

Evidence-based Practice Center Systematic Review Protocol

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

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(Amendments Details—see Section VII)

I. Background for the Systematic Review

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 will focus on treatment strategies for patients with LECVD, which will be defined as patients who have had signs or symptoms of 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 chronic venous disease 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 (CVI), and the annual prevalence of venous thromboembolism (VTE, including both pulmonary embolism [PE] and deep vein thrombosis [DVT]) is approximately 1 million people.¹ While the majority of patients with LECVD are asymptomatic, serious complications can occur, including LE amputation, acute and chronic VTE, chronic thromboembolic pulmonary hypertension, and mortality.² Furthermore, costs for the care of LECVD have increased substantially in the last few decades, with estimates in the United States of between \$150 million and \$1 billion per year.^{3,4}

Definitions of selected terms are provided in Table 1.

Table 1. Definitions of terms

Term	Definition
Venous obstruction	Defined as partial or complete blockage of venous flow in any venous segment; can result from internal blockage (e.g., thrombosis) or external compression of the vein

Term	Definition
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 (CVI)	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

Diagnostic Testing for Chronic Venous Disease

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

Potential Pitfalls or Adverse Events Associated with Misdiagnosis

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 Lower Extremity Chronic Venous Disease

The most common classification scheme for LECVD is the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification, shown in Table 2.^{6,7}

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

Clinical (C)†	Etiologic (E)	Anatomic (A)	Pathophysiologic (P)
C ₀ No visible sign of venous disease	E _c Congenital	A _s Superficial	P _r Reflux
C ₁ Telangectasia or reticular veins	E _p Primary	A _d Deep	P _o Obstruction, thrombosis
C ₂ Varicose veins	E _s Secondary (e.g. post-thrombotic, trauma)	A _p Perforator	P _{r,o} Reflux and obstruction
C ₃ Edema	E _n No venous cause identified	A _n No venous location identified	P _n No venous pathophysiology identified
C ₄ Changes in skin and subcutaneous tissue A Pigmentation or eczema B Lipodermatosclerosis or atrophie blanche	-	-	-
C ₅ Healed ulcer	-	-	-
C ₆ Active ulcer	-	-	-

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

Treatment of Lower Extremity Chronic Venous Disease

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). 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 a systematic review is warranted. Such a review will formally evaluate the evidence supporting the harms and benefits of the available treatments and 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.

Clinical Outcomes of Lower Extremity Chronic Venous Disease

After patients are diagnosed with LECVD and an initial treatment strategy is determined, symptoms are monitored clinically with subjective and objective measures as specified in the CEAP classification score and the Venous Clinical Severity Score (VCSS). More specifically, pre- and post-treatment vascular laboratory testing is compared, including venous refilling time (VRT) and/or ambulatory venous pressure. Patients with venous

insufficiency/incompetence/reflux typically undergo air plethysmography and duplex ultrasonography. Patients undergoing treatment for chronic venous thrombosis/obstruction normally undergo measurements of venous flow via duplex ultrasound 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 treatment strategies 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.

Timing, Setting, and Context

This systematic review will focus 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 will be included in the analyses.

Rationale for an Evidence Review

There is substantial variation in how patients with LECVD are diagnosed and treated. In the past, vascular surgeons were often the physicians who 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. 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 in the Topic Area

- 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 differences: 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.
- Evolution of surgical and endovenous techniques: improvements in both surgical and endovenous technology 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?

II. The 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:

- a. 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?
- b. What diagnostic method(s) and criteria were used in each study?
- c. 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)?
- d. 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):

- a. What is the comparative effectiveness of exercise, medical therapy, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) on health outcomes?

- b. What diagnostic method(s) and criteria were used in each study?
- c. 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)?
- d. 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 1: Diagnosis

- **Population(s):**
 - 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)
- **Diagnostic Measures:**
 - Air plethysmography, LE venous duplex ultrasonography (with and without compression), invasive venography, magnetic resonance venography, computed tomographic venography, serum D-dimer testing, Villalta score
- **Comparators:**
 - Diagnostic modalities listed above (air plethysmography, LE duplex venous ultrasonography [with and without compression], invasive venography, magnetic resonance venography, computed tomographic venography, serum D-dimer testing, Villalta score) will be compared to one another
- **Outcomes:**
 - Sensitivity, specificity, positive predictive value, negative predictive value, inter-rater reliability, internal consistency, test-retest reliability, false positives, false negatives, and positive and negative likelihood ratios for each diagnostic measure listed above will be compared
- **Timing:**
 - Not applicable
- **Settings:**
 - All clinical settings, including inpatient and outpatient

