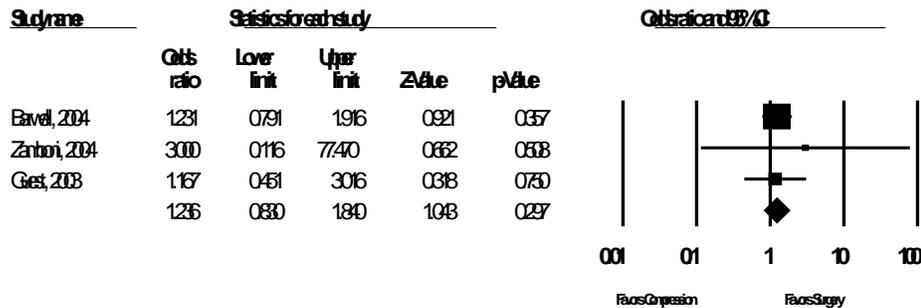
Two patients in the CHIVA arm underwent repeat interventions within 6 months of initial intervention.<sup>154</sup>

# Meta-Analysis of Any Surgery vs. 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<sup>88, 169, 170</sup> that examined the effect of surgical approaches versus compression on intermediate-term wound healing outcomes (2 months). One good-quality<sup>88</sup> and one fair-quality study<sup>170</sup> examined high ligation and stripping procedures and one poor-quality study<sup>169</sup> 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 18).

Figure 18. Forest plot of wound healing for surgical approaches vs. compression



Abbreviation: CI=confidence interval

## Strength of Evidence

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

**Table 25. Strength of evidence for major outcomes—KQ 2—invasive surgery vs. compression**

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	N Pts	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Bleeding (Short Term)	1 RCT: 500 pts.	Insufficient		Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - one of 242 surgical patients developed a postoperative hematoma, no compression patients
Changes on standardized symptom scores (Long Term)	1 RCT: 143 pts.	Insufficient		Medium	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>114</sup> - 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 followup, 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 ( $p = \text{NR}$ ).
Death (Long Term)	2 RCTs: 526 pts.	Low		Medium	Direct	Consistent	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - 16 percent in the surgery group versus 19 percent in the compression group ( $p = 0.245$ ) at 3 years <b>High ligation/stripping vs. compression</b> <sup>170</sup> - no deaths in either group over 6 months <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - 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), $p = \text{NR}$
Improvement in LE venous hemodynamics /reflux severity (Intermediate Term)	2 RCTs: 258 pts.	Low		Medium	Direct	Consistent	Imprecise	Suspected	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - 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. <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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 /reflux severity (Long Term)	2 RCTs: 258 pts. 1 RCT: 61 limbs	Insufficient		Medium	Direct	Inconsistent	Imprecise	Suspected	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - 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 percent among compression patients ( $p = 0.01$ ). No between-group comparison reported. <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-reported QOL (Intermediate Term)	2 RCTs: 156 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	3 years. <b>High ligation/stripping vs. compression</b> <sup>97</sup> - 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. <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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).
Insufficient							
Patient-reported QOL (Long Term)	2 RCTs: 308 pts.	Medium	Direct	Inconsistent	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>97</sup> - 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) <b>High ligation/stripping vs. compression</b> <sup>114</sup> - No between-group comparison in AVVQ at 1 or 2 years reported
Insufficient							
Qualitative reduction in LE pain (Long Term)	1 RCT: 199 pts.	Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>97</sup> - 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 pts. 1 RCT: 196 limbs	Medium	Direct	Consistent	Imprecise	Suspected	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - recurrence rate was 12 percent in the surgery group versus 28 percent with compression alone (p<0.0001) <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - At long-term followup, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression (p=NR) <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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).
Low							
Repeat Intervention (Long Term)	1 RCT: 21 pts.	Medium	Direct	NA	Imprecise	Suspected	<b>CHIVA vs. compression</b> <sup>154, 169</sup> - Two patients in the CHIVA arm underwent repeat interventions within 6 months of initial intervention
Insufficient							
Thrombophlebitis (Short Term)	1 RCT: 500 pts.	Low	Direct	NA	Imprecise	None	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - one of 242 surgical patients developed postoperative thrombophlebitis

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Term)								
Insufficient								
Venous thrombosis (Short Term)	1 RCT: 500 pts.	Low	Direct	NA	Imprecise	None		<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - one of 242 surgical patients developed a postoperative DVT
Insufficient								
Venous Wound Healing (Intermediate Term)	4 RCTs: 545 pts. 1 RCT: 196 limbs	Medium	Direct	Inconsistent	Imprecise	Suspected		<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - ulcer healing rate at 24 weeks was 65 percent in both groups (p=0.8) <b>High ligation/stripping vs. compression</b> <sup>167</sup> - 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) <b>High ligation/stripping vs. compression</b> <sup>170</sup> - 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) <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - 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) <b>CHIVA vs. compression</b> <sup>154, 169</sup> - In the CHIVA group, 100 percent of 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)
Insufficient								
Venous Wound Healing (Long Term)	1 RCT: 446 pts. 1 RCT: 196 limbs	Medium	Direct	Inconsistent	Imprecise	None		<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - overall ulcer healing rate over 3 years was 93 percent in the surgery group and 89 percent in the compression group (p=0.737) <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - 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)
Insufficient								
Venous Wound Infection (Long Term)	1 RCT: 76 pts.	Low	Direct	NA	Imprecise	None		<b>High ligation/stripping vs. compression</b> <sup>170</sup> - 1 episode of cellulitis requiring IV antibiotics in the 37 surgery patients by 6 months, versus 2 in the 39 compression patients (p=NR)

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
<b>Strength of Evidence</b>	<b>N Pts</b>	<b>Limitations</b>					
Insufficient							

## Comparisons of Mechanical Compression Therapies versus Placebo or Usual Care

### Description of Included Studies

Eleven RCTs (1522 patients) compared mechanical compression with either placebo compression or no compression.<sup>109, 113, 120, 122, 126, 136, 141, 152, 159, 161, 171</sup> 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.<sup>126</sup> 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.<sup>136</sup> 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.<sup>113, 120, 122</sup> 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,<sup>141</sup> 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,<sup>161</sup> 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.<sup>152</sup> We also identified 3 poor-quality studies: one study randomized 100 patients in Saudi Arabia to compression stockings for 1 month vs. standard medical therapy,<sup>109</sup> one study randomized 153 patients in Australia with recently healed leg ulcers to below-knee compression stockings vs. no compression therapy,<sup>171</sup> 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.<sup>159</sup>

Variability across studies in terms of the study interventions, outcome measures, duration of treatment, and timing of followup 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.<sup>126</sup> 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.<sup>136</sup>

