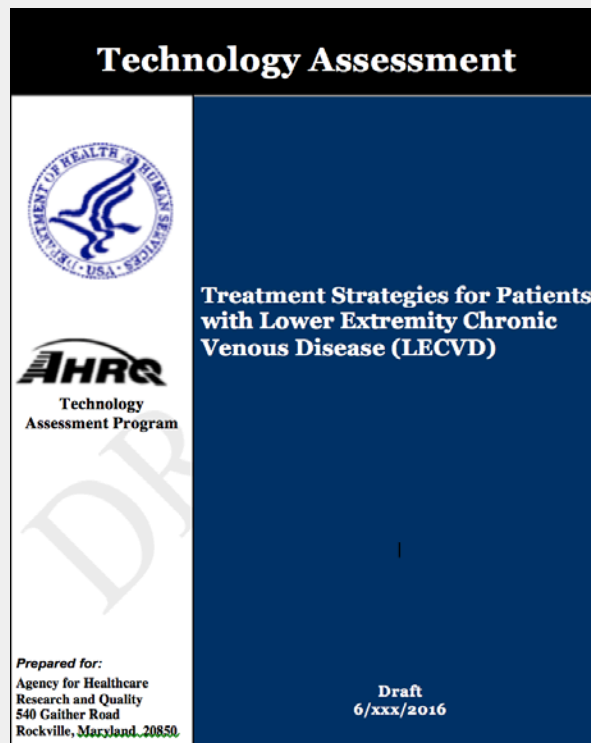


Treatment Strategies For Patients with Lower Extremity Chronic Venous Disease (LECVD)

Schuyler Jones, MD and Sreek Vemulapalli, MD

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Disclosures

W. Schuyler Jones, MD

- Research Grants to Institution: Agency for Healthcare Research & Quality, American Heart Association, AstraZeneca, Bristol-Myers Squibb, Doris Duke Charitable Foundation, Patient-Centered Outcomes Research Institute
- Advisory Board: none
- Honoraria/Other: American College of Physicians (modest), American College of Radiology (significant), Daiichi Sankyo (modest)
- Professional Society Roles: Chair, ACC PVI Research & Publications Committee

Disclosures

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- Research Grants to Institution: American College of Cardiology, Abbott Vascular; Agency for Healthcare Research and Quality; Society of Thoracic Surgeons
- Advisory Board: none
- Honoraria/Other: Premiere Research Inc (significant); Novella (modest)
- Professional Society Roles: STS / ACC TVT Registry Research and Publications Committee (non-voting); STS / ACC TVT Registry Steering Committee (non-voting); ACC-SHS Linked Dataset Expert Panel

Disclosures

Other Co-Authors

- No conflicts of interest to disclose

Note:

- Key Informants (TEP, Peer reviewers) must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained.
- The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

Lower Extremity Chronic Venous Disease (LECVD)

- Heterogeneous condition involving abnormalities in venous return from the lower limb(s)
- Includes patients with LE varicose veins, LE chronic venous insufficiency/incompetence/reflux, and LE chronic venous obstruction/thrombosis



Overview

- Description of Systematic Review Process
- Evidence Review Findings
 - KQ1: Diagnostic testing for LECVD
 - KQ2: Treatment for LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux
 - KQ3: Treatment for LE chronic venous thrombosis/ obstruction
- Limitations and Evidence Gaps
- Summary

Key Question 1

KQ 1: Narrative review of the diagnostic methods and diagnostic criteria for all patients with LECVD

Key Question 2

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

- a) **Comparative effectiveness of treatment modalities** on health outcomes?
- b) **Diagnostic method(s) and criteria** used?
- c) **Modifiers of effectiveness (i.e. patient characteristics)?**
- d) **Comparative safety concerns** of treatment modalities and modifiers of safety concerns

Key Question 3

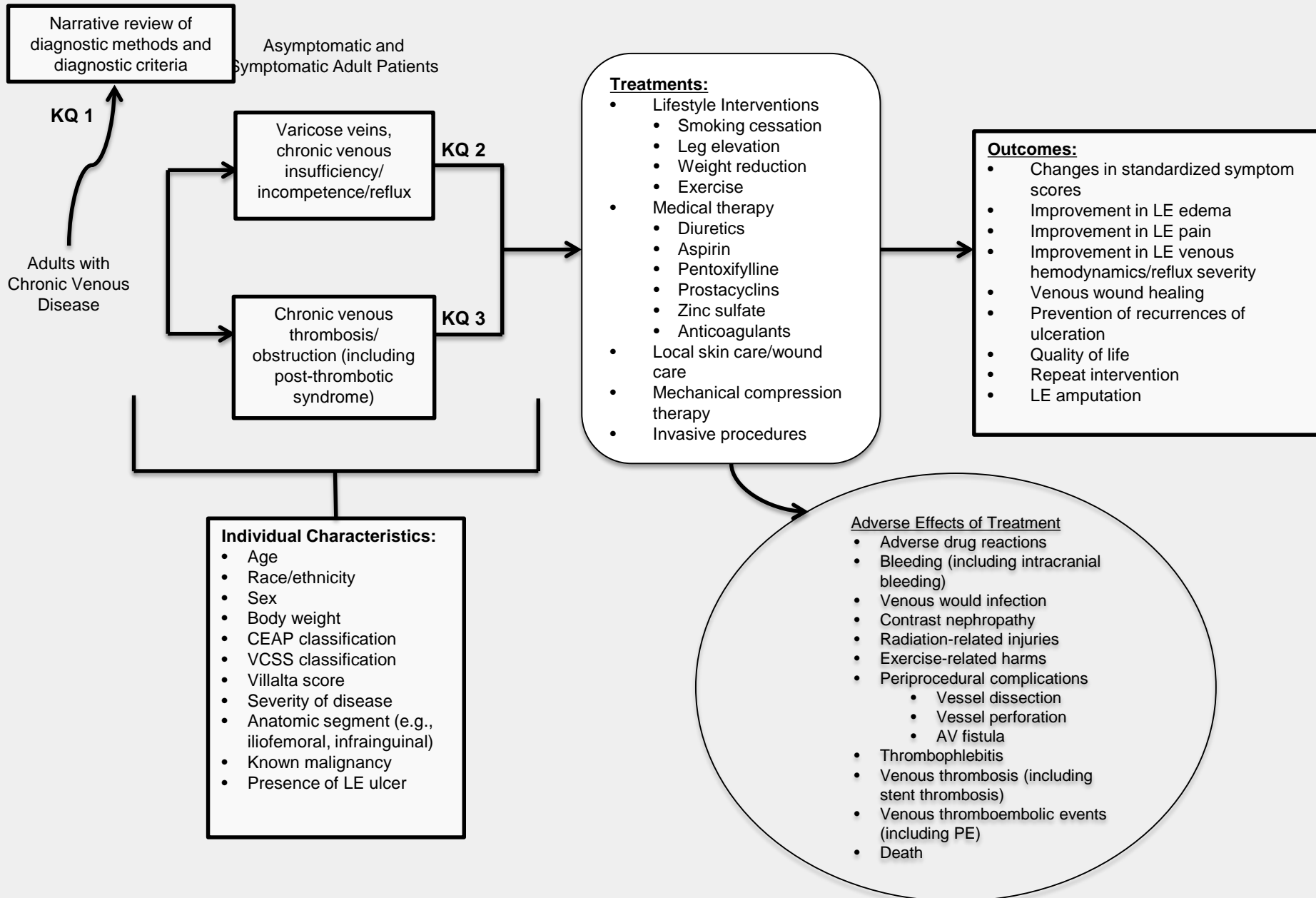
KQ 3: Regarding treatments for all adult patients (symptomatic and asymptomatic) with LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome):

- a) **Comparative effectiveness of treatment modalities** on health outcomes?
- b) **Diagnostic method(s) and criteria** used?
- c) **Modifiers of effectiveness (i.e. patient characteristics)?**
- d) **Comparative safety concerns** of treatment modalities and modifiers of safety concerns

Additional Topics for Consideration

- Are there important venous disease **evidence gaps** that have not been previously or sufficiently addressed?
- Are there any current venous disease **treatment disparities** and how might they affect the health outcomes of Medicare beneficiaries?
- Are there any mechanisms that might be supported by CMS that would more quickly **generate an improved evidence base** that would underpin improved care for the Medicare population affected by lower extremity chronic venous diseases?

Analytical Framework



Studies Addressing the Key Questions

Literature Search: January 2000 – December 2015
10,649 citations identified (454 duplicate articles)
10,201 abstracts reviewed

KQ1: Narrative review of the diagnostic methods and diagnostic criteria

7

KQ2: LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux

88

KQ3: LE chronic venous thrombosis/obstruction (including post-thrombotic syndrome)

8

- 103 overall studies
- Descriptive characteristics of studies of treatment modalities:
 - ▶ Indication for treatment (e.g. varicose veins, CVI)
 - ▶ Diagnostic modalities and criteria used
 - ▶ Clinical outcomes (and timing of outcomes)
 - ▶ Strength of evidence

Strength of the Evidence

High

- Further research is very unlikely to change the confidence in the estimate of effect.

Moderate

- Further research may change the confidence in the estimate of effect and may change the estimate.

Low

- Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

Insufficient

- Evidence either is unavailable or does not permit estimation of an effect.

Overview

- Description of Systematic Review Process
- Evidence Review Findings
 - ▶ KQ1: Diagnostic testing for LECVD
 - ▶ KQ2: Treatment for LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux
 - ▶ KQ3: Treatment for LE chronic venous thrombosis/obstruction
- Limitations and Evidence Gaps
- Summary

Key Question 1

KQ 1: Narrative review of the diagnostic methods and diagnostic criteria for all patients with LECVD

Definition of Terms

Venous obstruction	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	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	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

Diagnosis

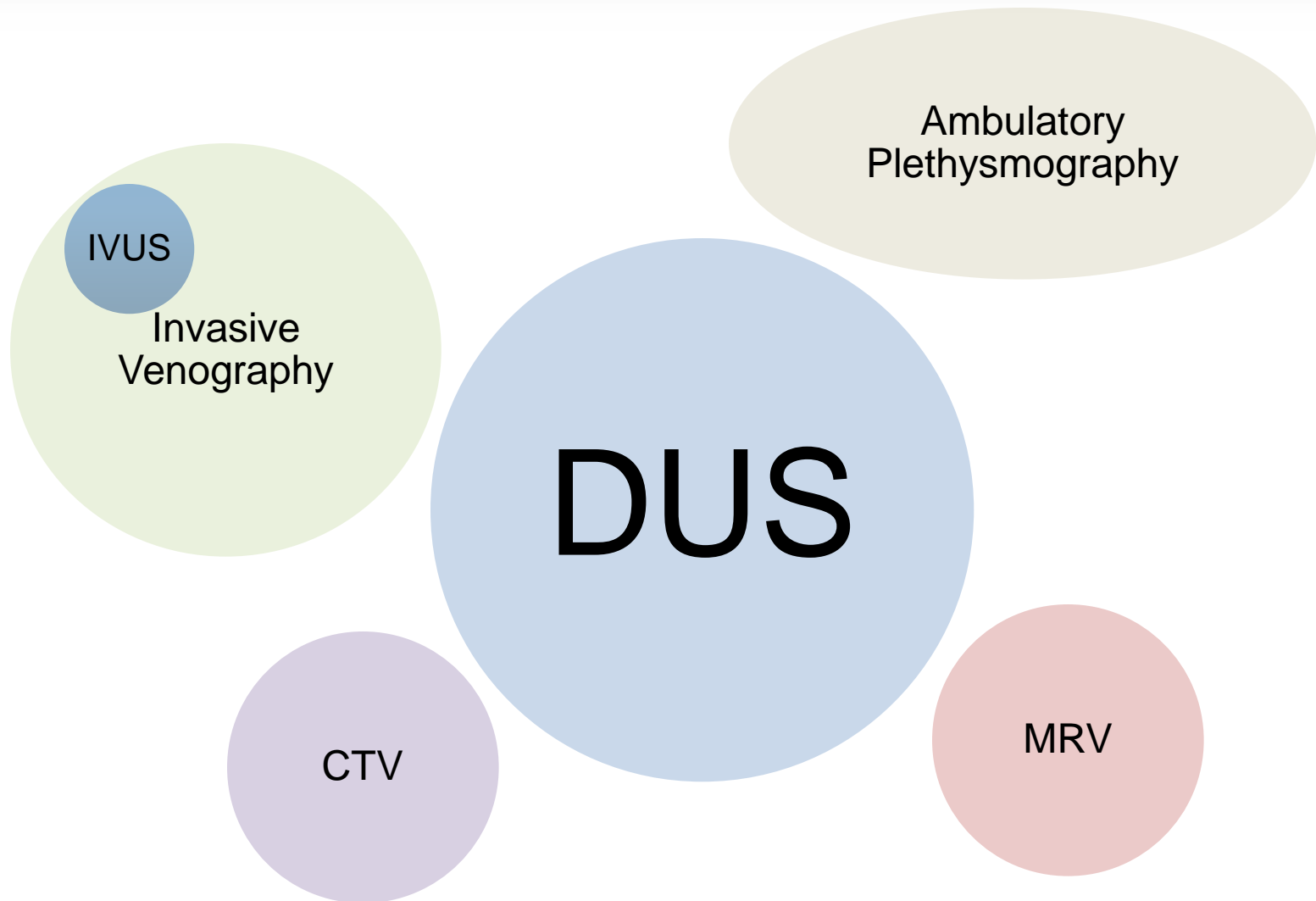
- **Medical History and Physical Examination**
- Ambulatory Plethysmography
- Duplex Ultrasonography (DUS)
- Magnetic Resonance Venography (MRV)
- Computed Tomography Venography (CTV)
- Invasive Venography (or Phlebography)