KQs 2-3: Treatment

- **Population(s):**
 - KQ 2: Asymptomatic or symptomatic adults (over age 18) with the diagnosis of LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux:
 - Subgroup analysis: age, race/ethnicity, sex, body weight, CEAP

- classification, VCSS classification, severity of disease, anatomic segment affected (e.g., iliofemoral, infrainguinal), known malignancy, presence of LE ulcer
- KQ 3: Asymptomatic or symptomatic adults(over age 18) with the diagnosis of LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome):
 - Subgroup analysis: age, race/ethnicity, sex, body weight, CEAP classification, VCSS classification, Villalta score, severity of disease, anatomic segment affected (e.g., iliofemoral, infrainguinal), known malignancy, presence of LE ulcer
- **Interventions:**
 - KQ 2: lifestyle interventions (e.g., smoking cessation, leg elevation, weight reduction, exercise), medical therapy, local skin care/wound care, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures)
 - Medical therapies: diuretics, aspirin, pentoxifylline, prostacyclins, zinc sulfate
 - Invasive surgical/endovascular procedures: sclerotherapy (liquid, foam, glue), radiofrequency ablation, thermal ablation, chemical ablation, ambulatory phlebectomy, transilluminated powered phlebectomy, venous ligation, venous excision
 - KQ 3: lifestyle interventions (e.g., smoking cessation, leg elevation, weight reduction, exercise), medical therapy, local skin care/wound care, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures)
 - Medical therapies: anticoagulants including warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran; diuretics
 - Invasive surgical/endovascular procedures: endovenous angioplasty/stenting, ultrasound accelerated thrombolysis for chronic DVT (EkoSonic® endovascular system), surgical thromboembolectomy
- **Comparators:**
 - Specific treatments will be compared to other included treatments as described above or to no treatment (placebo or usual care)
- **Outcomes:**
 - Changes on standardized symptom scores (Villalta score, CEAP classification, AVVQ score, and VCSS score); qualitative reduction in LE edema; qualitative reduction in LE pain; improvement in LE venous hemodynamics/reflux severity as measured by air plethysmography, duplex ultrasonography, or invasive venography; venous wound healing, recurrent ulceration, patient-reported quality of life (including AVVQ), repeat intervention, LE amputation
 - Adverse effects of treatment, including: adverse drug reactions; bleeding (including intracranial bleeding); venous wound infection; contrast

