A systematic review and meta-analysis of the treatments of varicose veins

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Objectives: **Several treatment options exist for varicose veins. In this review we summarize the available evidence derived from comparative studies about the relative safety and efficacy of these treatments.**

Methods: **We searched MEDLINE, Embase, Current Contents, Cochrane Central Register of Controlled Trials (CENTRAL) expert files, and the reference section of included articles. Eligible studies compared two or more of the available treatments (surgery, liquid or foam sclerotherapy, laser, radiofrequency ablations, or conservative therapy with compression stockings). Two independent reviewers determined study eligibility and extracted descriptive, methodologic, and outcome data. We used random-effects meta-analysis to pool relative risks (RR) and 95% confidence intervals (CI) across studies.**

Results: **We found 39 eligible studies (30 were randomized trials) enrolling 8285 participants. Surgery was associated with a nonsignificant reduction in the risk of varicose vein recurrence compared with liquid sclerotherapy (RR, 0.56; 95% CI, 0.29-1.06) and all endoluminal interventions (RR, 0.63; 95% CI, 0.37-1.07). Studies of laser and radiofrequency ablation and foam sclerotherapy demonstrated short-term effectiveness and safety. The quality of evidence presented in this review was limited by imprecision (small number of events), short-term follow-up, and indirectness (use of surrogate outcomes).**

Conclusion: **Low-quality evidence supports long-term safety and efficacy of surgery for the treatment of varicose veins. Short-term studies support the efficacy of less invasive treatments, which are associated with less periprocedural disability and pain. (J Vasc Surg 2011;53:49S-65S.)**

Approximately one-third of men and women aged 18 to 64 years have varicose veins.[1] The high prevalence leads to significant health care expenditure on treatments of varicose veins.[2] Surgical treatment of varicose veins includes high ligation and saphenous vein stripping, with or without phlebectomy; until the past few years, this procedure had been used most commonly by surgeons worldwide.[3-5] However, several other less invasive treatment modalities that are claimed to be as effective as surgery are currently available, including radiofrequency or laser ablation of the great (GSV) or small saphenous veins (SSV), or both, combined with or without phlebectomy, liquid sclerotherapy,[2,6] and foam sclerotherapy.[7-9] Numerous randomized controlled trials (RCTs) and observational studies have compared the efficacy of these procedures, but to our knowledge, no contemporary systematic synthesis is available to compare all available treatments.

The Society for Vascular Surgery (SVS) partnered with the American Venous Forum (AVF) to develop clinical practice guidelines to improve the care of patients with venous disease. To assist in venous guideline development, the SVS and the AVF commissioned us to conduct this systematic review and meta-analysis to summarize the best-available evidence about the benefits and harms of the different treatments of varicose veins.

METHODS

The report of this protocol-driven systematic review was approved by the Venous Disease Committee of the SVS and the AVF and adheres to the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of RCTs and reporting Meta-analyses of Observational Studies in Epidemiology (MOOSE).[10,11] The quality if evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[12]

Eligibility criteria. Eligible studies were RCTs and cohort studies that enrolled participants with primary varicose veins who were treated with surgery, sclerotherapy, foam sclerotherapy, percutaneous endovenous thermal interventions (ablation with radiofrequency or laser), or conservative management with compression stockings. We included studies that measured any of the outcomes of varicose veins recurrence, patient satisfaction, esthetics, time to return to work, pain, and procedurally related