Diagnosis of LECVD

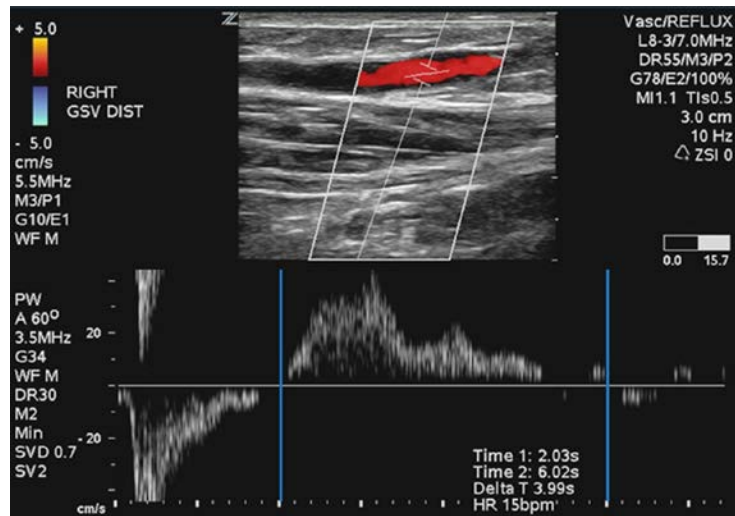
- High index of suspicion
- Thorough medical history (prior LE trauma, surgery, DVT; family history of LECVD)
- Complete physical examination



Diagnostic Testing in Patients with LECVD



Duplex Ultrasonography



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GRADE 1A Recommendations

- A complete history and detailed physical examination should be complemented by duplex scanning of the deep and superficial veins.
- Confirmation of reflux/valvular incompetence in the upright position of the patients be elicited in one of two ways: either with increased intra-abdominal pressure using a Valsalva maneuver to assess the common femoral vein and the saphenofemoral junction, or for the more distal veins, use of manual or cuff compression and release of the limb distal to the point of examination.

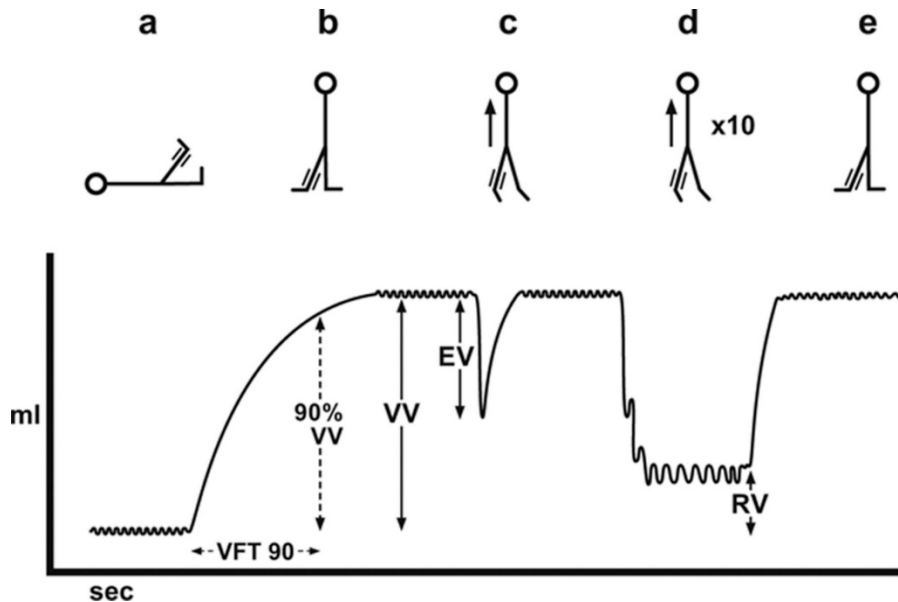
GRADE 1B Recommendations

- A cutoff value of 1 second for abnormally reversed flow (reflux) in the femoral and popliteal veins and of 500 ms for the great saphenous vein, the small saphenous vein, the tibial, deep femoral, and the perforating veins.
- The definition of “pathologic” perforating veins includes those with an outward flow of duration of 500 ms, with a diameter of 3.5 mm and a location beneath healed or open venous ulcers (CEAP class C5-C6).

Ambulatory Plethysmography

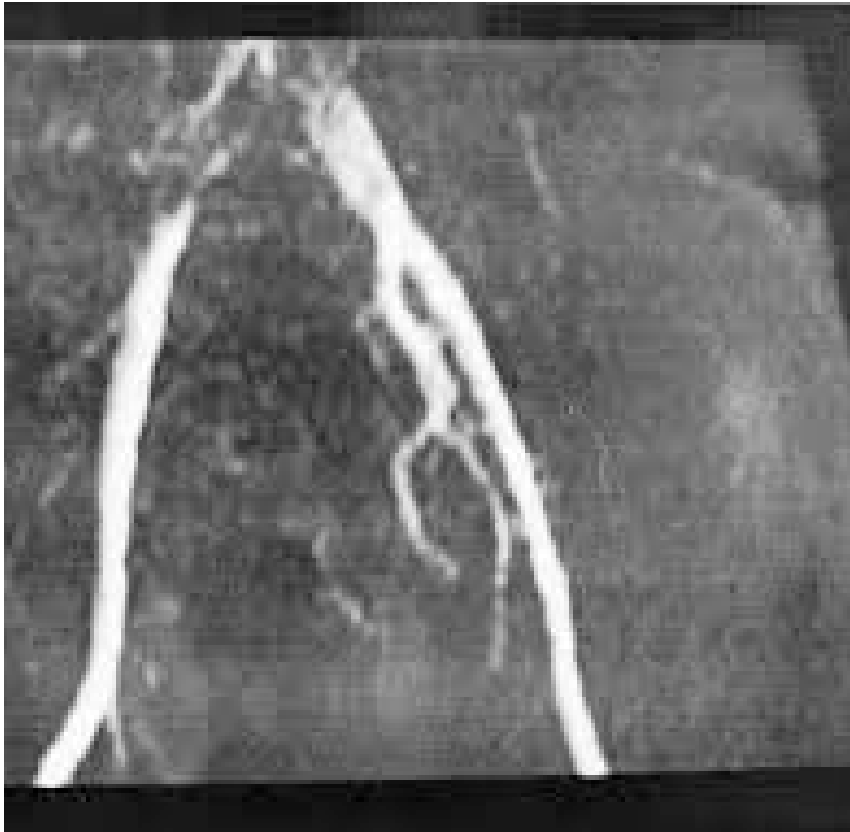
GRADE 1B recommendation

Ambulatory plethysmography should be used for the noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C3-C6).



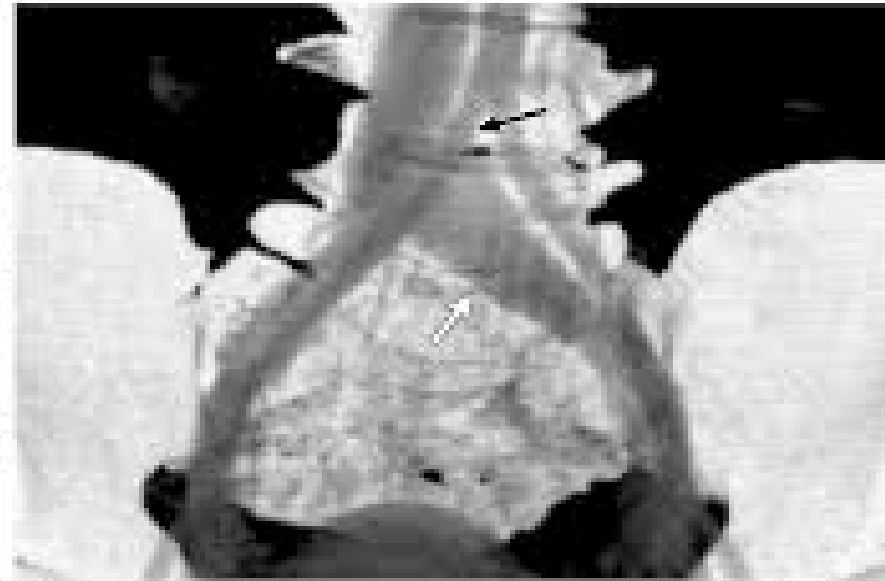
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Magnetic Resonance Venography (MRV)



GRADE 1B recommendation

We recommend that in patients with varicose veins and more advanced chronic venous disease, computed tomography venography, **magnetic resonance venography**, ascending and descending contrast venography, and intravascular ultrasonography are used selectively, including but not limited to post-thrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.

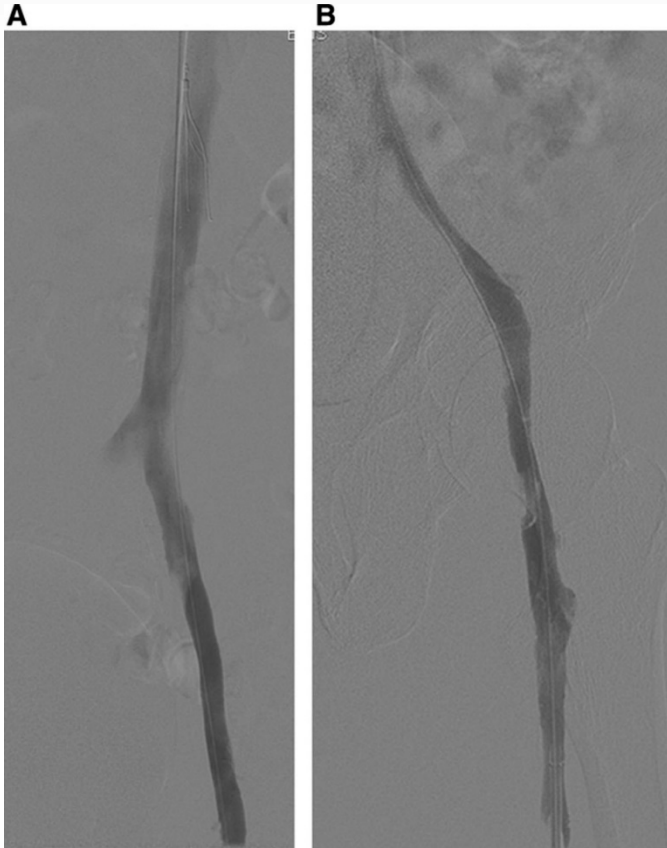


Reproduced from: Radiology 2004; 233:361–365

GRADE 1B recommendation

We recommend that in patients with varicose veins and more advanced chronic venous disease, **computed tomography venography**, magnetic resonance venography, ascending and descending contrast venography, and intravascular ultrasonography are used selectively, including but not limited to post-thrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.