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.<sup>113</sup> 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.<sup>120, 122</sup> 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.<sup>141</sup> 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.<sup>161</sup> 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.<sup>152</sup>

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.<sup>109</sup> The study that compared below-knee compression stockings with no compression therapy demonstrated reduced lipodermatosclerosis and ulcer recurrence associated with compression stockings.<sup>171</sup> 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<sup>2</sup>/day) relative to compression therapy alone (0.05 cm<sup>2</sup>/day; p<0.05). Intermittent pneumatic compression was not, however, found to decrease the incidence of ulcer recurrence.<sup>159</sup>

## **Strength of Evidence**

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

**Table 26. Strength of evidence for major outcomes—KQ 2—mechanical compression therapies vs. placebo or usual care**

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Changes on standardized symptom scores (Short-term)	6 RCTs: 637 pts.	Medium	Direct	Inconsistent	Imprecise	Suspected	1 poor-quality RCT representing 100 patients <sup>109</sup> and 1 good-quality RCT representing 123 patients <sup>120</sup> demonstrated significant improvement at 30 days associated with compression therapy. The other 4 RCTs did not demonstrate a difference between interventions.
Insufficient							
Improvement in LE venous hemodynamics/reflux severity (Intermediate-term)	1 RCT: 120 pts.	Low	Direct	NA	Imprecise	None	No significant improvement in LE venous hemodynamics at 1 month.
Insufficient							
Patient-reported QOL (Intermediate-term)	5 RCTs: 894 pts.	Low	Direct	Inconsistent	Imprecise	None	1 fair-quality RCT representing 200 patients demonstrated significant improvement in patient-reported QOL at 6 weeks. <sup>152</sup> The other 4 RCTs did not demonstrate a difference between interventions.
Insufficient							
Qualitative reduction in LE edema (Intermediate-term)	2 RCTs: 219 pts.	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. <sup>120</sup> The other fair-quality RCT did not demonstrate a difference between interventions.
Insufficient							
Qualitative reduction in LE pain (Intermediate-term)	4 RCTs: 675 pts.	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. <sup>120</sup> The other 3 RCTs did not demonstrate a difference between interventions.
Insufficient							

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Consistency</b>	<b>Precision</b>	<b>Reporting Bias</b>	<b>Findings</b>
Recurrent ulceration (Intermediate-term)	3 RCTs: 334 pts.	Medium	Direct	Consistent	Imprecise	None	No significant differences in recurrent ulceration at 1-4 months.
Insufficient							
Recurrent ulceration (Long-term)	1 RCT: 169 pts.	Medium	Direct	Consistent	Imprecise	None	No significant differences in recurrent ulceration at 12 months.
Insufficient							
Venous wound healing (Intermediate-term)	3 RCTs: 621 pts.	Medium	Direct	Inconsistent	Imprecise	None	1 poor-quality RCT representing 100 patients demonstrated significant improvement in venous wound healing. <sup>159</sup> The other 2 RCTs did not demonstrate a difference between interventions.
Insufficient							

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

## Comparisons of Medical Therapies versus 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.<sup>156</sup> 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.<sup>150</sup> 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: 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% vs. 53%;  $p=0.21$ ); four-layer bandages were associated with significantly higher healing rates relative to single layer bandages (67% vs. 49%;  $p=0.009$ ); and there was no difference in healing between knitted viscose and hydrocolloid dressings (58% vs. 57%;  $p=0.88$ ). 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% of patients who received pentoxifylline plus local therapy (without mechanical compression) versus 27.5% in patients who received local therapy alone after 24 weeks of treatment ( $p=0.013$ ).<sup>157</sup> These two studies demonstrate that pentoxifylline is not 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.<sup>125</sup> The rate of ulcer recurrence over the 42-week study period was lower in the aspirin group (25%) compared with the no aspirin group (33%) (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 healing (52.5%) than placebo drug plus local wound care and compression bandaging (32.7%;  $p=0.004$ ).<sup>158</sup> 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%) at 12 months than usual care only (60.56%;  $p<0.00001$ ), with the greatest between-group difference in ulcer healing rates observed among patients 80 years or older.<sup>121</sup> The recurrence rate of venous ulcers at 5 years was also apparently lower in the nadroparin group (26.76%) relative to usual care only (59.15%;  $p$ -value NR). Given the diversity of treatments, outcomes, and small number of patients, there was insufficient SOE for these studies.

## Comparisons of Exercise Therapy versus 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.<sup>137</sup> At 12 weeks, 38% of patients in the exercise group and 53% 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<sup>2</sup> in the exercise group and -2.92 cm<sup>2</sup> in the usual care group (p=0.08).

Table 27 summarizes the strength of evidence for these findings.

**Table 27. Strength of evidence for major outcomes—KQ 2—exercise therapy vs. usual care**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting	
						Bias	Findings
Venous wound healing (Intermediate-term)	1 RCT: 40 pts.	Medium	Direct	NA	Imprecise	Suspected	No differences in venous wound healing at 12 weeks. <sup>137</sup>
Insufficient							
Exercise-related harms (Intermediate-term)	1 RCT: 40 pts.	Medium	Direct	NA	Imprecise	Suspected	No differences in exercise-related harms at 12 weeks. <sup>137</sup>
Insufficient							

Abbreviations: KQ=key question; N=number; NA=not applicable; Pts=patients/study participants; 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.<sup>115</sup> 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 followup period was 9.3% in the balneotherapy group and 6.1% 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 followup assessment.

Table 28 summarizes the strength of evidence for these findings.

**Table 28. Strength of evidence for major outcomes—KQ 2—balneotherapy vs. usual care**

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting	
						Bias	Findings
Changes on standardized symptom scores (Intermediate-term)	1 RCT: 425 pts.	Low	Direct	NA	Imprecise	None	No differences in standardized symptom scores at 6 months. <sup>115</sup>
Insufficient							
Changes on standardized symptom scores (Long-term)	1 RCT: 425 pts.	Low	Direct	NA	Imprecise	None	Balneotherapy associated with improvement in the VCSS (-1.2 vs. -0.6, p=0.04) at 1 year <sup>115</sup>
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-reported QOL (Intermediate-term)	1 RCT: 425 pts.	Low	Low	Direct	NA	Imprecise	None	No differences in patient-reported QOL at 6 months. <sup>115</sup>
Insufficient								
Patient-reported QOL (Long-term)	1 RCT: 425 pts.	Low	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. <sup>115</sup>
Insufficient								
Adverse drug reactions (Long-term)	1 RCT: 425 pts.	Low	Low	Direct	NA	Imprecise	None	No differences in exercise-related harms at 18 months. <sup>115</sup>
Insufficient								
Venous thromboembolic events (Long-term)	1 RCT: 425 pts.	Low	Low	Direct	NA	Imprecise	None	No differences in thromboembolic events at 18 months. <sup>115</sup>
Insufficient								
Recurrent ulceration (Long-term)	1 RCT: 425 pts.	Low	Low	Direct	NA	Imprecise	None	No significant differences in improvement in recurrent ulceration at 1 year. <sup>115</sup>
Insufficient								