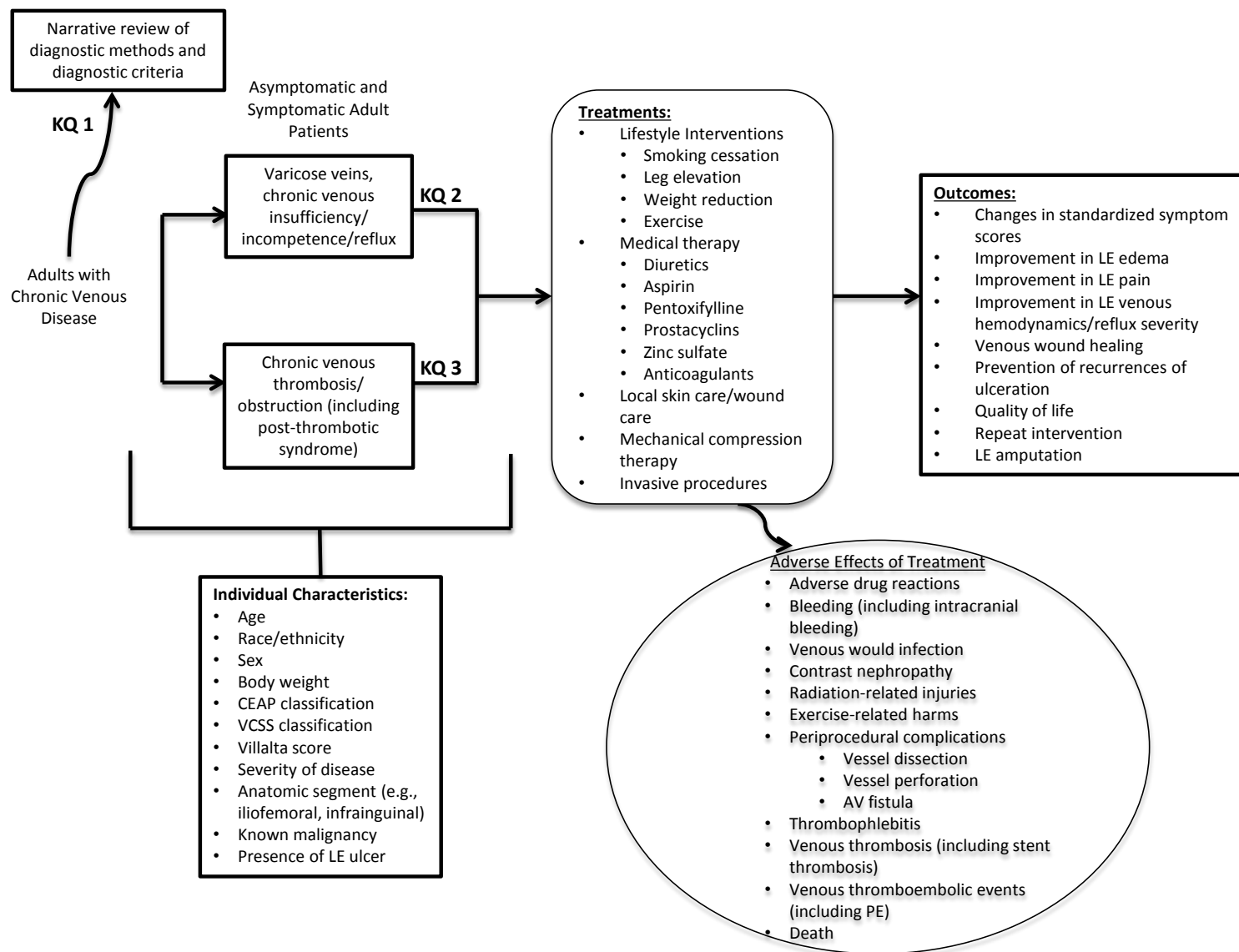
nephropathy; radiation-related injuries; exercise-related harms; periprocedural complications (vessel dissection, vessel perforation, and AV fistula), thrombophlebitis, venous thrombosis (including stent thrombosis), venous thromboembolic events (including PE), and death

- **Timing:**
 - Studies with all durations of followup will be included in the review; for symptomatic patients, we will attempt to categorize studies into those that evaluate short-term (≤ 30 days), intermediate-term (31 days to 6 months), and long-term (> 6 months) events.
- **Settings:**
 - Any

III. Analytic Framework

The analytic framework presented in Figure 1 illustrates the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis. This figure illustrates 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 key questions (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

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ)'s Evidence-based Practice Center (EPC) Program in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide).⁸ We will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer (TOO) and the Technical Expert Panel (TEP). We will follow the methodology recommended by the EPCs for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

Criteria for Inclusion/Exclusion of Studies in the Review

Table 3 summarizes the inclusion and exclusion criteria to be used in the review.