Invasive Venography

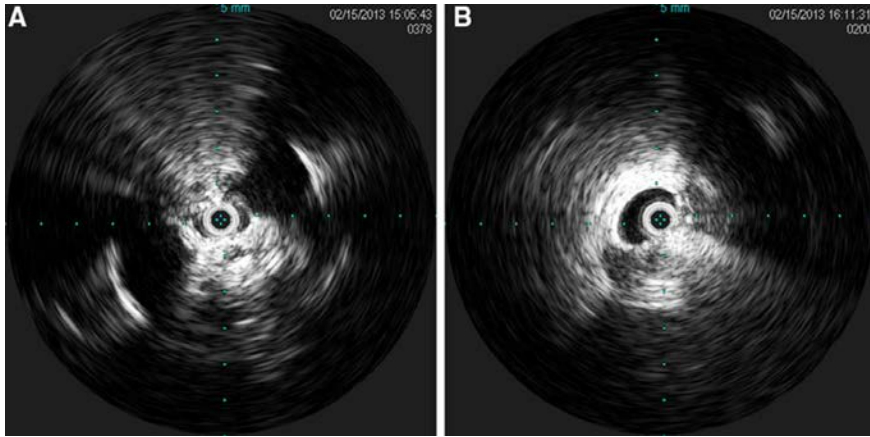


GRADE 1B recommendation

We recommend that in patients with varicose veins and more advanced chronic venous disease, computed tomography venography, magnetic resonance venography, **ascending and descending contrast venography**, and intravascular ultrasonography are used selectively, including but not limited to post-thrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.

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Adjuncts to Invasive Imaging



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GRADE 1B recommendation

We recommend that in patients with varicose veins and more advanced chronic venous disease, computed tomography venography, magnetic resonance venography, ascending and descending contrast venography, and **intravascular ultrasonography** are used selectively, including but not limited to post-thrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.

KQ1 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.

KQ1 Results

Author	Year	Diagnostic Test #1	Diagnostic Test #2	Gold Standard	N enrolled/ included	Conditions in patient population	Findings
Mantoni M, et al	2002	1. Ascending phlebography (AP) 2. Descending phlebography 3. Continuous wave doppler (CWD) 4. Ambulatory strain gauge plethysmography (ASGP)	Triplex ultrasound (TUS)	Triplex ultrasound (TUS)	39	LE chronic venous insufficiency/ reflux/ incompetency (KQ2)	For common and superficial venous system: Sensitivity=86%(AP), 70%(CWD), 4%(ASGP); Specificity=0%(AP), 38%(CWD), 100%(ASGP). For popliteal vein: Sensitivity=83%(AP), 48%(CWD), 5%(ASGP); Specificity=17%(AP), 75%(CWD), 100%(ASGP)

KQ1 Results (cont'd)

Author	Year	Diagnostic Test #1	Diagnostic Test #2	Gold Standard	N enrolled/ included	Conditions in patient population	Findings
Lee W, et al	2008	3-D CT Venography	Doppler Sonography	Doppler Sonography	100	LE varicose veins (KQ2)	GSV: Sensitivity=98.2%, Specificity=83.3%; SSV: Sensitivity=53.3%, Specificity=94.9%
Massenburg, 2015 et al		Magnetic resonance venography	Invasive venography + IVUS	Invasive venography + IVUS	46	LE venous thrombosis/ obstruction (KQ3)	Sensitivity=100%, Specificity=22.7%, PPV=58.5%, NPV=100%, False Positive rate=41.5%

KQ1 Results (cont'd)

Author	Year	Diagnostic Test #1	Diagnostic Test #2	Gold Standard	N enrolled/ included	Conditions in patient population	Findings
Antoch G, et al	2002	1. Color doppler ultrasonography, 2. Ascending phlebography	Surgical evaluation	Surgical evaluation	50	LE chronic venous insufficiency/ reflux/ incompetency (KQ2)	For color doppler ultrasound: Sensitivity=80%, Specificity=74% Ascending phlebography: Sensitivity=66% Clinical examination: Sensitivity=79%
Depalma RG, et al	2000	Color doppler ultrasound	Ascending and descending phlebography	Ascending and descending phlebography	33	LE chronic venous insufficiency/ reflux/ incompetency (KQ2)	For reflux detection, sensitivity=82%, specificity=75%, PPV=96%, NPV=37%; For saphenous reflux, sensitivity=95%, specificity=100%
Meyer T, et al	2000	1. Duplex ultrasound, 2. Ascending phlebography	Surgical evaluation	Surgical evaluation	87	LE chronic venous insufficiency/ reflux/ incompetency (KQ2)	Cockett I (p=1.0), Cockett II (p= 0.569), Cockett III (p=1.0)
Rabahie GN, et al	2011	Color doppler ultrasound	Surgical evaluation	Surgical evaluation	30	LE chronic venous insufficiency/ reflux/ incompetency (KQ2)	GSV: Sensitivity=70.3%, False-negative rate=29.7%

- Inconclusive evidence: diagnostic test of choice, best test prior to planned invasive treatment

Strength of Evidence: Insufficient

- 0 studies: Modifiers of effectiveness

Strength of Evidence: Insufficient

Clinical Practice Guidelines: Diagnostic Testing in Patients with LECVD

The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum

Peter Gloviczki, MD,^a Anthony J. Comerota, MD,^b Michael C. Dalsing, MD,^c Bo G. Eklof, MD,^d David L. Gillespie, MD,^e Monika L. Gloviczki, MD, PhD,^f Joann M. Lohr, MD,^g Robert B. McLafferty, MD,^h Mark H. Meissner, MD,ⁱ M. Hassan Murad, MD, MPH,^j Frank T. Padberg, MD,^k Peter J. Pappas, MD,^k Marc A. Passman, MD,^l Joseph D. Raffetto, MD,^m Michael A. Vasquez, MD, RVT,ⁿ and Thomas W. Wakefield, MD,^o Rochester, Minn; Toledo, Ohio; Indianapolis, Ind; Helsingborg, Sweden; Rochester, NY;

<i>Guideline No.</i>	<i>Guideline title</i>	<i>GRADE of recommendation</i>	<i>Level of evidence</i>
		1. Strong 2. Weak	A. High quality B Moderate quality C. Low or very low quality
2.1	2. Duplex scanning We recommend that in patients with chronic venous disease, a complete history and detailed physical examination are complemented by duplex scanning of the deep and superficial veins. The test is safe, noninvasive, cost-effective, and reliable.	1	A
2.2	We recommend that the four components of a complete duplex scanning examination for chronic venous disease should be visualization, compressibility, venous flow, including measurement of duration of reflux, and augmentation.	1	A

Diagnostic Testing and Criteria in KQ2 and KQ3

- KQ2 (88 total studies)
 - ▶ Clinical Assessment: **12 studies**
 - ▶ Duplex Ultrasound: **40 studies**
 - ▶ Clinical Assessment/Ultrasound: **28 studies**
 - ▶ Unclear/NR: **8 studies**
- KQ3 (8 total studies)
 - ▶ Clinical Assessment: **3 studies**
 - ▶ Duplex Ultrasound + Venography: **2 studies**
 - ▶ Venography Only: **1 study**
 - ▶ Other Modalities (MRV, CTV): **2 studies**

Key Question 2

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

- a) **Comparative effectiveness of treatment modalities** on health outcomes?
- b) **Diagnostic method(s) and criteria** used?
- c) **Modifiers of effectiveness (i.e. patient characteristics)?**
- d) **Comparative safety concerns** of treatment modalities and modifiers of safety concerns

Treatment Options



- Exercise Training
- Medical Therapy (e.g. diuretics, compression)
- Lifestyle Modification (e.g. weight reduction)
- Invasive Therapy
 - Endovenous intervention
 - Surgical intervention

Populations Assessed

Symptom Status	Included Studies
Symptomatic	73 studies (70 RCTs, 3 observational)
Asymptomatic/Symptomatic	4 studies (4 RCTs, 0 observational)
Unclear	15 studies (14 RCTs, 1 observational)

Condition	Included Studies
LE varicose veins	66 studies (64 RCTs, 2 observational)
LE chronic venous insufficiency/reflux/incompetency	74 studies (71 RCTs, 3 observational)
Unclear/NR	2 studies (1 RCT, 1 observational)

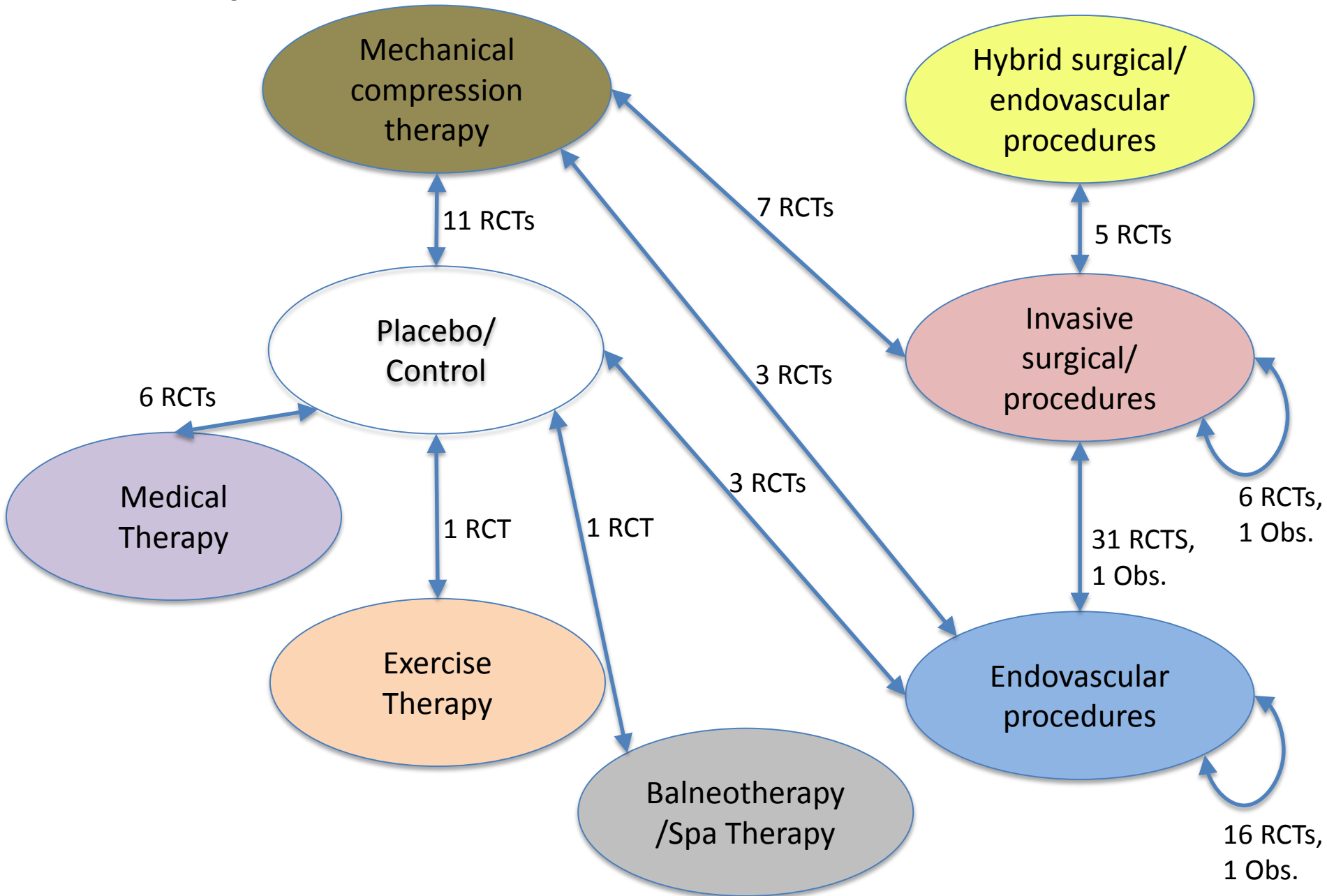
Outcomes Assessed

- Changes in standardized symptom scores
- Improvement in LE venous hemodynamics/reflux severity
- Improvement in LE edema
- Improvement in LE pain
- Venous wound healing
- Prevention of recurrences of ulceration
- Quality of life
- Repeat intervention
- LE amputation
- Periprocedural complications (hematoma, etc...)