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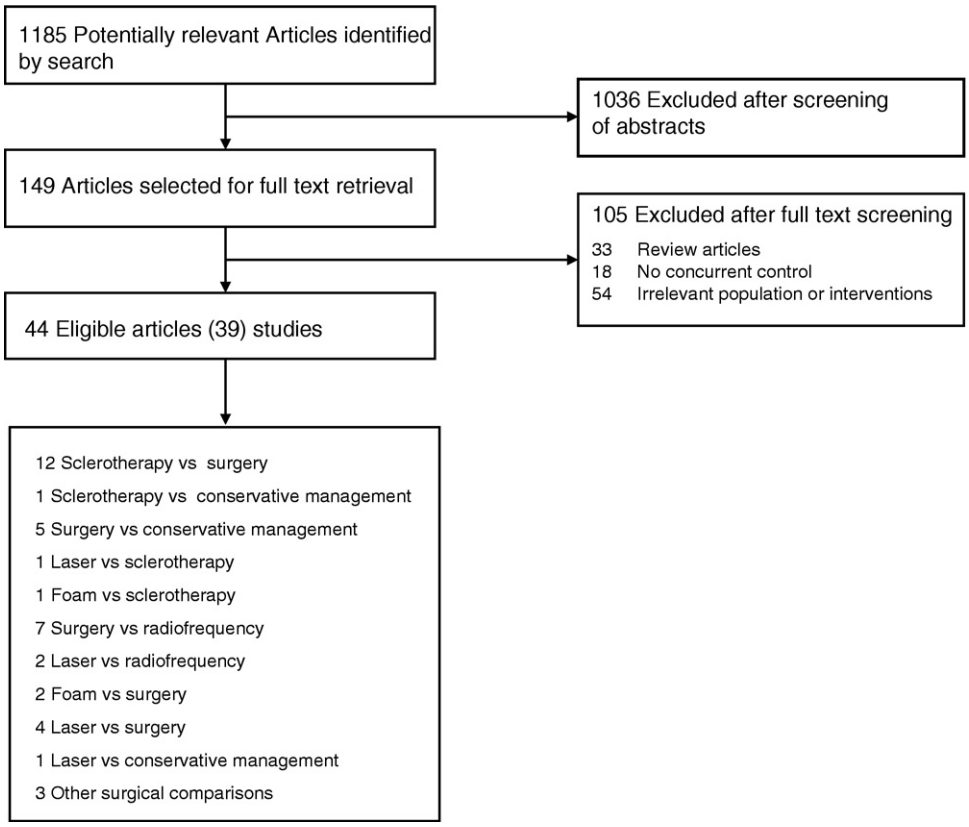

Fig. Flow chart shows the process of study selection for the meta-analysis.

complications, including local wound complications, such as infection and hematoma, and systemic complications, including deep vein thrombosis (DVT), pulmonary embolism (PE), air embolism, and pulmonary fibrosis. Studies were included regardless of their language, sample size, surgical technique, or duration of patient follow-up. We excluded single-cohort studies (ie, studies in which all patients received the same treatment without concurrent comparison groups).

Study identification and data collection. An expert reference librarian (P.J.E.) designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, we searched electronic databases (MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus) through February 2008 and monitored the literature for new publications thereafter. We also sought references from experts, bibliographies of included trials, and the Institute for Scientific Information Science Citation Index for publications that cited included studies. A combination of subject headings and text words were used as needed to define varicosities and the various procedures. Results were limited to comparative studies. The detailed search strategy is available from the authors upon request.

References were uploaded in a Web-based software package developed for systematic review data management (SRS, TrialStat Corp, Ottawa, Ontario, Canada). Paired reviewers working independently screened all titles and abstracts for eligibility. References that were deemed potentially relevant were retrieved in full text and uploaded for full text evaluation against eligibility criteria. The chance-adjusted inter-reviewer agreement (κ statistic) for study eligibility was 0.79 (95% confidence interval [CI], 0.66-0.93). Disagreements were resolved by consensus (the two reviewers discussed the study and reached a consensus), and when disagreement continued, by arbitration (a third reviewer adjudicated the study). Teams of two reviewers working independently and using a standardized form extracted data in duplicate from all eligible studies, including study description, methodologic quality, and outcome data.

Statistical analysis

Meta-analyses. When appropriate, we pooled relative risks (RR) for dichotomous outcomes from each trial using the DerSimonian-Laird random effects model and estimated the 95% CI for each outcome to reflect the uncertainty of point estimates of effect.[13] A RR of 1.0 indicates no difference between the two interventions in association with a particular outcome. A RR >1.0 indicates that compared with the control intervention, the procedure increased the risk of outcome occurrence. For continuous outcomes, we planned to estimate the weighted effect size

and the 95% CI, and for outcomes assessed with multiple scales, we planned to estimate the standarized mean difference. We used the I^2 statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance (ie, the percentage of variability in treatment effects across trials that is not due to chance or random error, but rather due to real differences in study patients, design or interventions).[14] The I^2 values of ≤25%, 50%, and ≥75% represent low, moderate, and high inconsistency, respectively. Statistical analysis was conducted using StatsDirect 2.5.4 software (StatsDirect Ltd, Cheshire, United Kingdom).

Subgroup and sensitivity analyses. Our a priori hypotheses to explore subgroup interactions and explain inconsistencies in the direction and magnitude of effect among studies included variation in bias protection measures and patient characteristics such as sex. We also planned to stratify results according to severity of chronic venous disease using the CEAP classification, when reported (published in 1994 and revised in 2004).[15] We planned to test the hypotheses of a subgroup effect using a test of interaction[16] and to conduct meta-regression to assess the correlation between the effect size and the length of study follow-up. Sensitivity analysis to exclude short-term studies that were unlikely to evaluate outcome of interest was also conducted.