Table 3. 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">• Age• Race/ethnicity• Sex• Body weight• CEAP classification• VCSS classification• Villalta score• Severity of disease• Anatomic segment affected (e.g., iliofemoral, infrainguinal)• Known malignancy• Presence of LE ulcer	<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	KQ 1: Any standard chronic venous disease diagnostic strategy, including: air plethysmography, LE duplex venous ultrasonography (with and without compression), invasive	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<p>venography, magnetic resonance venography, 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"> • Medical therapies: diuretics, aspirin, pentoxifylline, prostacyclins, zinc sulfate • Invasive surgical/endovascular procedures: sclerotherapy (liquid, foam, glue), radiofrequency ablation, thermal ablation, chemical ablation, ambulatory phlebectomy, transilluminated powered phlebectomy, venous ligation, venous excision <p>KQ 3: 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"> • Medical therapies: anticoagulants including warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran; diuretics • Invasive surgical/endovascular procedures: endovenous angioplasty/stenting, ultrasound accelerated thrombolysis for chronic DVT (EkoSonic® endovascular system), surgical thromboembolectomy 	
Comparators	<p>KQ1: Specific diagnostic modalities listed above will be compared to one another</p> <p>KQs 2-3: Specific treatments will be compared to other included treatments as described above or to no treatment (placebo or usual care)</p>	<p>Same treatment comparisons that vary by characteristics such as dose, timing, manufacturer, compression level, or energy level.</p> <p>Comparisons between interventions for local skin care/ wound care.</p>
Outcomes	<p>KQ 1:</p> <ul style="list-style-type: none"> • Accuracy of diagnostic strategy, as measured by: <ul style="list-style-type: none"> ○ Sensitivity ○ Specificity ○ Positive predictive value ○ Negative predictive value ○ Inter-rater reliability ○ Internal consistency ○ Test-retest reliability ○ False positives ○ False negatives ○ Positive likelihood ratio ○ Negative likelihood ratio <p>KQs 2-3:</p>	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> • Changes on standardized symptom scores (Villalta score, CEAP classification, AVVQ score, and VCSS score) • Qualitative reduction in LE edema • Qualitative reduction in LE pain • Improvement in LE venous hemodynamics/reflux severity as measured by air plethysmography, duplex ultrasonography, or invasive venography • Venous wound healing • Recurrent ulceration • Patient reported quality of life (including AVVQ) • Repeat intervention • LE amputation • Adverse effects of treatment, including: <ul style="list-style-type: none"> ◦ Adverse drug reactions ◦ Bleeding (including intracranial bleeding) ◦ Venous wound infection ◦ Contrast nephropathy ◦ Radiation-related injuries ◦ Exercise-related harms ◦ Periprocedural complications (vessel dissection, vessel perforation, and AV fistula) ◦ Thrombophlebitis ◦ Venous thrombosis (including stent thrombosis), ◦ Venous thromboembolic events (including PE) ◦ Death 	
Timing	Studies with all durations of followup will be included in the review, incorporating short-term (≤ 30 days), intermediate-term (31 days to 6 months), and long-term (> 6 months) events	
Settings	All clinical settings, including inpatient and outpatient (KQ 1 only)	
Study design	<ul style="list-style-type: none"> • Original data • RCTs, prospective and retrospective observational studies with comparator • RCTs: sample size ≥ 20 subjects • Observational studies: sample size ≥ 20 subjects 	<p>Editorials, nonsystematic reviews, letters, case series, case reports, abstract only, articles that have been retracted or withdrawn</p> <p>Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality, we will exclude them from our review</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Publications	<ul style="list-style-type: none"> English-language only Published January 1, 2000, to present Relevant systematic reviews, meta-analyses, or methods articles (used for background only) 	Given the high volume of literature available in English-language publications, the focus of our review on applicability to populations in the United States, and the scope of our current KQs, non-English articles will be excluded ^a

^aIt is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

Abbreviations: AV = arteriovenous; AVVQ = Aberdeen Varicose Vein Questionnaire; CEAP = Clinical, Etiologic, Anatomic, Pathophysiologic; DVT = deep vein thrombosis; KQ(s) = key question(s); LE = lower extremity; PE = pulmonary embolism; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCTs = randomized controlled trials; VCSS = Venous Clinical Severity Score

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

To identify relevant published literature, we will search PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews, limiting the search for studies to those published from January 1, 2000, to the present. This timeframe represents contemporary treatment strategies and corresponds to timings where significant changes in the available of endovascular techniques occurred within the peripheral vascular treatment community. Where possible, we will use existing validated search filters or build off existing systematic reviews (particularly those of the Cochrane Peripheral Vascular Diseases Group). Our proposed search strategy for PubMed is provided in Tables 4 and 5; this strategy will be adapted as appropriate for searching the other databases. An experienced search librarian will guide all searches. We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our database, and additional relevant manuscripts will be retrieved. All citations will be imported into an electronic bibliographical database (EndNote[®] Version X7; Thomson Reuters, Philadelphia, PA).