Study Quality

Quality	Included Studies
Good	24 studies (24 RCTs, 0 observational)
Fair	47 studies (45 RCTs, 2 observational)
Poor	17 studies (14 RCTs, 2 observational)

KQ2 Comparisons



Interventions vs Placebo or Usual Care

Compression vs. Placebo

Comparison	Population	Studies	Patients
Compression vs. placebo or no compression	Symptomatic ulcers or varicose veins	11 (5)	1522

(N) = # good quality studies
All performed outside of the US

Although these studies explored a variety of different compression therapy strategies and outcomes, compression therapy does appear to be effective relative to no compression therapy (or placebo) for a variety of the clinical outcomes

Strength of Evidence = Insufficient

Comparison	Population	Studies	Patients
Endovenous intervention vs. Conservative therapy	Symptomatic = 2 Unknown = 1	3 (2)	544

(N) = # good quality studies

Significant effect on VCSS, elimination of reflux, and QOL favoring foam sclerotherapy over placebo

Strength of Evidence = Moderate

Comparison	Population	Studies	Patients
Endovenous intervention vs. Conservative therapy	Symptomatic varicosities / reflux / ulcers	3 (0)	150

(N) = # good quality studies

For venous ulcer patients, EVLA was associated with significant improvement in ulcer healing and reduction in recurrence of ulceration compared to compression stockings

Strength of Evidence = Insufficient

Surgical Interventions vs. Medical

Comparison	Population	Studies	Patients
Surgical intervention vs. Medical therapy	Symptomatic ulcers and varicosities	7 (2)	1244

(N) = # good quality studies

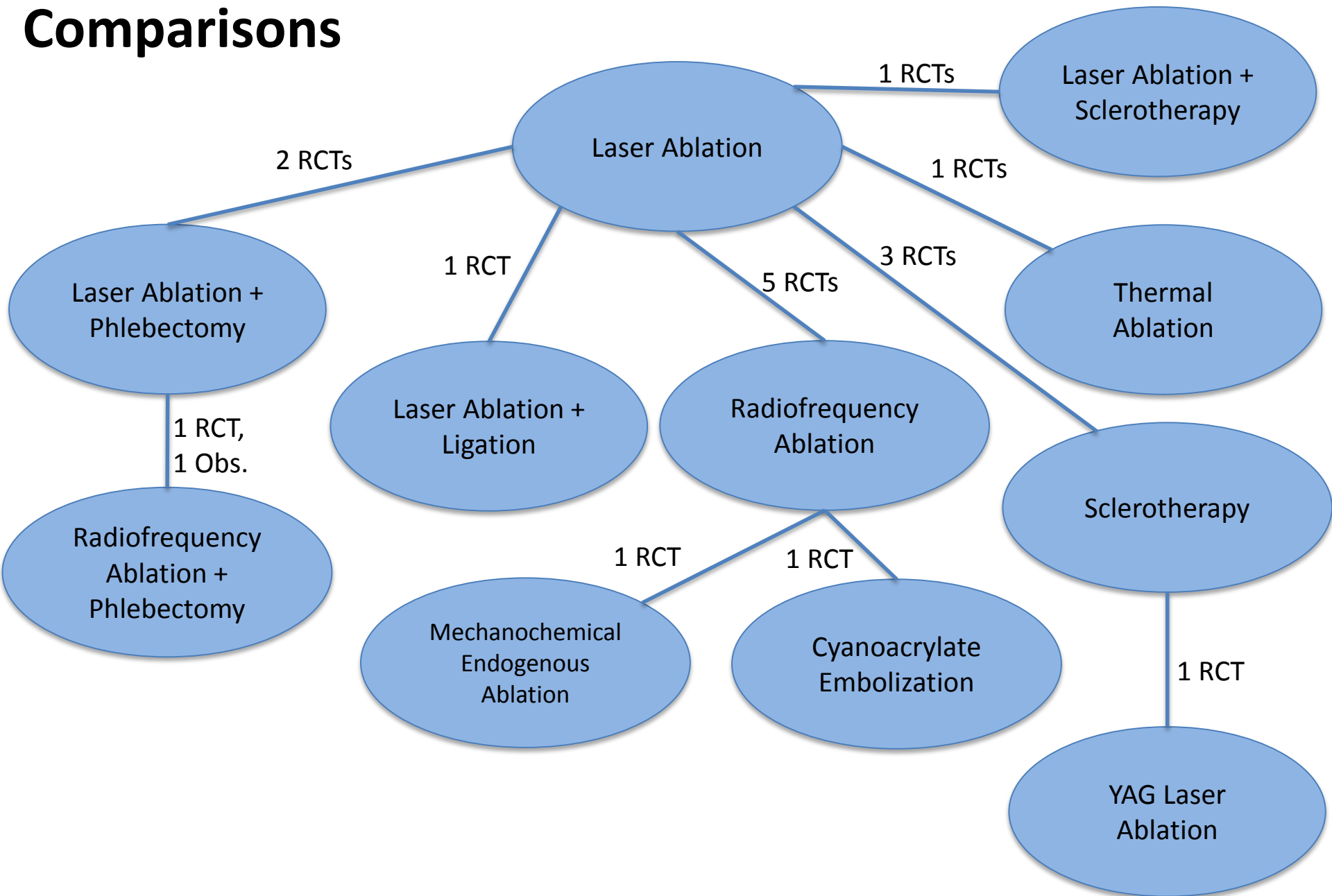
- No difference in ulceration healing rate (SOE = Insufficient)
- Significant difference in recurrence of ulceration, favoring surgery (SOE = Low)
- No significant differences in QOL or venous hemodynamics (SOE = Insufficient)
- Significant improvement in pain scores, favoring high surgery at 2 years (SOE = Insufficient)
- High rates of surgical wound infection (SOE = Insufficient)

Summary: Interventions vs. Placebo / Medical Therapy

- **Endovenous vs. medical / placebo:**
 - Significant effect on VCSS, elimination of reflux, and QOL favoring foam sclerotherapy over placebo (SOE = Moderate)
 - For venous ulcer patients, EVLA was associated with significant improvement in ulcer healing and reduction in recurrence of ulceration (SOE = Insufficient)
- **Surgery vs. Medical Therapy:**
 - No difference in ulceration healing rate, QOL, or venous hemodynamics (SOE = Insufficient)
 - Improved pain scores and reduced ulcer recurrence (SOE = Low)
- **Compression vs. no compression / placebo**
 - Appears effective compared to no compression / placebo for a variety of these clinical outcomes (SOE = Insufficient)

Within Intervention Comparisons

Endovascular vs. Endovascular Comparisons



EVLA vs Sclerotherapy

Comparison	Population	Studies	Patients
EVLA vs. Sclerotherapy	Symptomatic reflux / varicosities	3 (2)	1,408

(N) = # of good quality studies

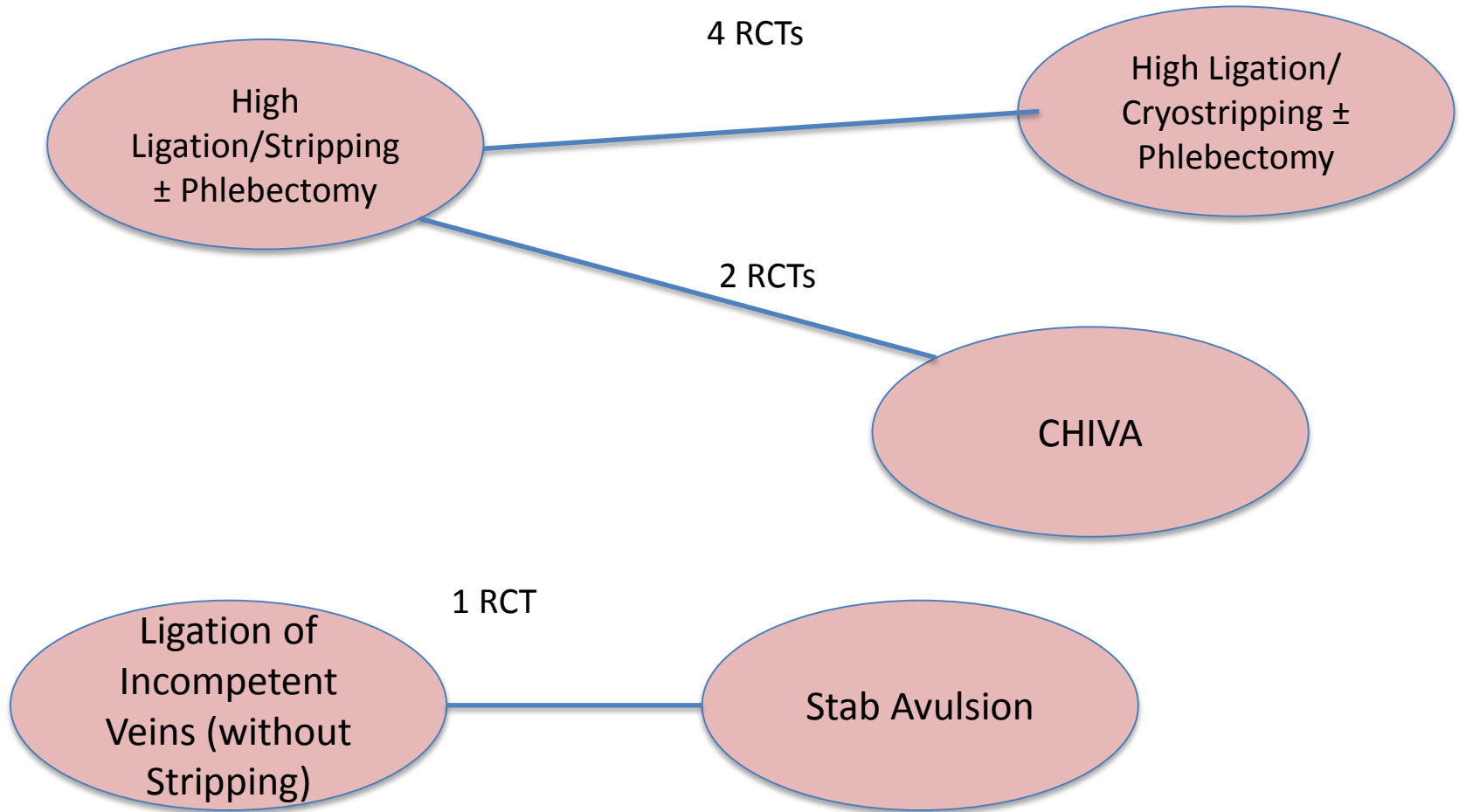
- No significant difference in efficacy between EVLA and RFA (long term QOL, standard symptom scores) (SOE = Low)
- Intermediate improvement in QOL favored EVLA (SOE = Low)
- Post procedure lower extremity pain favored sclerotherapy (2 studies) (SOE = Low)