Abbreviations: KQ=key question; N=number; NA=not applicable; Pts=patients/study participants; QOL=quality of life; RCT=randomized controlled trial

### 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)

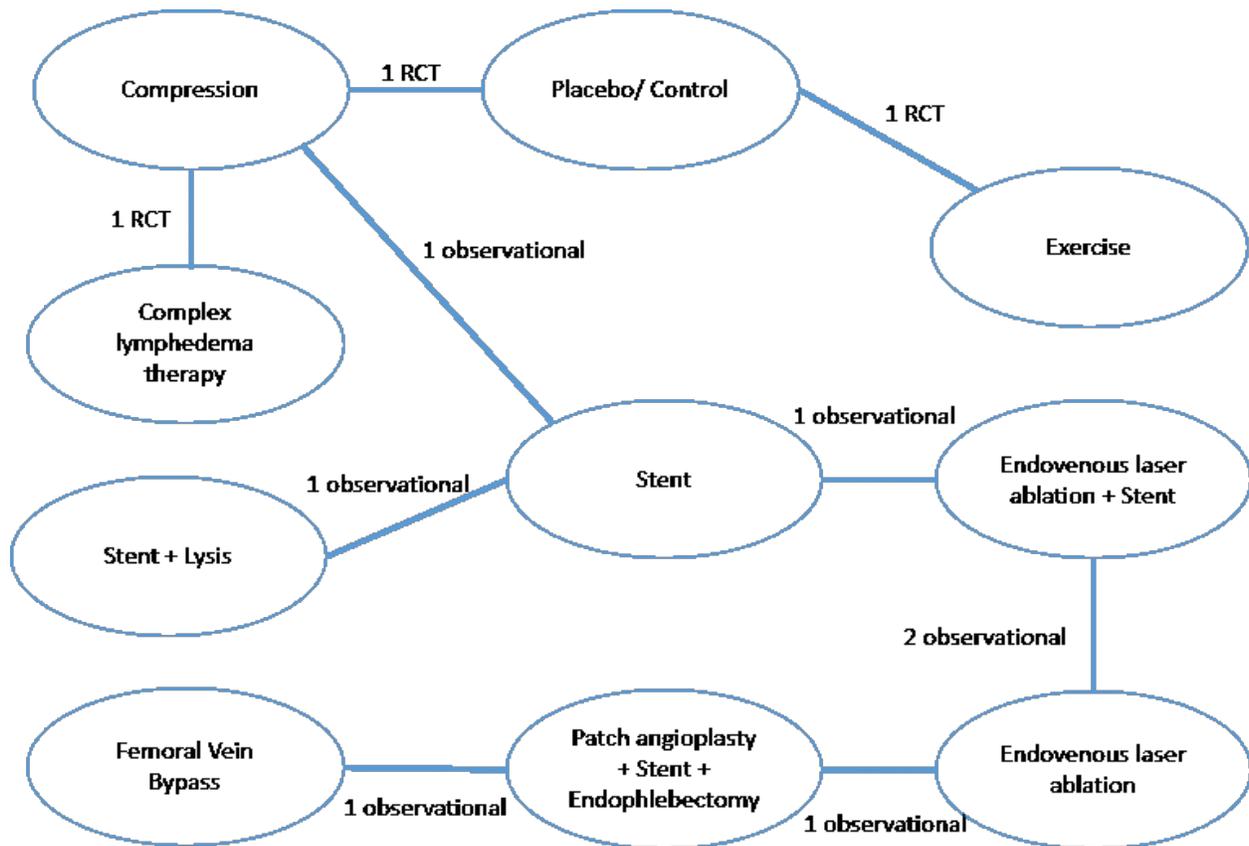
### Description of Included Studies

We identified eight studies that examined the treatments for patients with LE chronic venous thrombosis/obstruction.<sup>172-179</sup> In seven of the studies, all patients were symptomatic at baseline,

and in one only a small minority had unclear symptom severity.<sup>179</sup> Three of the studies were RCTs, representing a total of 109 patients.<sup>173, 175, 176</sup> Sample sizes of the remaining 5 observational studies ranged from 20 to 216 patients. Four studies were conducted in the United States,<sup>173, 174, 177, 179</sup> two in Canada,<sup>175, 176</sup> and two in Asia.<sup>172, 178</sup> All but one study<sup>175</sup> reported conducting the studies at a single center. Three studies reported government funding.<sup>172, 175, 178</sup> Two studies reported a combination of funding from government, industry, or nongovernment sources.<sup>173, 176</sup> Three studies did not report the funding source or the funding source was unclear.<sup>174, 177, 179</sup> All eight studies were conducted in a specialty practice. Of the three RCTs, two were rated as good quality,<sup>173, 175</sup> and one was rated as poor quality.<sup>176</sup> Of the five observational studies, three were rated as fair quality,<sup>172, 174, 178</sup> and the other two were rated as poor quality.<sup>177, 179</sup>

Figure 19 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 19. Treatment comparisons—KQ 3**



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

## Key Points

### *Effectiveness of interventions*

- In a RCT of patients with post-thrombotic syndrome able to exercise, the addition of exercise training to patient education and monthly phone followup, compared to patient education and monthly phone followup alone, improved quality of life but not severity of post-thrombotic syndrome symptoms (SOE= insufficient).
- For patients with post-thrombotic syndrome with iliofemoral obstruction and symptoms of at least moderate severity, endovascular stenting compared to compression stockings may improve intermediate-term changes on standardized symptoms scores and long-term recurrence free ulcer healing (SOE= insufficient).
- In a RCT of patients with symptomatic post-thrombotic syndrome after proximal deep venous thrombosis, active compression stocking therapy with 30-40 mmHg did not prevent worsening of symptoms compared to placebo stocking (SOE= insufficient).
- In patients with both May-Thurner Syndrome and superficial venous reflux who were undergoing EVLA, stent placement at the time of EVLA resulted in less recurrent ulceration, improvement in reflux severity and symptoms, and improvement in quality of life in long-term followup (SOE= insufficient).

### *Modifiers of effectiveness*

- Compression stockings used in addition to stenting does not change short- or long-term healing of ulcers (SOE= insufficient).
- In patients with severe post-thrombotic syndrome at baseline, the use of complex lymphedema therapy or endovenous stenting in addition to compression stockings may result in greater improvement in symptoms (SOE= insufficient).
- In patients with venous ulcers and documented venous obstruction and reflux who received EVLA with or without endovenous stenting, ulcer healing rates were significantly better among patients with smaller ulcer size (SOE= insufficient).