Table 4. PubMed search strategy: KQ 1 Diagnosis

Set	Terms
#1	"Varicose Veins"[Mesh] OR "Venous Insufficiency"[Mesh] OR "Venous Thromboembolism"[Mesh] OR "May-Thurner Syndrome"[Mesh] OR "Thrombophlebitis"[Mesh] OR "varicose vein"[tiab] OR "varicose veins"[tiab] OR varicosity[tiab] OR "venous ulcer"[tiab] OR "vein ulcer"[tiab] OR "varicose ulcer"[tiab] OR "venous ulcers"[tiab] OR "vein ulcers"[tiab] OR "varicose ulcers"[tiab] OR "stasis dermatitis"[tiab] OR "venous stasis"[tiab] OR "chronic vein insufficiency"[tiab] OR "venous insufficiency"[tiab] OR "vein incompetence"[tiab] OR "chronic venous incompetence"[tiab] OR "vein reflux"[tiab] OR "chronic venous reflux"[tiab] OR "post-thrombotic syndrome"[tiab] OR "postthrombotic syndrome"[tiab] OR "venous obstruction"[tiab] OR "vein obstruction"[tiab] OR thrombophlebitis[tiab] OR "venous outflow disease"[tiab] OR "venous outflow obstruction"[tiab] OR "impaired venous outflow"[tiab] OR "post phlebitis"[tiab] OR "post phlebitic"[tiab] OR postphlebitic[tiab] OR postphlebitis[tiab] OR "post thrombotic"[tiab] OR postthrombosis[tiab] OR postthrombotic[tiab] OR "post thrombosis"[tiab] OR

Set	Terms
	"chronic venous thrombosis"[tiab] OR "chronic vein thrombosis"[tiab] OR "May-Thurner Syndrome"[tiab] OR (("Venous Thrombosis"[Mesh] OR "deep vein thrombosis"[tiab] OR "venous thrombosis"[tiab] OR dvt[tiab]) AND chronic[tiab])
#2	"Varicose Veins/diagnosis"[Majr] OR "Venous Insufficiency/diagnosis"[Majr] OR "Venous Thromboembolism/diagnosis"[Majr] OR "May-Thurner Syndrome/diagnosis"[Majr] OR "Thrombophlebitis/diagnosis"[Majr] OR "Phlebography"[Mesh] OR "Ultrasonography"[Mesh] OR "Veins/ultrasonography"[Mesh] OR "Varicose Veins/ultrasonography"[Mesh] OR "Diagnostic Techniques and Procedures"[Mesh] OR phlebography[tiab] OR venography[tiab] OR "D-Dimer"[tiab] OR "villalta"[tiab] OR diagnosis[tiab] OR diagnostic[tiab]
#3	"Sensitivity and Specificity"[Mesh] OR "Diagnostic Errors"[Mesh] OR sensitivity[tiab] OR specificity[tiab] OR accuracy[tiab] OR "positive predictive value"[tiab] OR "negative predictive value"[tiab] OR "likelihood ratio"[tiab] OR (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH] OR "retrospective"[tiab] OR "Cross-Sectional Studies"[MeSH] OR cross-sectional[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[tiab] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] OR humans[mh]) AND English[la]
#4	#1 AND #2 AND #3
#5	#4 , limit since 2000