RESULTS

Study identification. The Fig depicts our search and selection procedures. The initial search yielded 1185 references, from which we found 44 eligible articles representing 39 unique studies. Table I summarizes the characteristics and quality indicators of the included studies. These studies compared different permutations of the available treatment modalities for varicose veins and enrolled 8285 participants, with a mean sample size of 225 and mean duration of follow-up of 31 months (range, 3 months-10 years). The study patients were a mean age of 49, and 70% were women.

Methodologic quality. We considered an ideal study to have randomization with concealed allocation, blinding of outcome assessors (realizing that blinding of patients and surgeon is not feasible) and follow-up duration that exceeded 3 years, with minimal loss to follow-up.

Of the included studies, 9 were observational,[17-25] 1 was quasi-randomized,[26] and 30 were randomized.[26-55] Allocation concealment was conducted in five of the RCTs (three by sealed envelope and two by central randomization),[32,33,52,55,56] only two RCTs used blind outcome assessors,[18,40] and one blinded patients.[37]

In the observational studies, it was difficult to ascertain whether study arms were comparable at baseline. Study arms were often imbalanced in size, suggesting surgical expertise or preference for a particular procedure; in some studies, sclerotherapy was restricted to patients without saphenofemoral or saphenopopliteal incompetence.[20] Analysis usually was adjusted for age and sex. Blinded outcome assessment was rarely conducted.[18] Loss to follow-up was often not reported, or was reported as high (median, 9%; range, 0%-50%), and was significantly different between study arms on several occasions.[32,34,44,55] Seven studies[17,18,32,34,43,48,55] reported for-profit funding sources, whereas most did not report a funding source.

Outcome ascertainment was judged to be adequate in all studies (clinical outcomes were ascertained by clinical encounter or record review, whereas patient satisfaction, pain, or quality of life were assessed by standarized questionnaires). Reviewers had adequate chance-adjusted agreement in judging study quality (k = .83-.92). Table I summarizes the methodologic quality of the included studies.

Outcomes. The results of different comparisons are presented in the following format: description of included studies, reported outcomes, meta-analysis if applicable or feasible, and the overall quality of evidence.

Sclerotherapy studies

Liquid sclerotherapy vs various surgical techniques. RCTs and observational studies published in the 1960s and 1970s showed that sclerotherapy was as effective as surgery, particularly in patients without incompetent perforating veins.[56] In addition, patients in these studies preferred sclerotherapy,[33] which gave better initial results[26] and was less likely to require additional treatment.[31] However, studies with longer follow-up periods suggested that the initial benefits of sclerotherapy declined over time. For instance, Hobbs et al[41] found that surgery seemed more effective than sclerotherapy after 6 years and when the condition involved the saphenous system and there was proximal incompetence. Similarly, in another RCT, 5-year failure rates were 10% in surgical patients vs 74% in the compression sclerotherapy group.[38]

Even when liquid sclerotherapy (hydroxypolyethoxydodecane injected in the main stem of GSV) was coupled with high ligation of the saphenofemoral junction under local anesthesia, it remained at 5 years inferior to stripping and ligation of GSV and incompetent perforators in patient satisfaction and cure rate.[46] Heated polidocanol administered via a catheter advanced in the GSV from the knee level to the saphenofemoral junction (SFJ) was similarly inferior to surgery (ligation of SFJ and incompetent veins detected by color duplex imaging) after 10 years of follow-up.[30]

When one RCT with 10-year follow-up compared six treatment options—liquid sclerotherapy, high-dose liquid sclerotherapy, multiple ligations, stab avulsion, foam-sclerotherapy, and high ligation, followed by sclerotherapy—all treatments appeared equally effective in recurrence.[28] Ambulatory phlebectomy was superior to compression sclerotherapy in one RCT, with lower recurrence rates at 1 and 2 years.[36] Likewise, the recurrence-free rate at 4 years (81.7%) in patients who received stripping was superior to the rates achieved by saphenofemoral ligation (64.5%) or liquid sclerotherapy with 1% to 2% polidocanol (51.3%).[22] Sclerotherapy was suggested as a more beneficial treatment than surgery when the SSV is involved