Comparison	Population	Studies	Patients
EVLA vs. RFA	Symptomatic reflux / varicosities	5 (2)	543

(N) = # of good quality studies

- No significant difference in efficacy between EVLA and RFA (QOL (SOE=Low), venous hemodynamics (SOE=Insufficient), intermediate term symptom scores (SOE = Low))
- Long term improvement in symptom score favoring EVLA (SOE = Low)
- Short term improvement in pain favoring RFA (2 good quality studies) (SOE = Low)
- Short term bruising / hematoma favored RFA (2 good quality studies) (SOE = Low)

Surgical versus Surgical Comparisons



Surgical vs. Surgical Interventions

Comparison	Population	Studies	Patients
High Ligation/Stripping ± Phlebectomy vs. High Ligation/Cryostripping ± Phlebectomy	Symptomatic (4) Unknown (1)	4 (1)	762
High Ligation/Stripping ± Phlebectomy vs. CHIVA	Symptomatic	2 (1)	11,527
Ligation of Incompetent Veins (without Stripping) vs. Stab Avulsion	Symptomatic	1 (0)	887*

(N) = # good quality studies; *multi-arm study, numbers for ligation and avulsion not reported

- **HL/S vs. HL/cryostripping:**
 - No difference in post-op pain, QOL, GSV recanalization. (SOE = Insufficient)
 - Heterogenous data re: periop complications (SOE = Insufficient)
- **HL/S vs. CHIVA:**
 - CHIVA with higher varicosity recurrence (1 study) (SOE = Insufficient)
 - No difference in perioperative complications (1 study) (SOE = Insufficient)
- **ligation vs. stab avulsion:** Insufficient data to evaluate (SOE = Insufficient)

Summary: Within Interventions Comparison

- **Endovenous vs. Endovenous**

- ▶ EVLA vs. Sclerotherapy: No significant difference in efficacy between EVLA and RFA (long term QOL, standard symptom scores) (SOE = Low)
- ▶ No significant difference in efficacy between EVLA and RFA (QOL, venous hemodynamics, intermediate term symptom scores) (SOE = Low)

- **Surgical vs. Surgical:**

- ▶ Few studies overall
- ▶ Few good quality studies
- ▶ No demonstrated difference in post-op pain, QOL, GSV recanalization (HL/S vs. HL/cryostripping). (SOE = Insufficient)

Comparisons of Hybrid Techniques



Comparisons Involving Hybrid Techniques

Comparison	Population	Studies	Patients
High Ligation/Stripping ± Phlebectomy vs. High Ligation/EVLA	symptomatic	1 (0)	449*
High Ligation/Stripping ± Phlebectomy vs. High Ligation/Foam Sclerotherapy	symptomatic	1 (0)	82*
Ligation of Incompetent Veins (without Stripping) vs. Ligation/Sclerotherapy	symptomatic	2(0)	1037**
High Ligation/Stripping ± Phlebectomy vs. High Ligation/Endovenous Microwave Therapy	symptomatic	1(0)	200

(N) = # of good quality studies); *3 armed study; +6 arm study

HL/S vs. HL/EVLA: (SOE = Insufficient)

- Inguinal recurrence favored HL/S (1 study)
- No difference in persistent pain (1 study)
- No difference in symptom score at 2 months (1 study)

HL/S vs. HL/sclerotherapy: less perioperative bleeding with sclerotherapy (1 study)

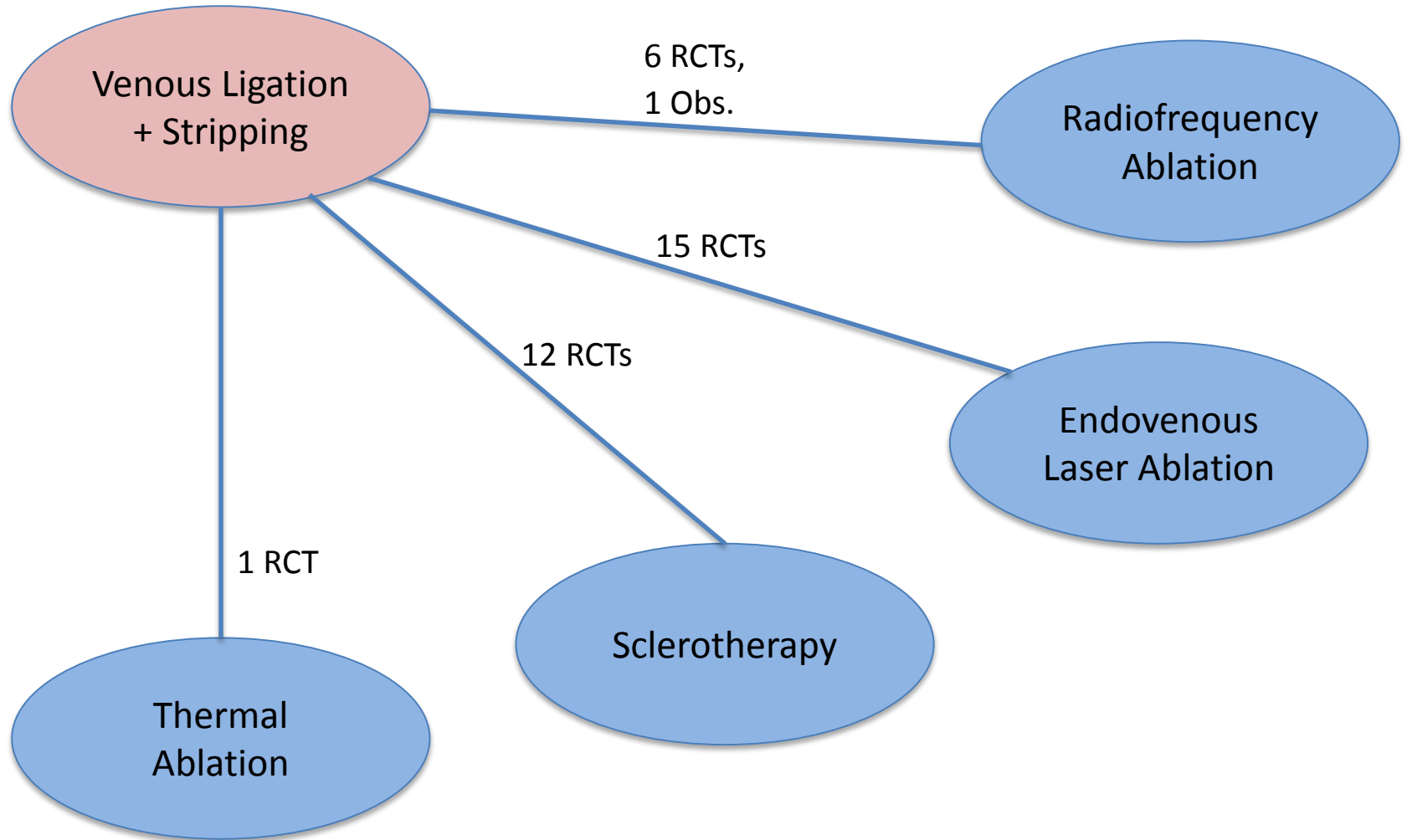
Ligation vs. Ligation/sclerotherapy: insufficient data on between group comparisons

HL/S vs. HL/EMT:

- lower recurrence in HL/EMT
- No difference in long term QOL or long term symptom scores

Surgical vs Endovenous Interventions

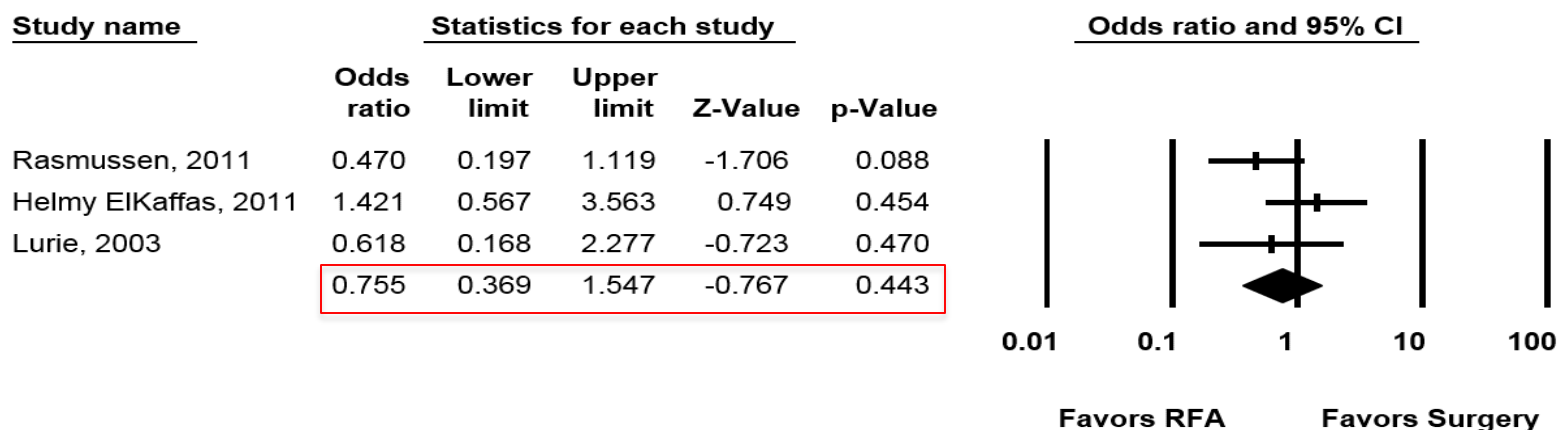
Surgical versus Endovascular Comparisons



RFA vs. High Ligation / Stripping

- Outcomes sufficient for metaanalysis:
 - Changes in standardized symptom scores
 - Improvement in LE venous hemodynamics/reflux severity
 - Improvement in LE edema
 - Improvement in LE pain
 - Venous wound healing
 - **Reflux recurrence rate**
 - Quality of life
 - Repeat intervention
 - LE amputation
 - **Periprocedural complications (ecchymosis)**