Table 5. PubMed search strategy: KQ 2-3 Treatment

Set	Terms
#1	"Varicose Veins"[Mesh] OR "Venous Insufficiency"[Mesh] OR "Venous Thromboembolism"[Mesh] OR "May-Thurner Syndrome"[Mesh] OR "Thrombophlebitis"[Mesh] OR "varicose vein"[tiab] OR "varicose veins"[tiab] OR varicosity[tiab] OR "venous ulcer"[tiab] OR "vein ulcer"[tiab] OR "varicose ulcer"[tiab] OR "venous ulcers"[tiab] OR "vein ulcers"[tiab] OR "varicose ulcers"[tiab] OR "stasis dermatitis"[tiab] OR "venous stasis"[tiab] OR "chronic vein insufficiency"[tiab] OR "venous insufficiency"[tiab] OR "vein incompetence"[tiab] OR "chronic venous incompetence"[tiab] OR "vein reflux"[tiab] OR "chronic venous reflux"[tiab] OR "post-thrombotic syndrome"[tiab] OR "postthrombotic syndrome"[tiab] OR "venous obstruction"[tiab] OR "vein obstruction"[tiab] OR thrombophlebitis[tiab] OR "venous outflow disease"[tiab] OR "venous outflow obstruction"[tiab] OR "impaired venous outflow"[tiab] OR "post phlebitis"[tiab] OR "post phlebitic"[tiab] OR postphlebitic[tiab] OR postphlebitis[tiab] OR "post thrombotic"[tiab] OR postthrombosis[tiab] OR postthrombotic[tiab] OR "post thrombosis"[tiab] OR "chronic venous thrombosis"[tiab] OR "chronic vein thrombosis"[tiab] OR "May-Thurner Syndrome"[tiab] OR (("Venous Thrombosis"[Mesh] OR "deep vein thrombosis"[tiab] OR "venous thrombosis"[tiab] OR dvt[tiab]) AND chronic[tiab])
#2	"Varicose Veins/prevention and control"[Majr] OR "Varicose Veins/therapy"[Majr] OR "Venous Insufficiency/prevention and control"[Majr] OR "Venous Insufficiency/therapy"[Majr] OR "Venous Thromboembolism/therapy"[Majr] OR "Venous Thromboembolism/prevention and control"[Majr] OR "May-Thurner Syndrome/prevention and control"[Majr] OR "May-Thurner Syndrome/therapy"[Majr] OR "Thrombophlebitis/therapy"[Majr] OR "Thrombophlebitis/prevention and control"[Majr] OR "Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Diuretics"[Mesh] OR "Diuretics" [Pharmacological Action] OR "Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors"[Pharmacological Action] OR "prasugrel"[Supplementary Concept] OR "Ticagrelor"[Supplementary Concept] OR "Prostaglandins I"[Mesh] OR "Sclerotherapy"[Mesh] OR "Sclerosing Solutions"[Mesh] OR "Stockings, Compression"[Mesh] OR "Intermittent Pneumatic Compression Devices"[Mesh] OR "Laser Therapy"[Mesh] OR "Catheter Ablation"[Mesh] OR "Ablation Techniques"[Mesh] OR "Vena Cava Filters"[Mesh] OR "Stents"[Mesh] OR "Tissue Plasminogen Activator"[Mesh] OR "Streptokinase"[Mesh] OR "Urokinase-Type Plasminogen Activator"[Mesh] OR "Mechanical Thrombolysis"[Mesh] OR "Bandages"[Mesh] OR "Pressure"[Mesh] OR "Wounds and Injuries/therapy"[Mesh] OR "Negative-Pressure Wound Therapy"[Mesh] OR "Skin Care"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Ligation"[Mesh] OR "Angioplasty"[Mesh] OR "Zinc Sulfate"[Mesh] OR "Hyperbaric Oxygenation"[Mesh] OR "Weight Loss"[Mesh] OR "Nutrition