Table I. Characteristics of included studies

First author, year	*Population (Anatomy, age, sex, CEAP)*	*Intervention 1 No. patient (limb)*	*Intervention 2 No. patient (limb)*	*Postprocedure surveillance*	*FU*
Surgery vs sclerotherapy					
Hobbs[41,56] (1968, 1974)	Lower extremity VV; nonpregnant, healthy population; age and sex NR	Sclerotherapy (injection-compression): 211 (542)	SF ligation, GSV/SSV stripping, multiple extrafascial ligations, removal of VV clumps and subfascial ligation of perforating veins: 170 (226)	Clinical assessment and photograph	1 year
Chant[33] (1972)	Lower extremity VV; age and sex NR	Sclerotherapy (Fagan: injection-compression): 115	Surgery: 100	Physical examination, interview, questionnaire	3 years
Doran[26] (1975)	Lower extremity VV; age and sex NR	Sclerotherapy (Fagan: injection-compression; Ethamolin): 182 (280)	Surgery: 149 (222)	Physical examination	2 years
Beresford[31] (1978)	Lower extremity VV; age 15-64; sex NR	Sclerotherapy (Fagan: injection-compression; Ethamolin): 125	Surgery: 124	Questionnaire, interview, physical examination	5 years
Trempe[23] (1991)	VV of SSV; age 43 (22-69); 93% women	Sclerotherapy (multiple agents): 138 (148)	Surgery: 112 (290)	Medical record review	7 years
Einarsson[38] (1993)	Symptomatic primary VV; age 42 (21-45); 69% women	Sclerotherapy: 84 (85)	Surgery: 80 (82)	Clinical tests and foot volumetry	5 years
Neglén[46] (1993)	Primary VV + GSV insufficiency; age 47; 64% women	Sclerotherapy: (78)	Surgery: (74)	Clinical interview, examination, foot-volumetry	5 years
Ishikawa[20] (1998)	Primary VV; age 56 (21-81); 82% women	Sclerotherapy: (81)	High saphenous ligation: (3)	Clinical assessment, Doppler US	26 months
Belcaro[30] (2000)	VV/pure superficial venous incompetence; age 53, 47% women	Endovascular sclerotherapy (polidocanol): 39	Flush ligation of SPJ, collaterals and all incompetent veins: 42	Color DUS, ambulatory venous pressure	10 years
Belcaro[28] (2003)	Primary VV; age 45, 69% women	Sclerotherapy (various techniques): 434	Stab avulsion or multiple ligation: 299	DUS	10 years
De Roos[36] (2003)	Chronic venous disease; age 42 (25-65); 98% women; C_2 E_p A_s P_r	Sclerotherapy (polidocanol): 48 (49)	Ambulatory phlebectomy: 48 (49)	Doppler US, continuous-wave US Doppler, digital photo-plethysmography	2 years
Miyazaki[22] (2005)	Primary VV due to GSV insufficiency; age 58; 76% women; C_{2-3} (76%), C_{4-6} (24%)	Sclerotherapy (polidocanol): (38)	Stripping: (244)	Clinical assessment	4 years
Sclerotherapy vs conservative management					
Abramowitz[27] (1973)	Pregnant women with lower leg VV, age NR	Conservative management with stockings: 56	Compressive sclerotherapy: 45	Physical examination	6-24 months

Table I. Continued

Design	*Funding*	*Lost to FU*	*Outcome assessors blinded?*	*Allocation concealed?*	*Control for risk factors in selection or analysis*[a]
R	NFP	NR	No/NR	Sealed envelope	NA
R	NFP	7%	No/NR	Sealed envelope	NA
R[a]	NR	36%; 29%	No/NR	No/NR	NA
R	NR	8.7%; 6.1%	No/NR	No/NR	NA
Non-R	NR	NR	No/NR	NA	No/NR
R	NR	22%; 24%	No/NR	No/NR	NA
R	NR	23%	No/NR	No/NR	NA
Non-R-R	NR	NR	No/NR	NA	Groups imbalanced (size and prognosis)[b]
R	NR	21%	No/NR	No/NR	NA
R	NFP	16%	No/NR	No/NR	NA
R	NR	2.49%	No/NR	No/NR	NA
Non-R-P	NR	NR	No/NR	NA	Analysis adjusted for age and sex
R	NFP	2%; 50%	No/NR	No/NR	NA