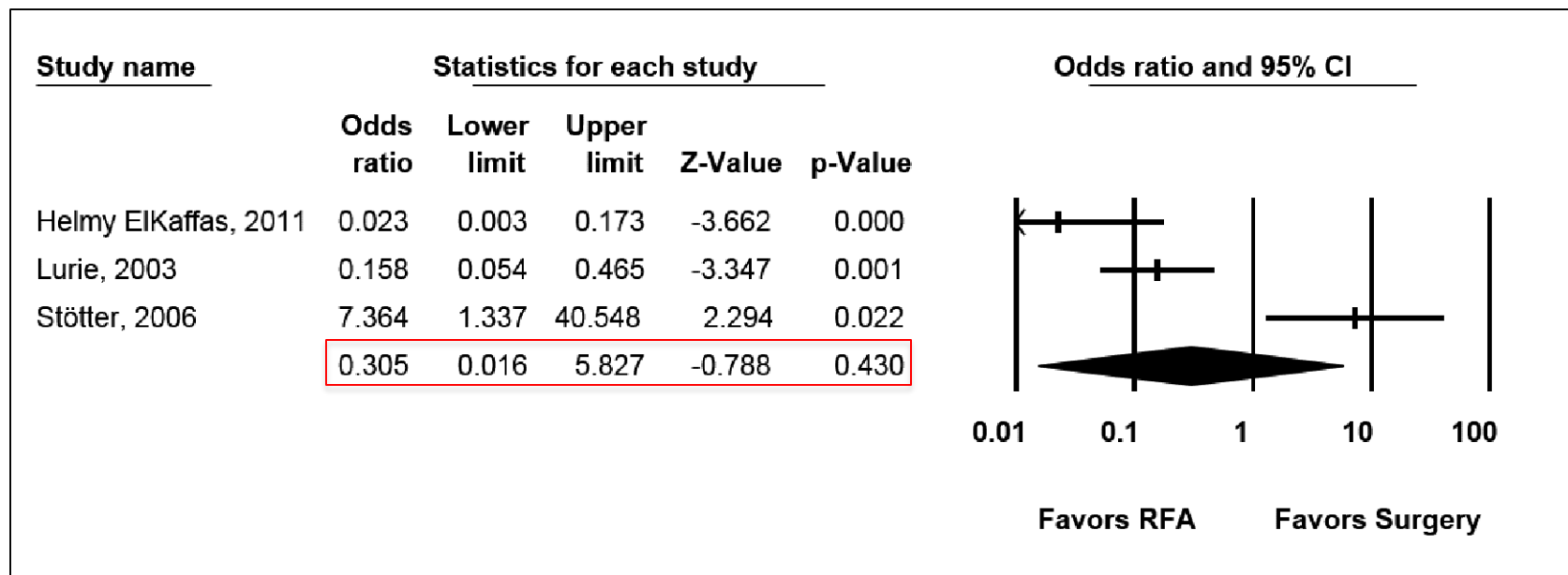
RFA vs High Ligation Plus Stripping Reflux Recurrence Rates at 1-2 years



Studies demonstrated a trend towards a reduction in recurrence rates for patients in the RFA arm but this finding was imprecise and did not reach statistical significance; OR = 0.755 (95% CI = 0.369 to 1.547)

Strength of Evidence: Insufficient

RFA vs High Ligation Plus Stripping Adverse Events



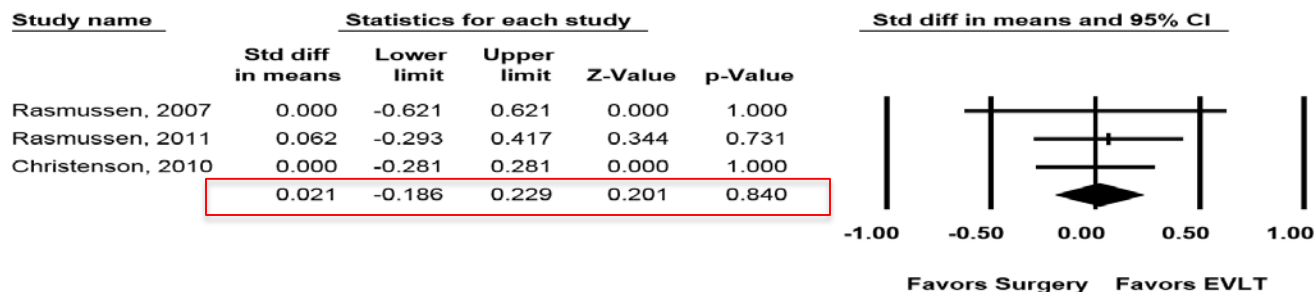
Studies demonstrated a trend towards a reduction in hematoma/ecchymosis rates for patients in the RFA arm but this finding was imprecise and did not reach statistical significance; OR = 0.305 (95% CI = 0.016 to 5.827)

Strength of Evidence: Insufficient

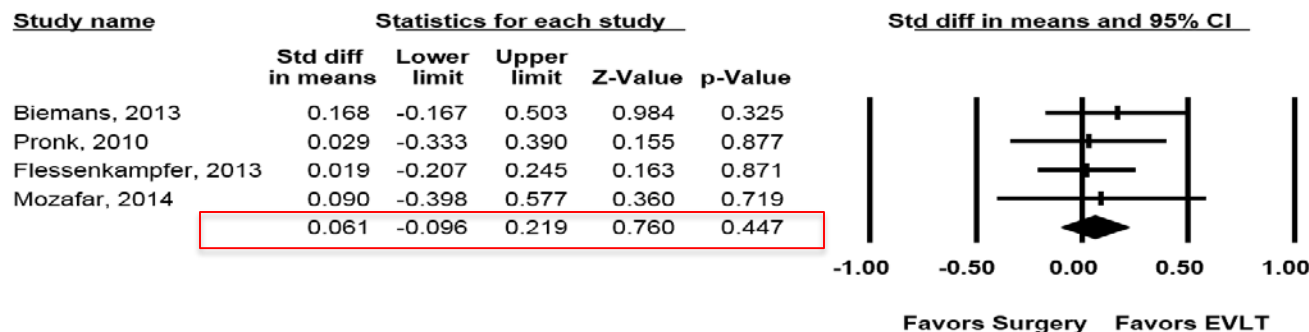
EVLA vs. High Ligation Plus Stripping

- Outcomes sufficient for metaanalysis:
 - Changes in standardized symptom scores (CEAP / VCSS)
 - Improvement in LE venous hemodynamics/reflux severity
 - Improvement in LE edema
 - Improvement in LE pain
 - Venous wound healing
 - Reflux Recurrence Rate
 - Quality of life
 - Repeat intervention
 - LE amputation
 - Periprocedural complications (ecchymosis / hematoma)

EVLA versus High Ligation Plus Stripping Symptom Scores



Long-Term
VCSS

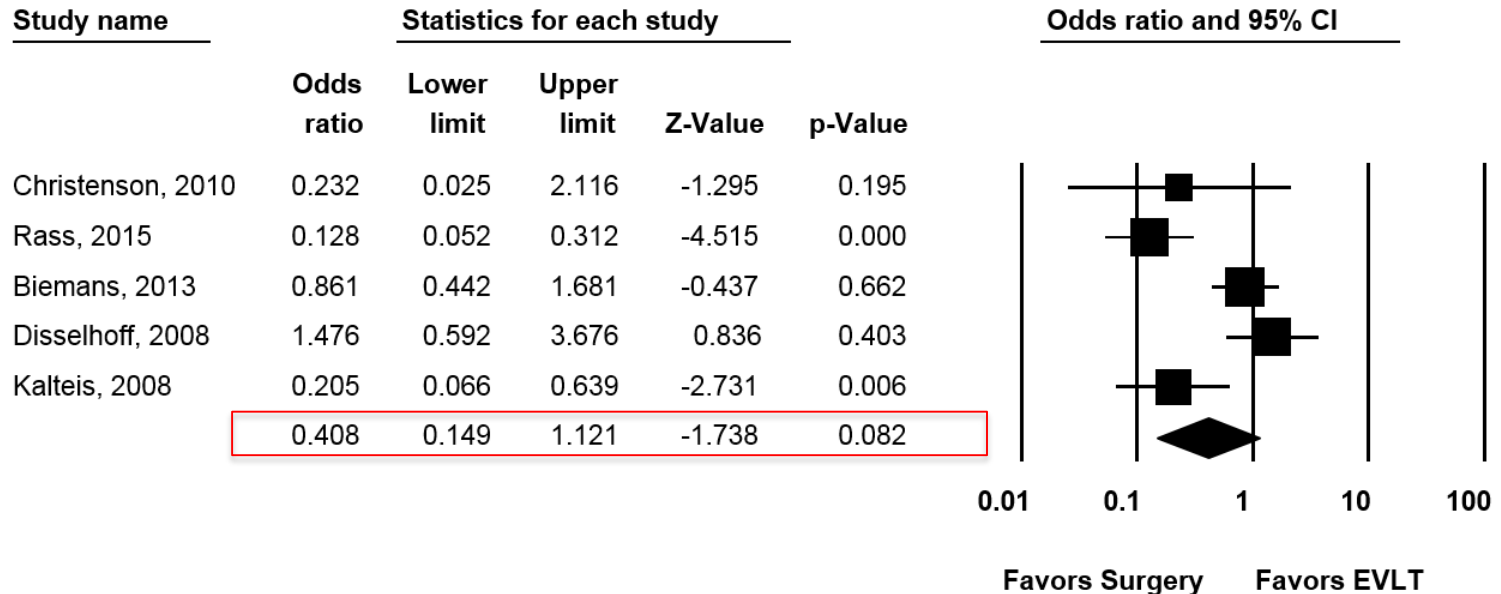


Long-Term
CEAP

- There was no significant difference between treatment strategies on VCSS after EVLA vs high ligation plus stripping. **Strength of Evidence: Low**
- There was no significant difference between treatment strategies on CEAP score after EVLA vs high ligation plus stripping. **Strength of Evidence: Moderate**

EVLA versus High Ligation Plus Stripping

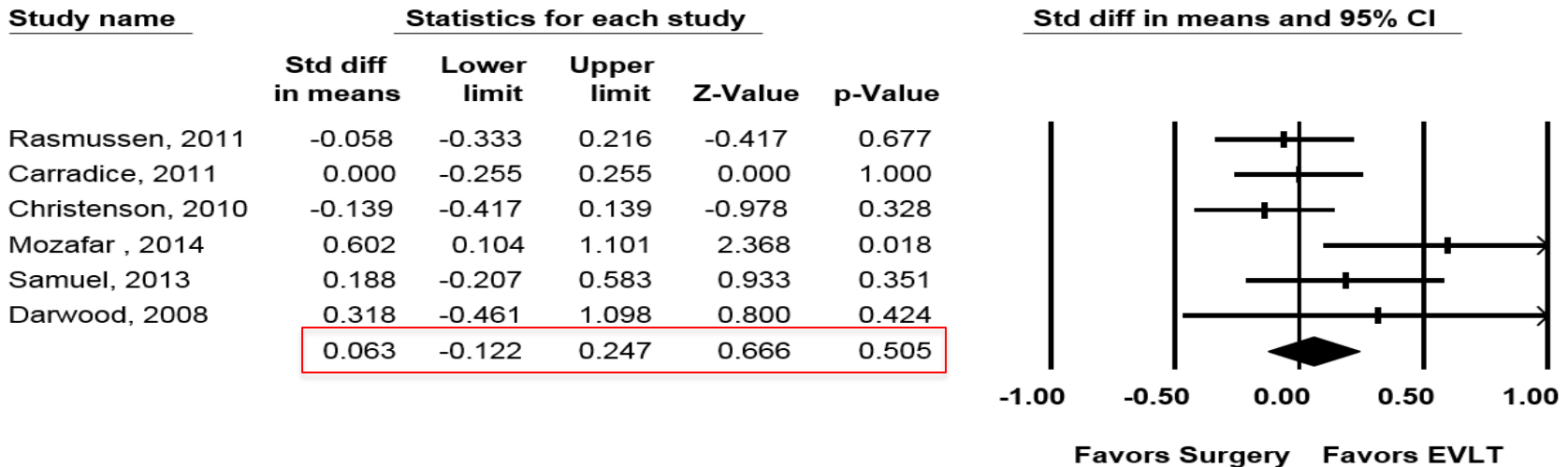
Changes in Reflux / Incompetence at 2 Years



The analysis demonstrated a non-statistically significant trend towards improvement in reflux / venous incompetence for surgery compared to EVLA (OR = 0.408, 95% CI 0.149 to 1.121)