Set	Terms
	Therapy"[Mesh] OR "Smoking Cessation"[Mesh] OR "Ultrasonography"[Mesh] OR anticoagulants[tiab] OR Apixaban[tiab] OR Coumadin[tiab] OR dabigatran[tiab] OR edoxaban[tiab] OR Eliquis[tiab] OR Jantoven[tiab] OR Lixiana[tiab] OR Marevan[tiab] OR Pradaxa[tiab] OR Prazaxa[tiab] OR rivaroxaban[tiab] OR Savaysa[tiab] OR warfarin[tiab] OR Xarelto[tiab] OR coumarol[tiab] OR phenocoumarol[tiab] OR diuretics[tiab] OR Aldactone[tiab] OR amiloride[tiab] OR Aquatensen[tiab] OR bendroflumethiazide[tiab] OR bumetanide[tiab] OR Bumex[tiab] OR chlorothiazide[tiab] OR chlorthalidone[tiab] OR Demadex[tiab] OR Diuril[tiab] OR Dyrenium[tiab] OR Edecrin[tiab] OR Enduron[tiab] OR Esidrix[tiab] OR "ethacrynic acid"[tiab] OR furosemide[tiab] OR hydrochlorothiazide[tiab] OR HydroDIURIL[tiab] OR hydroflumethiazide[tiab] OR Hygroton[tiab] OR Lasix[tiab] OR Metahydrin[tiab] OR methyclothiazide[tiab] OR metolazone[tiab] OR Microzide[tiab] OR Midamor[tiab] OR Mykrox[tiab] OR Naqua[tiab] OR Naturetin[tiab] OR Oretic[tiab] OR Saluron[tiab] OR spironolactone[tiab] OR Thalitone[tiab] OR torsemide[tiab] OR triamterene[tiab] OR Trichlorex[tiab] OR trichlormethiazide[tiab] OR Zaroxolyn[tiab] OR antiplatelets[tiab] OR "platelet aggregation inhibitors"[tiab] OR Aspirin[tiab] OR Agrylin[tiab] OR anagrelide[tiab] OR Brilinta[tiab] OR cilostazol[tiab] OR clopidogrel[tiab] OR dipyridamole[tiab] OR Effient[tiab] OR Pentoxifylline[tiab] OR pentoxil[tiab] OR Persantine[tiab] OR Plavix[tiab] OR Pletal[tiab] OR prasugrel[tiab] OR ticagrelor[tiab] OR Ticlid[tiab] OR ticlopidine[tiab] OR trental[tiab] OR vorapaxar[tiab] OR Zontivity[tiab] OR epoprostenol[tiab] OR prostacyclins[tiab] OR "prostaglandins 1"[tiab] OR "prostaglandins I"[tiab] OR sclerotherapy[tiab] OR Asclera[tiab] OR Aethoxysklerol[tiab] OR "chromated glycerin"[tiab] OR Cyanoacrylate[tiab] OR Dermabond[tiab] OR polidocanol[tiab] OR Scleremo[tiab] OR Sclerodex[tiab] OR "sodium chloride"[tiab] OR "sodium tetradecyl sulfate"[tiab] OR Sotradecol[tiab] OR Varisolve[tiab] OR Varithena[tiab] OR compression[tiab] OR Flexitouch[tiab] OR CircuFlow[tiab] OR BioCryo[tiab] OR Flowtron[tiab] OR VPulse[tiab] OR "laser ablation"[tiab] OR VenaCure[tiab] OR "Pro V Laser"[tiab] OR CoolTouch[tiab] OR ELVes[tiab] OR "Lumenis Sharplan"[tiab] OR Medilas[tiab] OR "catheter ablation"[tiab] OR "closure catheter"[tiab] OR venefit[tiab] OR ("vena cava"[tiab] AND (filter[tiab] OR filters[tiab])) OR stenting[tiab] OR stent[tiab] OR stents[tiab] OR activase[tiab] OR alteplase[tiab] OR kinytic[tiab] OR streptase[tiab] OR streptokinase[tiab] OR "tissue plasminogen activator"[tiab] OR urokinase[tiab] OR "mechanical thrombectomy"[tiab] OR ekosonic[tiab] OR trerotola[tiab] OR amplatzer[tiab] OR trellis[tiab] OR angiojet[tiab] OR penumbra[tiab] OR Exercise[tiab] OR "physical therapy"[tiab] OR "zinc sulfate"[tiab] OR "elastic stockings"[tiab] OR bandage[tiab] OR bandages[tiab] OR bandaged[tiab] OR "pressure"[tiab] OR "wound therapy"[tiab] OR "skin care"[tiab] OR (leg[tiab] AND elevat*[tiab]) OR ablation[tiab] OR phlebectomy[tiab] OR ligation[tiab] OR excision[tiab] OR ((hyperbaric[tiab] OR "high pressure"[tiab] OR "high tension"[tiab]) AND (oxygen[tiab] OR oxygenation[tiab])) OR HBO[tiab] OR HBOT[tiab] OR HBO2[tiab] OR HBO2T[tiab] OR "hyperbaric chamber"[tiab] OR "hyperbaric chambers"[tiab] OR boots[tiab] OR "wound vac"[tiab] OR "wound vacuum"[tiab] OR angioplasty[tiab] OR "weight loss"[tiab] OR diet[tiab] OR smoking[tiab] OR tobacco[tiab] OR ultrasound[tiab] OR thromboembolectomy[tiab]
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#4	#1 AND #2 AND #3
#5	2000 – English only

As a mechanism to ascertain publication bias in recent studies, we will search ClinicalTrials.gov to identify completed but unpublished studies (we will also explore the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques). 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 will use several approaches to identifying relevant gray literature, including a search of study registries for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal, and the National Guidelines Clearinghouse. Additional grey literature will be solicited through a notice posted in the Federal Register and other information solicited through the AHRQ Effective Health Care website.