Table I. Continued

First author, year	*Population (Anatomy, age, sex, CEAP)*	*Intervention 1 No. patient (limb)*	*Intervention 2 No. patient (limb)*	*Postprocedure surveillance*	*FU*
Surgery vs conservative management					
Stacey[50] (1988)	Chronic insufficiency with healed venous ulcers; age 61 (38-80); 43% women	Ligation + below knee graduated compression elastic stocking: (20)	Below-knee graduated compression elastic stocking: (21)	Ascending phlebography, plethysmography, foot-volumetry	1 year
Belcaro[29] (1992)	Superficial venous incompetence; age 39, 67% women	Selective saphenous vein repair with plication (SSVR): 22	Conservative management with stockings: 22	Color DUS, high-resolution DUS, ambulatory venous pressure and normal maximum venous outflow (by plethysmography)	5 years
Michaels[44] (2006)	Uncomplicated primary VV lower extremities; age 45, 69% women	Flush ligation of reflux + GSV stripping: 124	Conservative management: 122	Postal questionnaires interview and examination	2 years
Van Gent[52] (2006)	Active venous leg ulcers; age 66, 61% women	Subfacial endoscopic perforating vein surgery + compression therapy: 97	Compression therapy: 103	Examination; DUS	2 years
Gohel[39] (2007) and Barwell[67] (2004)	Open or recently healed leg ulcers and superficial venous reflux; age 73, 58% women	Saphenous surgery + compression: 242	Compression therapy: 258	Examination and QOL questionnaires	4 years
Laser vs sclerotherapy					
Coles[18] (2002)	Untreated VV & lower extremity reflux, small diameter (0.25 and 3 mm) leg veins; age 48 (28-68); all women	Long pulsed ND:YAG laser: 20	Sclerotherapy (Sotradecol): 20	Clinical examination, photography	3 months
Surgery vs radio frequency					
Chandler[17] (2000)	Primary venous insufficiency with GSV reflux; age 47; 77% women; mean CEAP C = 2.3 for ligation; 2.6 no ligation group	GSV obliteration with Closure System: (120)	SFJ ligation: (60)	Clinical examination and DUS	1 year
Colli[19] (2005)	Osteal and truncal GSV insufficiency; C_1 (13%), C_2 (40%), C_3 (33%), C_4 (14%)	Radiofrequency/closure procedure (crossotomy 5/15; crossectomy 1/15; ligation 8/15): 15	Short striping preceded by crossectomy; phlebectomy in 11/15: 15		6 months
Lurie[43,58] (2003, 2005)	Symptomatic VV and GSV incompetence; age 48; 73% women; C_2 (78%-82%), C_3 (9%-11%), C_4 (9-11%)	GSV obliteration with temperature-controlled radiofrequency without adjunctive high ligation (closure procedure): (43) 44	Stripping with high ligation: 36 (36)	Clinical, DUS, and QOL questionnaire	2 years

Table I. Continued

Design	*Funding*	*Lost to FU*	*Outcome assessors blinded?*	*Allocation concealed?*	*Control for risk factors in selection or analysis*[a]
R	NR	NR	No/NR	No/NR	NA
R	NR	16%	No/NR	No/NR	NA
R	NFP	35% 17%	No/NR	No/NR	NA
R	NFP	2%	No/NR	Central randomization	NA
R	NFP	11%	No/NR	Sealed envelopes	NA
NonR-P	FP	0%	Blinded post treatment evaluators	NA	No/NR
NonR-P	FP	0%	No/NR	NA	Matched for age, sex, and CEAP class
NonR-R	NR	NR	NR	NA	Matched for clinical and anatomic CEAP class
R	FP	19%	No/NR	No/NR	NA

Table I. Continued

First author, year	*Population (Anatomy, age, sex, CEAP)*	*Intervention 1 No. patient (limb)*	*Intervention 2 No. patient (limb)*	*Postprocedure surveillance*	*FU*
Perälä[47,59] (2005)	Symptomatic primary GSV tributary VV; age 35; 93% women; median scores in the 2 groups: VCSS 5/4, VSDS 1/1, VDS 1/1	Radiofrequency endovenous obliteration procedure (VNUS closure): 15	Stripping: 13	Clinical assessment, color DUS	3 years
Hinchliffe[40] (2006)	Bilateral recurrent GSV VV previously treated by SF ligation; age 54 (44-66); 75% women; ≥C_2	Endoluminal thermal ablation (VNUS): 16 (16)	Re-do groin surgery and GSV stripping: 16 (16)	DUS	1 year
Kianifard[21] (2006)	SFJ reflux; age 54 (28-83); 37% women	Radiofrequency ablation (VNUS closure): 51 (55)	Open high saphenous tie and stripping: 51 (55)	DUS + physical examination	1 year
Stotter[51] (2006)	Primary VV; age 46; 72% women	Radiofrequency endoluminal ablation: 20	SFJ ligation with extended tributary ligation and invagination GSV stripping: 20	Clinical assessment, DUS, analog scale pain scoring and activity impairment assessments CIVIQ 2 questionnaire	1 year
Laser vs surgery					
De Medeiros[35,57] (2006)	Symptomatic VV and bilateral GSV insufficiency; age 46 (23-71); 95% women; C_2 (50%) C_3 (18%), C_4 (15%), C_5 (13%), C_6 (4%)	Endovenous diode laser photocoagulation: (20)	Conventional stripping: (20)	DUS, air plethysmography, questionnaire and physical examination	2 years
Vuylsteke[54] (2006)	Primary VV & GSV insufficiency; age 40; 67% women; C_2-C_4	Endovenous laser obliteration: 80 (118)	Conventional stripping: 84 (124)	Color DUS and physical examination	9 months
Rasmussen (2007)[48]	VV due to GSV insufficiency; age 53 (22-79); 69% females; 84% C_2 and the rest C_3-C_4	Endovenous laser ablation: 62 (69)	High ligation and stripping: 59 (68)	Clinical assessment, DUS	6 months
Darwood[34] (2008)	Symptomatic VV and primary SF incompetence; age 48 (31-59); 57% women; most C_2, the rest are C_3-C_5	Endovenous laser ablation: 65	SF ligation, GSV stripping to the knee and multiple phlebectomies: 30	DUS, clinical examination	1 year
Foam vs surgery					
Bountouroglou[32] (2006)	Symptomatic primary VV due to GSV incompetence; age 43 (20-72); 53% women	SFJ ligation, GSV stripping and phlebectomies: 28	SFJ ligation under local anesthetic and foam sclerotherapy to the GSV: 30	DUS, physical examination, questionnaire	3 months