### *Safety concerns*

- Active compression therapy was not reported to result in increased risk for death or new deep venous thrombosis over intermediate followup in patients with post-thrombotic syndrome (SOE= insufficient).
- Catheter-directed urokinase treatment at the time of endovenous stenting for chronic iliac vein obstruction had higher technical failure, and bleeding risk, than endovenous stenting alone (SOE= insufficient).

## **Detailed Synthesis**

### **Effectiveness of Interventions**

#### **Exercise Training + Patient Education/Engagement vs. Patient Education/Engagement Alone**

One study, an RCT rated good quality, compared a standardized education and phone call followup 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.<sup>175</sup> 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 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 vs. 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 vs. 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 vs. 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.<sup>176</sup> 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.<sup>173</sup> 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 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.<sup>176</sup> 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).<sup>173</sup>

**Table 31. Effect of compression stockings vs. 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).<sup>173</sup>

**Table 32. Effect of compression stockings vs. 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 vs. 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 followup.<sup>172</sup> 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 vs. 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 vs. 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,<sup>177</sup> one compared EVLA alone to combined EVLA/stenting,<sup>178</sup> 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).<sup>179</sup> 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,<sup>178</sup> IVUS,<sup>179</sup> or varying use of all these modalities, including additional use of MRI.<sup>177</sup> The studies included 419 patients, and followup 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.<sup>179</sup> The mean age was 43-51 years in two studies,<sup>177, 178</sup> and in another was presented as a median of 59 years.<sup>179</sup> 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,<sup>177, 179</sup> with unclear funding source, and another was a single center study in Asia with government funding source.<sup>178</sup>

**Effect on LE Venous Hemodynamics**

In the study assessing stenting with thrombolysis versus stenting alone, 58 percent (7/12) of 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.<sup>177</sup> In the study of combined EVLA and stenting versus EVLA alone, over 5.9 years followup, 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 ( $p = 0.218$ ).<sup>178</sup> Over the same followup 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 Quality of Life**

Quality-of-life changes were assessed in two of the studies.<sup>177, 178</sup> For 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.<sup>177</sup> 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 vs. 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).<sup>178</sup> 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 vs. 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.<sup>178</sup> Among patients who received stenting plus EVLA, 16 percent had venous ulcer before treatment and 2 percent had ulcer at followup (p=0.001). Among patients receiving EVLA alone, 13 percent had venous ulcer before treatment and 6 percent had ulcer at followup (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.<sup>179</sup> 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 vs. 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.<sup>174</sup> 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 followup 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.<sup>172-174, 179</sup> The RCT examined compression therapy versus complex lymphedema therapy (including compression stockings).<sup>173</sup> The retrospective studies examined EVLA versus EVLA with stenting,<sup>179</sup> endovenous stenting versus compression therapy,<sup>172</sup> and femorofemoral vein bypass versus hybrid reconstruction.<sup>174</sup>

Findings are summarized in Table 36. Subgroups analyzed included patients with severe baseline post-thrombotic syndrome,<sup>172, 173, 175</sup> use of compression stockings leading into and during study,<sup>173, 179</sup> size of ulcer and severity of venous reflux at baseline,<sup>179</sup> and post-thrombotic syndrome patients with the additional diagnosis of May-Thurner syndrome.<sup>174</sup> Only patients with moderate to severe post-thrombotic syndrome at baseline experienced significant improvement with complex lymphedema therapy.<sup>173</sup> Only patients with severe post-thrombotic syndrome at baseline benefited from endovascular stenting.<sup>172</sup> 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.<sup>173</sup> 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.<sup>179</sup> The diagnosis of May-Thurner syndrome in patients with post-thrombotic syndrome undergoing femorofemoral 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; Study Population	Study Design; N Analyzed; Comparison; Quality	Subgroup	Results Reported by Authors
Garg, 2011 <sup>174</sup>  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).

Study; Study Population	Study Design; N Analyzed; Comparison; Quality	Subgroup	Results Reported by Authors
Holmes, 2014 <sup>173</sup>  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. 0.1, 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)
Raju, 2013 <sup>179</sup>  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 <sup>2</sup> ) vs. Large (≥500 mm <sup>2</sup> ) 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 <sup>172</sup>  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.<sup>175</sup> 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.<sup>172</sup> 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.<sup>174, 178</sup> In the retrospective analysis of catheter-directed thrombolysis at the time of stenting for May-Thurner syndrome,<sup>177</sup> 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. Strength of evidence for major outcomes—KQ 3 (treatments for LE chronic venous thrombosis/obstruction, including post-thrombotic syndrome)**

Outcome (Timeframe)	Studies (N and Design)	Strength of Evidence	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes on standardized symptom scores (Intermediate-term)	2 RCTs 1 Obs 287	Insufficient	Low	Direct	Inconsistent	Imprecise	None	<p>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).<sup>175</sup></p> <p>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).<sup>173</sup></p> <p>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&lt;0.01).<sup>172</sup></p>
Changes on standardized symptom scores 20 (Long-term)	1 Obs	Insufficient	High	Direct	NA	Imprecise	None	<p>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).<sup>177</sup></p>
Improvement in LE venous hemodynamics/ reflux severity (Long-term)	3 Obs 226	Insufficient	High	Direct	Inconsistent	Imprecise	None	<p>In a fair-quality observational study, stenting with thrombolysis vs. stenting alone resulted in no difference in US-assessed patency of stented vein at followup.<sup>177</sup></p> <p>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).<sup>174</sup></p> <p>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&lt;0.001) but not deep venous reflux disease (51% vs. 35%, p=0.254) measured by Doppler US. EVLA alone did not have statistical significance for superficial (67% vs. 52%, p=0.099) or deep (33% vs 27%, p=0.218) venous reflux disease.<sup>178</sup></p>

Outcome (Timeframe)	Studies (N and Design)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Patient-reported QOL (Intermediate-term)	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. <sup>175</sup>
Insufficient							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. <sup>173</sup>
Patient-reported QOL (Long-term)	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). <sup>178</sup>
Insufficient							
Qualitative reduction in LE edema (Intermediate-term)	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). <sup>172</sup>
Insufficient							
Qualitative reduction in LE pain (Intermediate-term)	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). <sup>172</sup>
Insufficient							
Recurrent ulceration (Intermediate-term)	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). <sup>172</sup>
Insufficient							

Outcome (Timeframe)	Studies (N and Design)	Study					Reporting		Findings
		N	Pts	Limitations	Directness	Consistency	Precision	Bias	
Recurrent ulceration (Long-term)	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 followup (2%), p=0.001, but not patients receiving EVLA alone (13% to 6%, p=0.151). <sup>178</sup>	
Insufficient									
Venous wound healing (Long-term)	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). <sup>179</sup>	
Insufficient									

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 127 articles representing 103 studies of diagnostic and treatment choices for patients with lower extremity chronic venous disease (LECVD). We identified the following studies:

- Seven observational studies involving 384 patients that assessed diagnostic methods in adult patients with LECVD (key question [KQ] 1);
- Eighty-eight studies (84 randomized controlled trials [RCTs], 4 observational) involving 36,727 patients with lower extremity (LE) varicose veins and LE chronic venous insufficiency/incompetence/reflux 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 (KQ 2); and
- Eight studies (3 RCTs, 5 observational) involving 804 patients with LE chronic venous obstruction/thrombosis 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 (KQ 3).