Strength of Evidence: Low

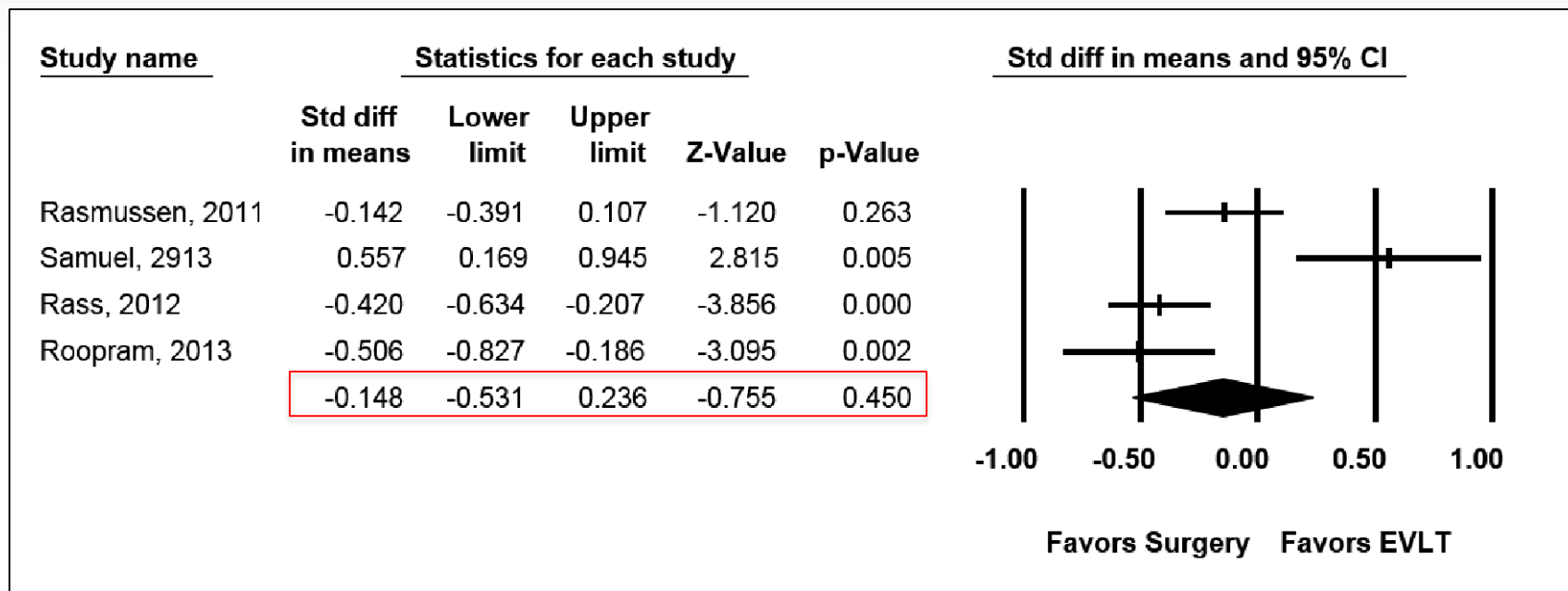
EVLA versus High Ligation Plus Stripping Changes in Quality of Life (AVVQ) at 2 Years



The analysis demonstrated no statistically significant difference in quality of life (AVVQ) for surgery compared to EVLA (OR = 0.063, 95% CI -0.122 to 0.247)

Strength of Evidence: Moderate

EVLA versus High Ligation Plus Stripping Adverse Events: Reduction in Pain Score

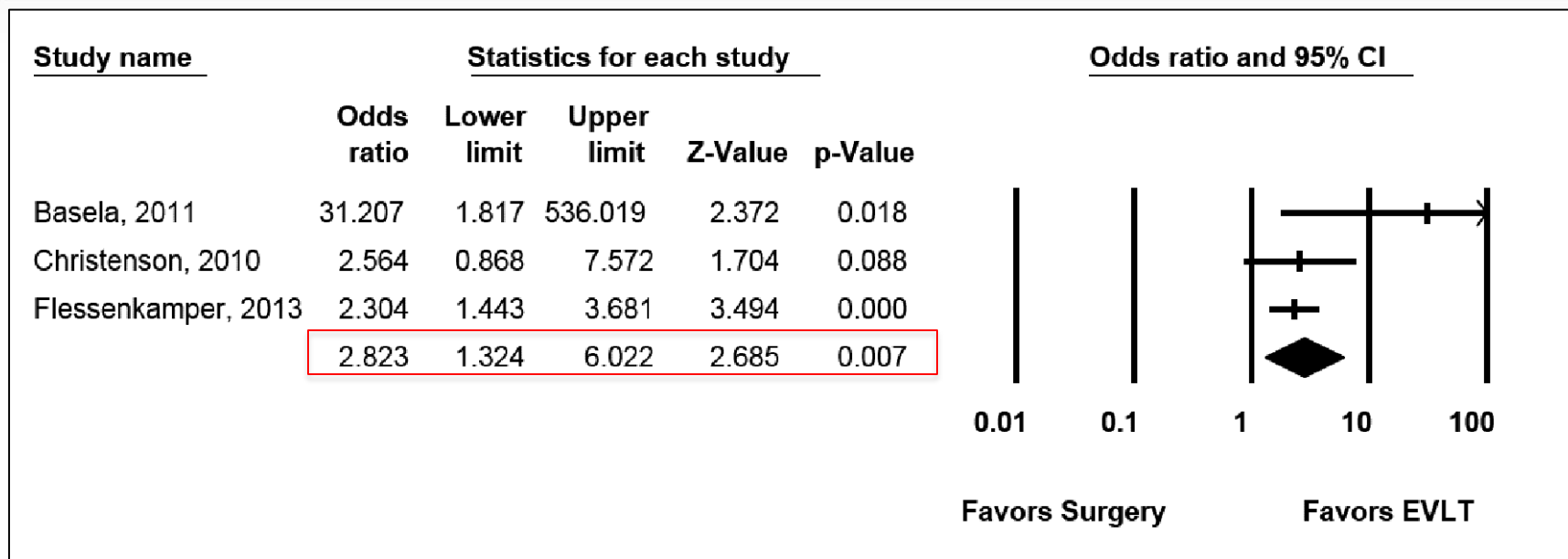


These studies demonstrated a -0.148 standard difference in means (95% CI -0.531 to 0.236) showing no difference between treatment strategies.

Strength of Evidence: Low

EVLA versus High Ligation Plus Stripping

Adverse Events: Ecchymosis/Bruising



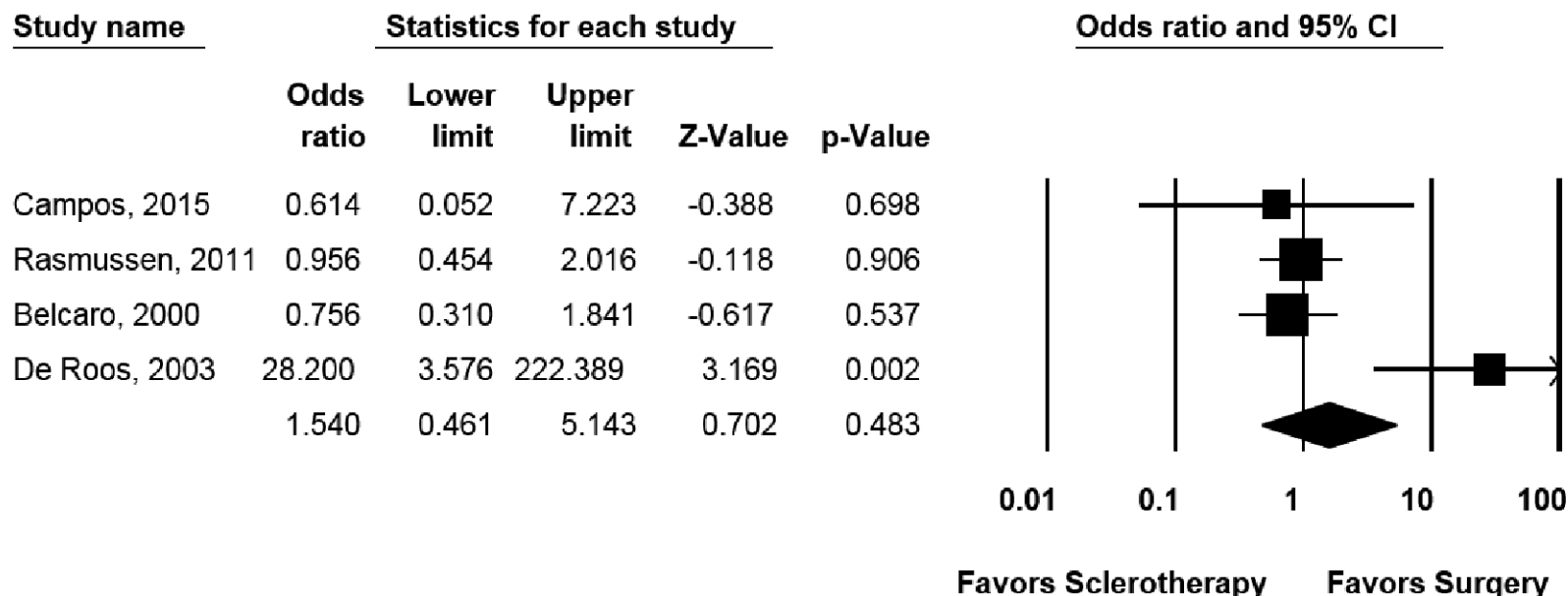
This analysis demonstrated a statistically significant benefit of EVLA compared with surgery regarding reduction in bleeding risk (OR = 2.823, 95% CI = 1.324 to 6.022)

Strength of Evidence: Moderate

Sclerotherapy vs High Ligation Plus Stripping

- Outcomes sufficient for metaanalysis:
 - Changes in standardized symptom scores (CEAP / VCSS)
 - Improvement in LE venous hemodynamics/reflux severity
 - Improvement in LE edema
 - Improvement in LE pain
 - Venous wound healing
 - **Recurrence Rate**
 - **Quality of life**
 - Repeat intervention
 - LE amputation
 - **Periprocedural complications (ecchymosis / hematoma)**

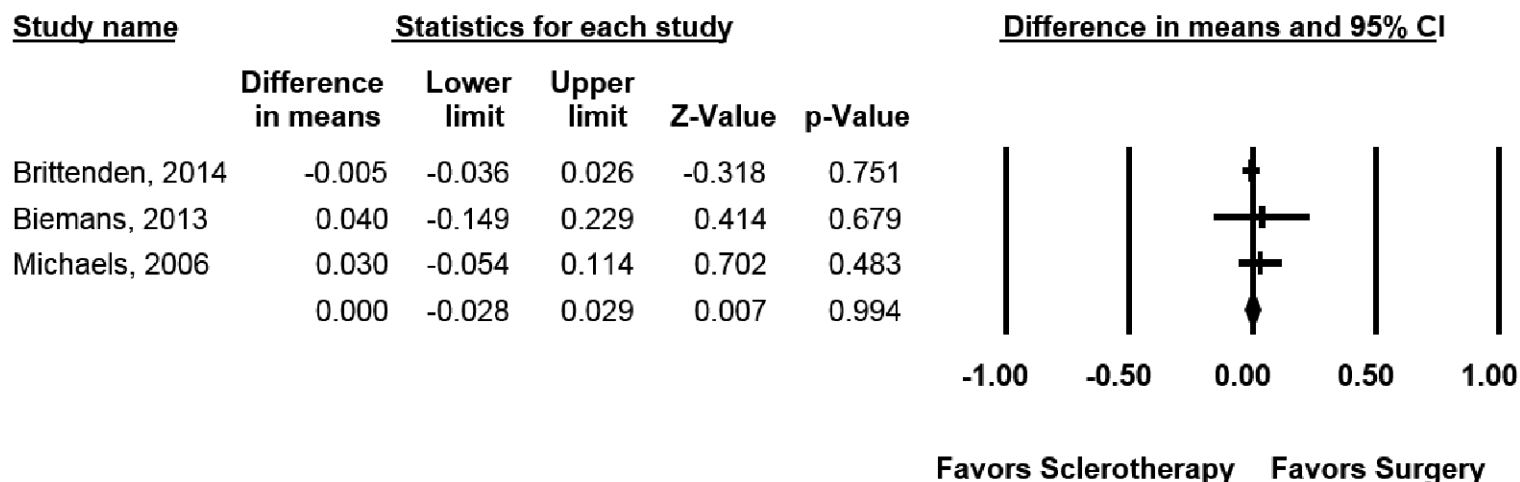
Sclerotherapy versus High Ligation Plus Stripping Long Term Recurrence Rates ≥ 1 Year