Table I. Continued

Design	*Funding*	*Lost to FU*	*Outcome assessors blinded?*	*Allocation concealed?*	*Control for risk factors in selection or analysis*[a]
R	NR	0%	No/NR	No/NR	NA
R	NFP	NR	Y	No/NR	NA
NonR-P	NFP	NR	No/NR	NA	Adjusted for age, sex
R	NR	5%	No/NR	No/NR	NA
R	NR	0%	No/NR	No/NR	NA
R	NR	0%	No/NR	No/NR	NA
R	FP	27%	No/NR	No/NR	NA
R	FP	14% 7%	No/NR	No/NR	NA
R	FP	17.9% 6.7%	No/NR	Sealed envelope	NA

Table I. Continued

First author, year	*Population (Anatomy, age, sex, CEAP)*	*Intervention 1 No. patient (limb)*	*Intervention 2 No. patient (limb)*	*Postprocedure surveillance*	*FU*
Wright (2006)[55]	VV with GSV and/or SSV incompetence; age 50 (18-75); 68% women; C_3-C_4	Varisolve microfoam injected under US guidance in 5 stages; other sclerotherapy unspecified; Varisolve (A) = 178; Varisolve (B) = 259; other sclerotherapy = 125; total = 562	Surgery: High ligation (91.5%); stripping (88.3%); avulsion phlebectomy (53.2%); total = 94	Clinical assessment, DUS	1 year
Foam vs sclerotherapy					
Yamaki[24] (2004)	Isolated GSV incompetence who refused surgical interventions; age 54; 81% women; $C_{2:}$ (75%), C_3 (8%), C_4 (10%), C_5 (7%)	Duplex-guided sclerotherapy using foamed 1% and 3% polidocanol: 37	DUS-guided liquid sclerotherapy: 40	DUS and air plethysmography	1 year
Laser vs radio frequency					
Morrison[45] (2005)	Bilateral GSV reflux	Endovenous laser ablation: 50	Radiofrequency ablation: 50	Interview, physical examination, DUS	1 year
Ravi[25] (2006)	Symptomatic VV; age 51 (15-90); 62% women; C_2 (29%), C_3 (11%), C_4 (46%), C_5-C_6 (14%)	Endovenous laser ablation: (1091)	Radiofrequency ablation: (159)	Physical assessment, DUS, questionnaire	3 years
Laser vs conservative management					
Viarengo[53] (2007)	VV in lower limbs with active ulcers; age 59; 75% women; C_6	Endovenous laser: 27	Conservative management (compression therapy): 25	Digital photograph, US, physical examination	1 year
Other					
Jakobsen[42] (1979)	Untreated saphenous VV; 81% women	Surgery (SP/SF ligation/tributaries avulsion): 161	Minimally invasive surgery (ligation under local anesthesia) and sclerotherapy: 157	Physical examination + interview	3 years
Rutgers[49] (1994)	Isolated incompetence of GSV	Surgery (stripping and local avulsions of VV): 89	High ligation of SFJ and sclerotherapy: 92	DUS, physical examination	3 years
Dwerryhouse[37,61] (1999)	Primary uncomplicated GSV VV with SFI	Flush ligation of the SFJ with diathermy avulsion of all visible tributaries: 39	Stripping to the knee and ligation: 39	DUS, physical examination	5 years

DUS, Duplex ultrasound; *FU,* follow-up; *GSV,* great saphenous vein; *NA,* not applicable; *Non-R-P,* nonrandomized prospective; *Non-R-R,* nonrandomized retrospective; *NR,* not reported; *QOL,* quality of life; *SFI,* saphenofemoral incompetence; *SFJ,* saphenofemoral junction; *SSV,* short saphenous vein; *US,* ultrasound; *VCSS,* Venous Clinical Severity Score; VSD, Venous Disability Score; *VSDS,* Venous Segmental Disease Score; *VV,* varicose veins.