We encountered multiple challenges while creating this report, including difficulty in grouping studies into valid comparisons of treatment modalities (specifically in KQ 2) and difficulty in defining studies of acute versus chronic venous thrombosis. Furthermore, there were significant differences in outcomes assessed and the timepoints of outcome assessment. In many cases, these differences did not allow us to quantitatively analyze the results.

The evidence base was greatest for the comparative safety and effectiveness of noninvasive treatments, endovenous intervention, and surgical intervention for LE varicose veins and LE chronic venous insufficiency/incompetence/reflux. The contemporary literature on diagnostic methods used in LECVD is limited, although there is insufficient evidence to suggest that the current clinical practice of duplex ultrasound (DUS) to support the initial diagnosis and inform treatment decisions is either correct or incorrect. Very few comparative studies exist on patients with LE chronic venous obstruction/thrombosis—a significant gap in the literature regarding patients with LECVD.

In the current review, we provide important information on the strength of evidence (SOE) that supports, or requires more evidence to support the use of exercise training, medical therapy, weight reduction, compression therapy, skin/wound care, endovenous intervention, and/or surgical intervention in the treatment of LECVD. This information will help to inform clinical decision-making by health care providers and patients and will also help inform policymakers about which treatment patterns have an adequate evidence-base and which findings are less robust. We also define important gaps in knowledge and identify areas in need of future research that will guide funding agencies in prioritizing these research areas.

## **KQ 1: Narrative Review of Diagnostic Methods and Criteria for Adult Patients with LLECVD**

Our review of diagnostic testing methods for LECVD demonstrated that very few comparative studies exist in the contemporary literature. In a qualitative 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 when planning endovenous and/or surgical interventions for LECVD. 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. Seven observational studies assessed these diagnostic methods in the evaluation of patients with LECVD.

One study evaluated ambulatory plethysmography as compared with triplex ultrasound.<sup>49</sup> 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<sub>2</sub>) is GRADE 2C, while its use in patients with advanced LECVD (CEAP class C<sub>3</sub>-C<sub>6</sub>) is GRADE 1B.<sup>53</sup>

Six studies evaluated the use of DUS with another imaging modality in the diagnosis of LECVD.<sup>46-49, 51, 52</sup> 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).

One study<sup>50</sup> 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<sup>48</sup> 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.

Five studies evaluated the use of invasive phlebography or venography with another imaging modality in the diagnosis of LECVD.<sup>46, 47, 49-51</sup> 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**

Eighty-eight studies (84 RCTs, 4 observational; 36,727 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. Studies that assessed individual treatment modalities or combinations of treatment modalities were analyzed, including (1) surgical intervention versus endovenous intervention (35 RCTs, 1 observational; 35 with 11,435 patients, 1 with 130 limbs); (2) surgical intervention versus surgical intervention (6 RCTs, 1 observational; 12,964 patients); (3) surgical interventions versus hybrid/endovenous procedures (6 RCTs, 1 observational; 12,964 patients); (4) endovenous intervention versus endovenous intervention (15 RCTs, 2 observational; 16 with 6,887 patients, 1 with 979 limbs); (5) surgical intervention versus medical therapy (8 RCTs; 1,264 patients); (6) endovenous intervention versus other therapies (7 RCTs; 895 patients); (7) surgical interventions versus compression therapy (7 RCTs; 1,161 patients); (8) compression therapy versus placebo or usual care (11 RCTs; 1,522 patients); (9) medical therapy versus placebo or usual care (6 RCTs; 1,149 patients); (10) exercise training versus usual care (1 RCT; 40 patients); and (11) other strategies (1 RCT; 425 patients). Differences in the treatment comparisons, measures, and followup time points reduced the number of studies that could be pooled for analysis of direct comparisons.

Table 38 summarizes the SOE by treatment comparison within KQ 2. The most frequently reported endpoints included quality-of-life scores, Venous Clinical Severity Score (VCSS) scores, peri-procedural 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 38 summarizes the strength of evidence findings for KQ2 which were graded as either low, moderate, or high.

**Table 38. Summary strength of evidence for major outcomes—KQ 2**

Outcome (Timeframe)	Studies (N and Design)	Findings
<b>Strength of Evidence N Pts</b>		
<b>Venous ligation plus stripping vs. EVLA</b>		
Vein recurrence/ Repeat intervention (Long Term)	5 RCTs: 1,261 pts.	Five studies evaluated long-term thrombophlebitis. <sup>75, 82, 94, 105, 131</sup> The findings of these studies were imprecise and inconsistent demonstrating no difference in thrombophlebitis between the two strategies (OR = 1.009, 95% CI = 0.686 to 1.484) (Figure 6)
Low		
Improvement hemodynamics	5 RCTs: 887 pts.	Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics. <sup>61, 71, 94, 105, 131</sup> The analysis suggested a trend towards improvement in reflux/incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121) (Figure 7)
Low		
Clinical symptom scores (VCSS)	3 RCTs: 487 pts.	We synthesized three studies representing 487 patients for treatment effect on long-term VCSS score. <sup>64, 75, 131</sup> There was no significant difference between treatment strategies (standard difference of means = 0.021, 95% CI = -0.186 to 0.229) (Figure 8).
Low		
Clinical symptom scores (CEAP)	4 RCTs 867 pts.	We also explored the CEAP after 12 months in 4 studies representing 867 patients. <sup>78, 94, 100, 117</sup> No difference was found (standard difference of means = 0.061, 95% CI -0.096 to 0.219)(Figure 9).
Moderate		
Patient-reported Quality of Life (EQ- 5D)	4 RCTs 1,436 pts.	Four studies <sup>66, 80, 94, 164</sup> 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.
Low		
Patient-reported Quality of Life (AVVQ-583 Short Term)	4 RCTs: 583 pts.	We synthesized four studies representing 583 patients which evaluated short-term AVVQ effects. <sup>80, 82, 117, 164</sup> These studies showed a -0.014 standardized difference in means (95% CI -0.340 to 0.311) showing no difference between strategies (Figure 10).
Low		
Patient-reported Quality of Life (AVVQ-426 Intermediate Term)	4 RCTs: 426 pts.	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon. <sup>82, 117, 147, 164</sup> Again there was no different in AVVQ scores (standard difference of means = -0.011, 95% CI 0-0.212 to 0.190) (Figure 11).
Low		
Patient-reported Quality of Life (AVVQ-663 Long Term)	6 RCTs: 663 pts.	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ. <sup>75, 80, 82, 117, 131, 147</sup> These studies also consistently found no difference between treatment strategies (standard difference of means = 0.063, 95% CI -0.122 to 0.247) (Figure 12).
Moderate		
Reduction in LE Pain	4 RCTs: 778 pts.	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale. <sup>75, 82, 128, 164</sup> 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 of means = -0.148, 95% CI -0.531 to 0.236) (Figure 13).
Low		
Adverse Events (Bleeding risk)	3 RCTs: 822 pts.	We were able to perform a meta-analysis on three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis). <sup>99, 100, 131, 165</sup> 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).
Moderate		
<b>Venous stripping plus ligation vs. Radiofrequency Ablation (RFA)</b>		
Clinical Symptom Scores (VCSS)	3 RCTs: 356 pts.	For one study, the mean decrease in Venous Clinical Severity Score (VCSS) at 50 days followup was 5.1 (standard deviation [SD] 1.5) for RFA and 4.4 (SD 1.1) for surgery (p=0.19). <sup>68</sup> One study <sup>74</sup> reported mean VCSS scores at several time points but only found a significant difference, with lower symptoms scores in the
Low		