For citations retrieved from MEDLINE, Embase, and the Cochrane Database of Systematic Reviews, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. Inclusion at the title screening level will be liberal; if a single reviewer believes an article may contain relevant information based on title, the article will move to the next level (abstract) for further screening. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Disagreements that cannot be resolved by the two reviewers will be resolved by a third expert member of the team. Articles meeting eligibility criteria (see Table 3) will be included for data abstraction. At random intervals during screening, quality checks by senior team members will occur to ensure that screening and abstraction is consistent with inclusion/exclusion criteria and abstraction guidelines. We will make screening decisions and abstract data based on the published literature and available online appendices. We will not contact study authors for additional data. All results will be tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. We will link studies to avoid duplication of patient cohorts. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project 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). We will pay particular attention 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 – infrainguinal versus suprainguinal), patient characteristics (e.g., symptom status via CEAP and Villalta scores, presence or absence of LE

venous wounds, comorbidities, age), and study design (e.g., randomized controlled trial [RCT] versus observational) that may be related to outcomes. In addition, we will describe comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes will be 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. Data necessary for assessing quality and applicability, as described in the Methods Guide,⁸ will also be abstracted. Before they are used, abstraction form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency and reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles. Final abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) per EPC requirements.

Assessment of Methodological Risk of Bias of Individual Studies

We will assess methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias⁹ tool for RCTs, and the Newcastle-Ottawa Scale¹⁰ for observational studies. We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ's Methods Guide.⁸ Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. For all studies, the overall study quality will be assessed as follows:

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

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

Data Synthesis

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

We will review and highlight studies using a hierarchy-of-evidence approach. The best evidence available will be the focus of our synthesis for each key question. If high quality evidence is not available we will describe any lower quality evidence we were able to identify, but we will underscore the issues that make it lower quality and the uncertainties in our findings. We will assess and state whether the inclusion of lower quality studies would change any of our conclusions and perform sensitivity analyses excluding this evidence where appropriate.

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature (we will require 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis is appropriate, we will use random-effects models to synthesize the available evidence quantitatively. We will test for heterogeneity using graphical displays and test statistics (Q and I² statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses. We will perform quantitative and qualitative syntheses separately by study type and discuss their consistency qualitatively.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. The strength of evidence will be assessed using the approach described in AHRQ's Methods Guide.⁸ 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. Additional domains to be used when appropriate (most relevant to observational studies) are coherence, dose-response association, impact of plausible residual confounders, and strength of association (magnitude of effect). These domains will be considered qualitatively, and a summary rating of high, moderate, or low strength of evidence will be assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn.

In these situations, a grade of “insufficient” will be assigned. This four-level rating scale consists of the following definitions:

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

Assessing Applicability

We will assess applicability across our key questions using the method described in AHRQ’s Methods Guide.⁸ 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 are different across studies that recruit different populations (e.g., age groups, risk factors, comorbidities, characteristics of disease) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We will use a checklist to guide the assessment of applicability. We will use these data 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 will summarize issues of applicability qualitatively.

V. References

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VI. Definition of Terms

AHRQ	Agency for Healthcare Research and Quality
AV	arteriovenous
AVVQ	Aberdeen Varicose Vein Questionnaire
CEAP	Clinical, Etiologic, Anatomic, Pathophysiologic

CVI	chronic venous insufficiency/incompetence
DVT	deep vein thrombosis
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
ICTRP	International Clinical Trials Registry Platform
KQ	key question
LE	lower extremity
LECVD	lower extremity chronic venous disease
PAD	peripheral artery disease
PE	pulmonary embolism
PICOTS	population, interventions, comparators, outcomes, timing, settings
PVD	peripheral venous disease
RCT	randomized controlled trial
SOE	strength of evidence
SRDR	Systematic Review Data Repository
TEP	Technical Expert Panel
TOO	Task Order Officer
VCCS	Venous Clinical Severity Score
VRT	venous refilling time
VTE	venous thromboembolism
WHO	World Health Organization

VII. Summary of Protocol Amendments

Changes made to the protocol are summarized in the table below. Changes are not incorporated into the protocol body.

Table 6. Summary of Amendment Changes

Date	Section	Original Protocol	Revised Protocol	Rationale
5/6/2016	Section IV. Methods	The original protocol study design inclusion/exclusion criteria allowed observational studies to be included across all KQs.	KQ 2 will be limited to RCTs and to observational studies that include 500 or more patients relevant to the KQ2 population. Observational study designs remain included for KQs 1 and 3.	A large volume of RCT data has been identified for the population and interventions of interest in KQ 2, thus allowing the literature considered for this question to be focused on RCTs and larger observational

				studies that are less prone to confounding.
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VIII. Review of Key Questions

The EPC refined and finalized the key questions with input from the TEP. This input is intended to ensure that the key questions are specific and relevant.

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XII. Role of the Funder

This project was funded under Contract No. HHSA290201500004I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.