[a]Only applicable to nonrandomized studies.

[b]Surgical procedure alone performed in very little group compared with sclerotherapy group, and they restricted the treatment of sclerotherapy alone to patients without SFI and SPI.

[c]Patients were blinded.

Table I. Continued

Design	*Funding*	*Lost to FU*	*Outcome assessors blinded?*	*Allocation concealed?*	*Control for risk factors in selection or analysis*[a]
R	FP	22% 4%	No/NR	Central randomization	NA
NonR-P	NR	NR	No/NR	NA	Matched for age, sex and CEAP
R	NR	NR	No/NR	No/NR	NA
NonR-R	NFP	NR	No/NR	NA	No/NR
R	NR	0%	No/NR	No/NR	NA
R	NR	1.90%	No/NR	No/NR	NA
R	NR	9%	No/NR	No/NR	NA
R	NR	41%	No/NR[c]	No/NR	NA

and when no saphenofemoral or saphenopopliteal incompetence is present.[20,23,41]

When all 10 studies[22,23,26,28,31,33,36,38,41,46] were included in meta-analysis, surgery was associated with nonsignificant reduction in the risk of varicosity recurrence compared with liquid sclerotherapy (RR 0.56; 95% CI, 0.29-1.06; I = 93%). However, when the three studies with ≤2 years follow-up were excluded, the decreased risk of recurrence with surgery became statistically significant (RR, 0.45; 95% CI, 0.22-0.93; I^2 = 93%). Moreover, when older studies (<1980) were excluded in sensitivity analysis,[26,31,33,41] the results remained statistically significant (RR, 0.38; 95% CI, 0.16-0.90; I^2 = 94%). No significant associations were found with other outcomes such as the risk of PE in four studies (RR 0.30; 95% CI, 0.06-1.46; I^2 = 0%) and the proportion of patients satisfied (86% vs 82%; P = .71); however, the small number of events makes these estimates imprecise. Data on quality of life and DVT were sparse and insufficient for meta-analysis.

The included trials had significant methodologic limitations, considering that randomization methods were not well described, allocation concealment was only conducted in two studies,[33,56] follow-up duration was short in several studies,[26,36,56] and outcome assessors were not blinded in all studies. In addition, many studies focused on ultrasound measurements rather on patient-important outcomes. Considering the overall limitations, indirectness of outcomes, and imprecision, the quality of evidence in these studies is low but supports that surgery is associated with a lower risk of varicosity recurrence.

Sclerotherapy vs conservative management. In pregnant women with lower leg varicosities, one RCT showed that liquid sclerotherapy (using the Fegan technique with injection of sodium tetradecyl in probable sites of perforator vein incompetence) was superior to conservative management with compression stockings in cosmetic results and symptomatic relief. The treatment was rated as "poor" by 2% of the patients who received sclerotherapy and by 50% of those who received conservative management.[27] The quality of this evidence is low due to poor reporting of bias protection measures.

Sclerotherapy vs laser therapy. We did not find comparative studies of endovascular laser ablation of the saphenous veins. We found a small pilot study that used transcutaneous long-pulse laser in the treatment of small leg veins (branch varicosities and spider veins). Results were similar to sclerotherapy with sodium tetradecyl in esthetic results and patient satisfaction. The patients in this study were nonpregnant women with small leg vein varicosities of 0.25 to 3 mm.[18] The quality of evidence supporting equivalence is considered very low due to lack of randomization, imprecision (very small sample size), and the short follow-up duration (3 months).

Liquid sclerotherapy vs foam sclerotherapy. An observational study by Yamaki et al[24] showed that at 1 year, duplex-guided foam sclerotherapy was superior to duplex-guided liquid sclerotherapy in achieving complete occlusion of the GSV (67.6% vs 17.5%; P = .0001) and varicose vein recurrence (8.1% vs 25%; P = .048). However, the inference from this study that supports the superiority of foam is weakened by the small sample size (77 limbs), the short duration of follow-up, and the observational nature of the study; all these factors make the assessment of the outcome of varicose recurrence less valid.

Laser and radiofrequency studies

Endovenous laser ablation vs surgery. We found four RCTs that compared endovenous laser ablation with standard ligation and stripping. No difference was detected between the two procedures at 3 months in improvements in quality of life scores (Short Form-36),[48] disease-specific quality of life (Aberdeen Varicose Vein Symptom Score [AVVSS]),[34] and symptoms (Venous Clinical Severity Score [VCSS]).[48] There was slightly increased postoperative pain and bruising in the high ligation and stripping group.[48] In studies with relatively longer follow-up, no difference was detected at 26 months between the two procedures in esthetic results, patient satisfaction, and pain.[35,57] Compared with surgery, the laser group had faster return to normal activity (median, 2 vs 7 days),[34] return to work (median, 4 vs 17 days),[34] and shorter duration of postoperative disability (total days of sick leave, 8.6 vs 22.4 days).[54] DVT and PE outcomes were mostly not reported.