- No statistically significant difference in recurrence rates for sclerotherapy compared to surgery (OR = 1.54, 95% CI 0.461 to 5.143)
- **Strength of Evidence: Low**

Sclerotherapy versus High Ligation Plus Stripping

Quality of Life at 2 Years



The analysis demonstrated no statistically significant difference in quality of life for sclerotherapy compared to surgery (difference in means = 0.0 , 95% CI - 0.028 to 0.029)

Strength of Evidence: High

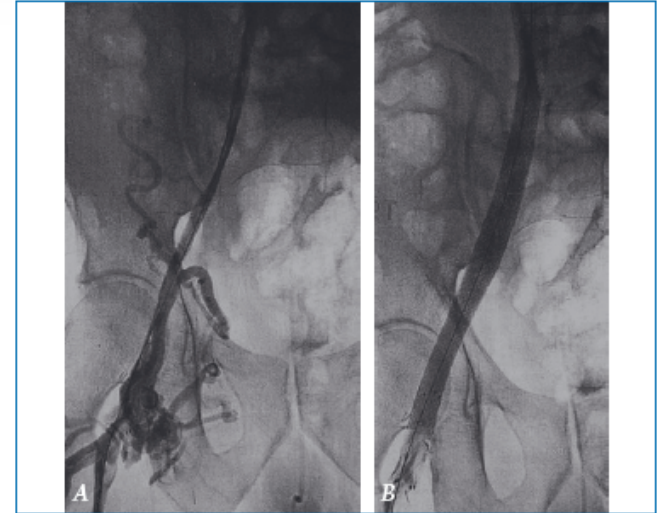
- Limited evidence to support the use of endovenous and/or surgical intervention over compression therapy or conservative therapy
- Endovenous and surgical interventions were associated with improvements in symptom scores and QOL scores (from baseline to post-treatment), in general
- Limited evidence to support the use of one treatment modality over another

Key Question 3

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

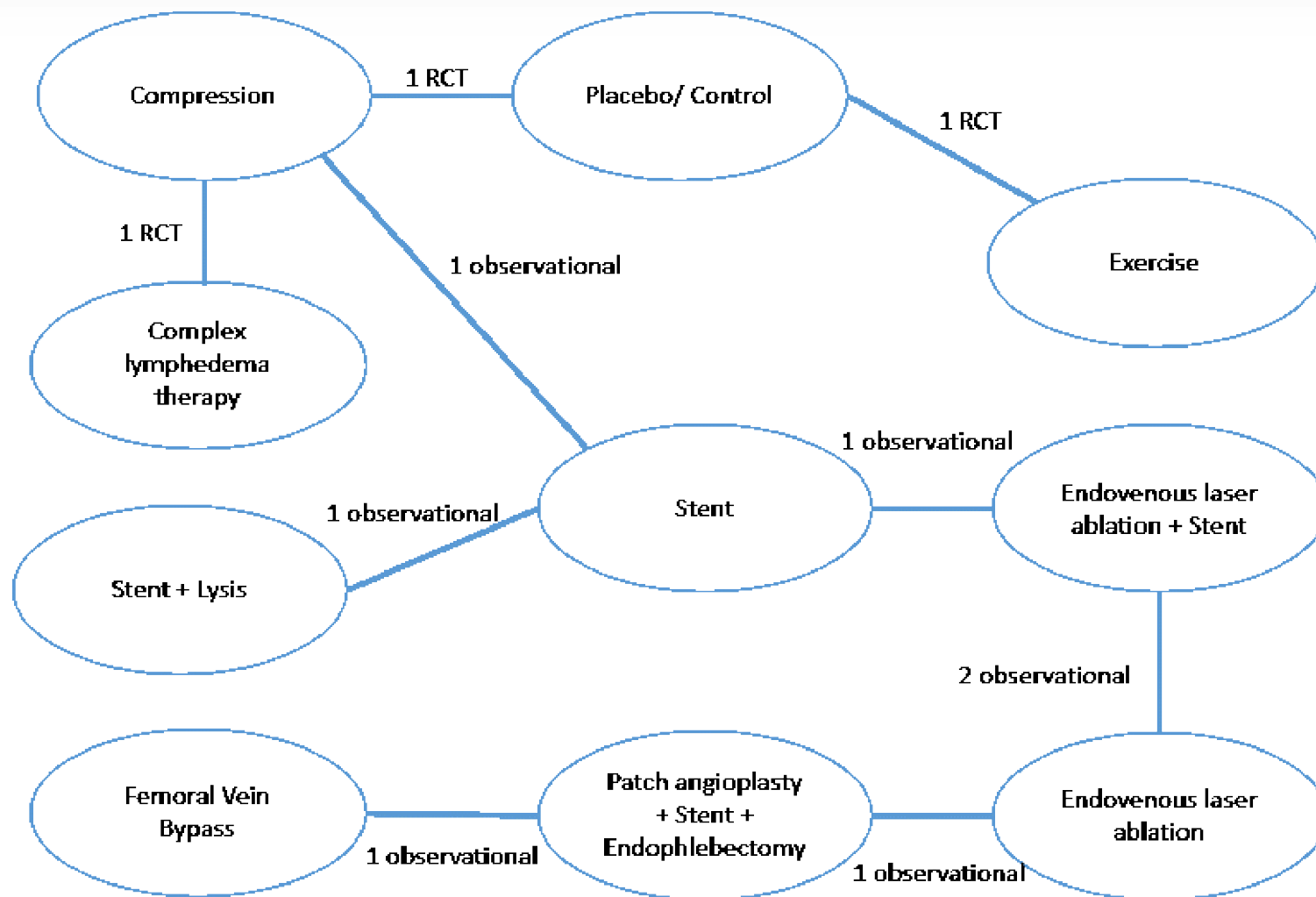
- a) **Comparative effectiveness of treatment modalities** on health outcomes?
- b) **Diagnostic method(s) and criteria** used?
- c) **Modifiers of effectiveness (i.e. patient characteristics)?**
- d) **Comparative safety concerns** of treatment modalities and modifiers of safety concerns

Treatment Options



- Exercise Training
- Medical Therapy (e.g. anticoagulation)
- Lifestyle Modification (e.g. weight reduction)
- Invasive Therapy
 - Endovenous intervention
 - Surgical intervention

KQ3 Treatment Comparisons



Exercise Training vs. Patient Education/Engagement

- 1 good-quality RCT
- 43 patients with postthrombotic syndrome
- Exercise intervention: strengthening, stretching, and aerobic components (15 sessions)
- Outcomes assessed at 6 months

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 Score	+5.4 (0.5 to 10.4)	0.03	0.09
SF-36 Mental Component Score	+0.4 (-4.2 to 4.9)	0.87	0.68

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

Strength of Evidence: Insufficient

Compression Therapy vs. Usual Care

- 2 RCTs
- 66 Patients with postthrombotic syndrome and chronic venous ulcer
- Outcomes assessment: 2 years in one study, 3 months in other study
- No significant differences in QOL or postthrombotic syndrome severity between groups

Strength of Evidence: Insufficient

Compression Therapy vs. Endovenous Intervention

- 1 retrospective study
- 216 patients with postthrombotic syndrome (Villalta score ≥ 10)
- Recurrence-free ulcer healing was significantly higher, favoring endovenous stenting

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

Strength of Evidence: Insufficient

Endovenous Intervention Alone vs. Combined Endovenous Interventions

- 3 retrospective studies
- 419 patients with May-Thurner syndrome
- Main comparisons:
 - ▶ Endovenous stenting alone vs. endovenous stenting + thrombolysis
 - ▶ EVLA alone vs. EVLA + endovenous stenting
 - ▶ Endovenous stenting alone vs. endovenous stenting + GSV ablation
- Outcomes assessed were heterogeneous
- Timepoints of outcome assessment were disparate

Strength of Evidence: Insufficient

- Insufficient evidence to demonstrate a benefit of one therapy over another for treatment of LE chronic venous thrombosis/obstruction
- Insufficient evidence to show a benefit of different forms of oral anticoagulation or duration of anticoagulation in patients with LE chronic venous thrombosis/obstruction

Conclusions

Diagnostic Methods

- Very few comparative studies exist in the contemporary literature
- Insufficient evidence to support or refute the use of DUS as a first-line test to confirm the diagnosis of LECVD and plan invasive treatment

LE Varicose Veins and LE Chronic Venous Insufficiency/Incompetence/reflux

- Patients who underwent surgical or endovenous interventions had significant improvement in symptom scores and hemodynamics
- When directly compared, there were no significant differences in CEAP, VCSS, QOL for surgical vs. endovenous interventions
- Insufficient evidence to support the use of any treatment modality over another

LE Chronic Venous Obstruction/Thrombosis

- Very few studies that assessed medical therapy, lifestyle modification (i.e. weight reduction), or skin/wound care.
- Insufficient evidence to support the use of any treatment modality over another

Overview

- Description of Systematic Review Process
- Evidence Review Findings
 - ▶ KQ1: Diagnostic testing for LECVD
 - ▶ KQ2: Treatment for LE varicose veins and/or LE chronic venous insufficiency/incompetence/reflux
 - ▶ KQ3: Treatment for LE chronic venous thrombosis/obstruction
- Limitations and Evidence Gaps
- Summary

Limitations of the Evidence-base

- English-language-only studies
- Few treatment strategy studies (e.g. treatment X first, then treatment Y) exist
- Unable to stratify analysis by disease severity (e.g. varicose veins, CEAP class)
- Numerous and heterogeneous endpoints
- In KQ2, there were 84 RCTs and a decision was made to abstract data from these studies + observational studies with > 500 subjects – thus creating the possibility that KQ2 is biased towards data from RCTs

Challenges in Evaluating the Existing Literature in LECVD patients

Population differences

Endpoint differences

Length of follow-up

Evolution of endovenous techniques

Descriptive characteristics of included patients

- KQ1
 - ▶ Which patients should undergo additional DUS testing after clinical diagnosis?
 - ▶ Which patients should undergo other diagnostic tests (e.g. MRV, CTV) prior to invasive treatment?

- KQ2
 - ▶ Additional studies needed to determine which patients benefit the most from invasive treatment (stratified by CEAP score, VCSS score, and anatomy)
 - ▶ More studies of treatment strategy (e.g. invasive therapy vs. weight loss/compression therapy/invasive therapy)
 - ▶ Standardization of endpoints, more uniform use of allocation concealment and double blinding

- KQ3
 - ▶ Should patients with LE chronic venous thrombosis/obstruction be treated with oral anticoagulation? If so, for how long?
 - ▶ Should treatment be different when compared with treatment for patients with uncomplicated DVT?

RECENT STUDIES

Original Article

Clinical Trials in Peripheral Vascular Disease Pipeline and Trial Designs: An Evaluation of the ClinicalTrials.gov Database

Sumeet Subherwal, MD, MBA; Manesh R. Patel, MD; Karen Chiswell, PhD;
Beth A. Tidemann-Miller, MS; W. Schuyler Jones, MD; Michael S. Conte, MD;
Christopher J. White, MD; Deepak L. Bhatt, MD, MPH; John R. Laird, MD;
William R. Hiatt, MD; Asba Tasneem, PhD; Robert M. Califf, MD

Conclusions—PVD studies represent a small group of trials registered in ClinicalTrials.gov, despite the high prevalence of vascular disease in the general population. This low number, compounded by the decreasing number of PVD trials in the United States, is concerning and may limit the ability to inform current clinical practice of patients with PVD. (*Circulation*. 2014;130:00-00.)