Outcome (Timeframe)	Studies (N and Design)	Findings
<b>Strength of Evidence</b>	<b>N Pts</b>	<b>Findings</b>
		RFA compared to high ligation plus stripping, at 3 days and 1 week postintervention. However, this difference was not apparent at 2-year followup (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]). <sup>74</sup> 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). <sup>75</sup>
Reduction in LE Pain	1 RCT: 60 pts.	Two RCTs <sup>75, 168</sup> reported less pain on a visual analog scale (VAS) in the RFA arms vs. surgery arms. One study <sup>75</sup> 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' followup (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. <sup>168</sup>
Low	1 RCT: NR	
Adverse Events (Surgical Site Infection)	2 RCTs, 1 Obs.: 2,850 pts.	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. <sup>74</sup> 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. <sup>132</sup> 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). <sup>110</sup>
Low		
Adverse Events (Thrombo phlebitis)	3 RCTs 695 pts.	Two RCTs reported lower rates of 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 thrombophlebitis, <sup>132</sup> whereas a good-quality study reported 9.9% of the RFA group vs. 4.2% of the surgery group had thrombophlebitis (Fisher exact test p=0.006 across the four arms; no p-value reported for arm-to-arm comparison). <sup>75</sup> One study <sup>68</sup> reported one out of 15 RFA patients vs. zero out of 13 surgery patients reported an incidence of thrombophlebitis at 3 years' followup.
Low		
Vein recurrence/ Repeat intervention (Long Term)	5 RCTs: 1,261 pts.	Five studies evaluated long-term thrombophlebitis. <sup>75, 82, 94, 105, 131</sup> The findings of these studies were imprecise and inconsistent demonstrating no difference in thrombophlebitis between the two strategies (OR = 1.009, 95% CI = 0.686 to 1.484) (Figure 6)
Low		
Improvement hemodynamics	5 RCTs: 887 pts.	Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics. <sup>61, 71, 94, 105, 131</sup> The analysis suggested a trend towards improvement in reflux/incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121) (Figure 7)
Low		
Clinical symptom scores (VCSS)	3 RCTs: 487 pts.	We synthesized three studies representing 487 patients for treatment effect on long-term VCSS score. <sup>64, 75, 131</sup> There was no significant difference between treatment strategies (standard difference of means = 0.021, 95% CI = -0.186 to 0.229) (Figure 8).
Low		
Clinical symptom scores (CEAP)	4 RCTs 867 pts.	We also explored the CEAP after 12 months in 4 studies representing 867 patients. <sup>78, 94, 100, 117</sup> No difference was found (standard difference of means = 0.061, 95% CI -0.096 to 0.219)(Figure 9).
Moderate		
Patient-reported Quality of Life (EQ-5D)	4 RCTs 1,436 pts.	Four studies <sup>66, 80, 94, 164</sup> 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.
Low		
Patient-reported	4 RCTs:	We synthesized four studies representing 583 patients which evaluated short-term

<b>Outcome (Timeframe)</b>	<b>Studies (N and Design)</b>	<b>Findings</b>
<b>Strength of Evidence</b>	<b>N Pts</b>	<b>Findings</b>
Quality of Life (AVVQ- Short Term)	583 pts.	AVVQ effects. <sup>80, 82, 117, 164</sup> These studies showed a -0.014 standardized difference in means (95% CI -0.340 to 0.311) showing no difference between strategies (Figure 10).
Low		
Patient-reported Quality of Life (AVVQ- Intermediate Term)	4 RCTs: 426 pts.	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon. <sup>82, 117, 147, 164</sup> Again there was no different in AVVQ scores (standard difference of means = -0.011, 95% CI 0-0.212 to 0.190) (Figure 11).
Low		
Patient-reported Quality of Life (AVVQ- Long Term)	6 RCTs: 663 pts.	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ. <sup>75, 80, 82, 117, 131, 147</sup> These studies also consistently found no difference between treatment strategies (standard difference of means = 0.063, 95% CI -0.122 to 0.247) (Figure 12).
Moderate		
Reduction in LE Pain	4 RCTs: 778 pts.	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale. <sup>75, 82, 128, 164</sup> 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 of means = -0.148, 95% CI -0.531 to 0.236) (Figure 13).
Low		
Adverse Events (Bleeding risk)	3 RCTs: 822 pts.	We were able to perform a meta-analysis on three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis). <sup>99, 100, 131, 165</sup> 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).
Moderate		
<b>Venous stripping plus ligation vs. Sclerotherapy</b>		
Vein recurrence/	3 RCTs: 395 pts. 1 RCT: 96 limbs	We synthesized evidence from 4 RCTs (3 RCTs with 395 patients, 1 RCT with 96 limbs) which 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).
Low		
Patient-reported Quality of Life (AVVQ)	3 RCTs: 583 pts.	Three good-quality studies <sup>65, 66, 75, 106</sup> reported AVVQ as an outcome at various time points ranging from baseline to three years followup. All studies showed decreased scores at followup, indicating an improvement in symptom scores but no difference between groups.
Low		
Patient-reported Quality of Life (EQ-5D)	3 RCTs: 900 pts.	We synthesized evidence from 3 RCTs (900 patients) which explored the long-term change quality of life as measured by EQ-5D. These studies did not demonstrate a difference between strategies (difference in means = 0, 95% CI -0.028 to 0.029) (Figure 16).
High		
Reduction of LE Pain	3 RCTs: 1,498 pts. 1 RCT: NR	Four RCTs <sup>65, 66, 75, 96, 166</sup> reported VAS pain scores at various time points ranging from baseline to 1 year. Three studies <sup>75, 96, 166</sup> reported significantly lower pain scores in the sclerotherapy group when compared with the surgery group.
Low		
Adverse Events (Hematoma)	3 RCTs: 1,142 pts. 1 RCT: 96 limbs	We synthesized evidence from 4 RCTs (3 RCTs with 1,142 patients, 1 RCT with 96 limbs) <sup>59, 124, 155, 166</sup> which 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).
Low		
<b>EVLA vs. sclerotherapy</b>		
Changes on standardized symptom scores (Intermediate- term)	2 RCTs: 885	VCSS improved in both groups. No statistically difference between groups. <sup>66, 91</sup>
Low		
Patient-reported QOL (Intermediate-term)	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. <sup>66, 91</sup>
Low		

Outcome (Timeframe)	Studies (N and Design)	Findings
<b>Strength of Evidence</b>	<b>N Pts</b>	<b>Findings</b>
Patient-reported QOL (Long-term) Low	2 RCTs: 580	QOL improved in both group. No statistically difference between groups. <sup>75, 91</sup>
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 ( $p=0.005$ ). <sup>66, 91</sup>
<b>EVLA vs. RFA</b>		
Bleeding (Short-term) Low	2 RCTs 249 1 Obs 979 limbs	According to <i>Shepherd et al</i> , 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 ( $p<0.001$ ). <sup>101, 102, 104, 133</sup> <i>Gale et al</i> reported the number of patients with bruising at 1 week. There was a significant more bruising in the EVLA group at 1 week ( $p=0.01$ ). <sup>133</sup>
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. <sup>104, 133, 142</sup>
Changes on standardized symptom scores (Intermediate- term) Low	3 RCTs 336	VCSS improved in both group. No statistically difference between groups <sup>101, 102, 133, 142</sup>
Changes on standardized symptom scores (Long-term) Low	2 RCTs 249	VCSS improved in both group. No statistically difference between groups <sup>101, 102, 133</sup>
Patient-reported QOL (Short-term) Low	3 RCTs 372	QOL improved in both group. No statistically difference between groups <sup>101, 102, 127, 142</sup>
Patient-reported QOL (Intermediate-term) Low	4 RCTs 490	QOL improved in both group. No statistically difference between groups SOE= high <sup>101, 102, 127, 133, 142</sup>
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 ( $p=0.01$ ). <sup>101, 102, 127</sup>
<b>Endovascular Treatment vs. Placebo</b>		
Changes on standardized symptom scores (Intermediate- term) Moderate	2 RCTs 440	<sup>103, 119</sup> Two good-quality RCTs 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.  The percentage of patient that changed VSSymQ at 8 weeks in the 0.5% polidocanol endovenous group was 83.1% in the 1% polidocanol endovenous group was 77.8% and in the placebo group was 21.2%. Demonstrating a statistically significant difference in favor of 0.5% polidocanol endovenous group ( $p<0.0001$ ) and 1% polidocanol endovenous group ( $p<0.0001$ ) when compared with placebo group.

Outcome (Timeframe)	Studies (N and Design)	Findings
<b>Strength of Evidence</b>	<b>N Pts</b>	<b>Findings</b>
Improvement in LE venous hemodynamics/reflux severity (Intermediate-term) Moderate	3 RCTs 465	<sup>103, 119, 153</sup> 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
Patient-reported QOL (Intermediate-term) Moderate	2 RCTs 443	<sup>103, 119</sup> The mean within group change of VEINES-QOL in the 0.5% polidocanol endovenous group was 22.79, in the 1% polidocanol endovenous group was 20.42 and in the placebo group was 7.42. Demonstrating a statistically significant difference in favor of 0.5% polidocanol endovenous group (p<0.0001) and 1% polidocanol endovenous group (p<0.0001) when compared with placebo group.
<b>Invasive surgery vs. invasive surgery</b>		
Qualitative reduction in LE pain (Short Term) Low	1 RCT: 40 pts. 1 RCT: NR	<b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>148</sup> - no significant difference between procedures at 24 hours <b>High ligation/stripping vs. High ligation/cryostripping</b> <sup>151</sup> - no significant difference between procedures at 7, 14, and 28 days
<b>Invasive surgery vs. compression</b>		
Death (Long Term) Low	2 RCTs: 526 pts. 1 RCT: 196 limbs	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - 16 percent in the surgery group versus 19 percent in the compression group (p=0.245) at 3 years <b>High ligation/stripping vs. compression</b> <sup>170</sup> - no deaths in either group over 6 months <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - 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 pts.	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - 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. <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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 pts. 1 RCT: 196 limbs	<b>High ligation/stripping vs. compression</b> <sup>85, 88</sup> - recurrence rate was 12 percent in the surgery group versus 28 percent with compression alone (p<0.0001) <b>High ligation/stripping/SEPS vs. compression</b> <sup>89, 90</sup> - At long-term followup, 22 of 45 limbs in the surgery group had recurrent ulceration versus 33 of 35 with compression (p=NR) <b>CHIVA vs. compression</b> <sup>154, 169</sup> - 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).
<b>Venous ligation plus stripping vs. EVLA</b>		
Vein recurrence/ Repeat intervention (Long Term) Low	5 RCTs: 1,261 pts.	Five studies evaluated long-term thrombophlebitis. <sup>75, 82, 94, 105, 131</sup> The findings of these studies were imprecise and inconsistent demonstrating no difference in thrombophlebitis between the two strategies (OR = 1.009, 95% CI = 0.686 to 1.484) (Figure 6)
Improvement hemodynamics Low	5 RCTs: 887 pts.	Five studies representing 887 patients were combined in a meta-analysis to explore improvement in hemodynamics. <sup>61, 71, 94, 105, 131</sup> The analysis suggested a trend towards improvement in reflux/incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121) (Figure 7)
Clinical symptom	3 RCTs: 487	We synthesized three studies representing 487 patients for treatment effect on

Outcome (Timeframe)	Studies (N and Design)	Findings
<b>Strength of Evidence</b>	<b>N</b>	<b>Pts</b>
scores (VCSS)	pts.	long-term VCSS score. <sup>64, 75, 131</sup> There was no significant difference between treatment strategies (standard difference of means = 0.021, 95% CI = -0.186 to 0.229) (Figure 8).
Low		
Clinical symptom scores (CEAP)	4 RCTs 867 pts.	We also explored the CEAP after 12 months in 4 studies representing 867 patients. <sup>78, 94, 100, 117</sup> No difference was found (standard difference of means = 0.061, 95% CI -0.096 to 0.219)(Figure 9).
Moderate		
Patient-reported Quality of Life (EQ-5D)	4 RCTs 1,436 pts.	Four studies <sup>66, 80, 94, 164</sup> 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.
Low		
Patient-reported Quality of Life (AVVQ-Short Term)	4 RCTs: 583 pts.	We synthesized four studies representing 583 patients which evaluated short-term AVVQ effects. <sup>80, 82, 117, 164</sup> These studies showed a -0.014 standardized difference in means (95% CI -0.340 to 0.311) showing no difference between strategies (Figure 10).
Low		
Patient-reported Quality of Life (AVVQ-Intermediate Term)	4 RCTs: 426 pts.	Four studies representing 426 patients explored the impact on AVVQ over an intermediate time horizon. <sup>82, 117, 147, 164</sup> Again there was no different in AVVQ scores (standard difference of means = -0.011, 95% CI 0-0.212 to 0.190) (Figure 11).
Low		
Patient-reported Quality of Life (AVVQ-Long Term)	6 RCTs: 663 pts.	We synthesized data from 6 studies (663 patients) which evaluated long-term quality of life with the AVVQ. <sup>75, 80, 82, 117, 131, 147</sup> These studies also consistently found no difference between treatment strategies (standard difference of means = 0.063, 95% CI -0.122 to 0.247) (Figure 12).
Moderate		
Reduction in LE Pain	4 RCTs: 778 pts.	Four studies representing 778 patients were synthesized quantitatively to explore reduction in LE pain as measured by a visual analog scale. <sup>75, 82, 128, 164</sup> 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 of means = -0.148, 95% CI -0.531 to 0.236) (Figure 13).
Low		
Adverse Events (Bleeding risk)	3 RCTs: 822 pts.	We were able to perform a meta-analysis on three studies representing 822 patients that evaluated bleeding (hematoma / ecchymosis). <sup>99, 100, 131, 165</sup> 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).
Moderate		

### 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 followup time points eliminated the possibility that study results could be pooled for analysis of direct comparisons.

One study evaluated the effect of exercise training versus usual care/control in 43 patients with post-thrombotic syndrome over a 6 month followup period.<sup>175</sup> There was a significant effect on the Venous Insufficiency Epidemiological and Economic Study Quality-of-Life questionnaire (VEINES-QOL) and Short Form 36-item Health Survey SF-36) physical component score, favoring exercise training, but there was no effect on Villalta score (measure of post-thrombotic syndrome severity).

One observational study evaluated the effect of compression therapy versus endovenous intervention in 216 patients with moderate-severe post-thrombotic syndrome (Villalta score  $\geq 10$ ) over a 3 month followup period.<sup>172</sup> In the patients with venous ulceration at study entry, recurrence-free ulcer healing rates were 87 percent in the stenting group compared to 71 percent in the compression group ( $p < 0.01$ ). There were not clinically significant differences between the two treatment options on the severity of post-thrombotic syndrome (Villalta score or edema score).

Three observational studies evaluated the effect of endovenous interventions (stenting or EVLA) versus combination endovenous interventions (stenting, EVLA, or thrombolysis) in 419 patients with post-thrombotic syndrome and/or May-Thurner (proximal venous obstruction) syndrome over long-term followup.<sup>177-179</sup> For patients with May-Thurner Syndrome, the literature suggests that a treatment strategy of catheter-directed thrombolysis with urokinase followed by stenting, compared to stent alone had a higher procedural failure rate and less long-term clinical improvement (low SOE). In patients with both May-Thurner Syndrome and superficial venous reflux who were undergoing EVLA, stent placement at the time of EVLA resulted in less recurrent ulceration, improvement in reflux severity and symptoms, and improvement in quality of life in long-term followup (fair SOE).

We found very few studies that assessed medical therapy, lifestyle modification (i.e. weight reduction), or skin/wound care. 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. One observational study reported variations in the treatment effectiveness by subgroup, Villalta score. 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,<sup>53</sup> and the United Kingdom's (UK's) National Institute for Health and Care Excellence (NICE) has published a clinical guideline on varicose veins.<sup>55</sup>

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 contemporary 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.<sup>175</sup>

## 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 followup:* Study followup was heavily weighted towards short-term followup, and there was variable reporting of duration of followup. While study outcomes were grouped into short-, intermediate-, and long-term followup, 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 39 shows the potential issues with applicability in included studies of patients with LECVD.

**Table 39. Potential issues with applicability of included studies**

Issues	KQ 1 N=7	KQ 2 N=88	KQ 3 N=8	Total N=103
<b>Population (P)</b>				
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
<b>Intervention (I)</b>				
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
Followup not reflective of current practice	0	4	1	5
<b>Comparator (C)</b>				
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	0	1	1
<b>Outcomes (O)</b>				
Composite outcomes that mix outcomes of different significance	0	3	0	3
Short-term followup	0	24	0	24
Surrogate outcomes	0	8	0	8
<b>Timing (T)</b>				
Duration of participant followup was inadequate	0	14	1	15
<b>Setting (S)</b>				
Study conducted solely outside the United States	4	81	4	89
Study was conducted only at a single site	5	49	7	61

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 health care 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 health care 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 peri-procedural 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<sub>1</sub> and C<sub>2</sub>), 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.

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 vs. not. Finally, since endovenous intervention 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 84 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.

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. 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 followup 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) followup 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.

### **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 treated and how they should be treated 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 consensus outcomes at clinically-relevant timepoints. Additionally, existing RCTs often fail to adequately address allocation

concealment, blinding of outcomes assessors, and patient blinding. Lastly, there is a paucity of studies investigating efficacy and safety in biologically 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.

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. Additionally, very little data exists for long-term effectiveness and safety for many of the treatment choices available to patients with LE chronic venous insufficiency/incompetence/reflux. Future studies should also address the relatively sparse existing data comparing new endovenous techniques (e.g., thermal/mechanochemical ablation and cyanoacrylate [CA] embolization) and hybrid procedures (surgical plus endovascular) with established techniques. 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. There is also insufficient evidence in support of the use of mechanical compression as a treatment for LE varicose veins, either as primary treatment or in conjunction with invasive treatments.

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). 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. Very little comparative effectiveness data has been generated 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 contemporary literature. 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	polydocanol 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
VSIDS	Venous Segmental Disease Score
VTE	chronic venous insufficiency/incompetence
VVSymQ	Varicose Veins Symptoms Questionnaire
WHO	World Health Organization

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