In general, these trials had short follow-up, which made it difficult to assess varicose vein recurrence; hence, a meta-analysis was not feasible. Two of the four trials reported for-profit funding,[34,48] and none reported allocation concealment or blinded outcome assessment. The overall quality of evidence supporting equivalence is considered very low in this comparison.

Radiofrequency vs surgery. Four RCTs and three observational studies compared radiofrequency endoluminal ablation with surgery in patients with symptomatic varicose veins.[17,19,21,40,43,47,51,58,59] These studies had short-term follow-up, with the longest study extending to 3 years. Endovascular obliteration of the GSV compared with conventional vein stripping was associated with faster return to work (1.15 vs 3.89 days; P = .02), shorter time to return to normal activity (7 vs 14 days; P < .05),[51] lower pain scores,[58] better short-term quality of life scores,[58] and higher patient satisfaction.[51] A meta-analysis of these studies shows no significant difference between the two procedures on varicosity recurrence (RR, 0.94; 95% CI, 0.25-3.46; I^2 = 50%; 4 studies).

The RCTs in this comparison did not report bias protection measures, whereas the observational studies had comparable groups in age, sex, and clinical CEAP class; therefore, the evidence of this comparison is of low quality.

Laser saphenous ablation vs radiofrequency ablation. Morrison reported results in 50 patients with varicosity and bilateral GSV reflux whose legs were randomized to saphenous vein ablation using laser energy or radiofrequency energy. At 1 year, they reported complete occlusion of GSV in 66% of the laser-treated legs compared with 80% of the radiofrequency-treated legs (P < .05). DVT inci-

dence (extension of the thrombus into the femoral vein) was <1% in both groups.[45]

Ravi et al[25] compared laser and radiofrequency endovenous ablation of GSV and SSV in a nonrandomized retrospective study and were unable to detect a difference between the two procedures in effectiveness and safety. The rate of saphenous vein occlusion 2 weeks after the procedure was about 96% in both groups. Ultrasound examination of the saphenofemoral junction demonstrated a lack of neovascularity and the presence of a patent saphenofemoral junction with physiologic drainage in all patients. Follow-up at a mean of 3 years showed no neovascularization in the groin and marked symptomatic improvement in most patients in both groups. Most of the patients in this series required additional procedures, however, such as microphlebectomy or sclerotherapy at the time of endovascular ablation, making these results less reliable. There were no DVTs in either group. Conclusions regarding the superiority of one of these two interventions were quite limited.

Endovenous laser ablation vs conservative management for venous ulcers. Viarengo et al[53] randomized 52 patients presenting with varicose veins with active ulcers for >1 year to endovenous laser ablation of GSV and SSV or to elastic and inelastic compression therapy. The laser group had higher healing rate at 3 months (63% vs 12%; $P = .0002$) and 12 months (82% vs 24%; $P = .0001$). No patient in either group experienced a DVT or PE. They reported complete occlusion, with no treatment failures or recanalization in all patients treated with laser ablation. Transient paresthesia occurred in 22% but completely resolved after 6 months. Minor adverse effects were reported such as hyperpigmentation (4%), ecchymoses (63%), periprocedural pain (33%), lipoid necrosis (4%), and scarring (4%).

Methodologic limitations (randomization, allocation concealment, and blinding procedures were not reported) and imprecision (small number of events despite statistical significance) lower the quality of evidence supporting the superiority of laser treatment.

Surgery studies

Surgery vs conservative management. Five RCTs compared various surgical techniques vs conservative management with compression stockings. Michaels et al[44] randomized patients with uncomplicated primary varicose veins of the lower extremities to flush ligation of the saphenous vein and GSV stripping or to conservative management. After 2 years of follow-up, surgical patients reported better quality of life in quality-adjusted life years (QALYs) based on the SF-6D score (0.083; 95% CI, 0.005-0.16) and on the EQ-5D score (0.13; 95% CI, 0.016-0.25). Significant benefits were also seen in symptomatic and anatomic measures.[44]

van Gent et al[52] compared ambulatory compression therapy with subfacial endoscopic perforating vein surgery vs conservative management in patients with active venous leg ulcers. They could not detect a significant difference between the two groups in healing rates (83% in the surgical group and 73% in the conservative group; $P > .05$) or recurrence rates (22% surgical vs 23% conservative; $P > .05$); however, patients with recurrent ulceration or with medially located ulcers treated surgically had higher ulcer-free rates of 62% vs 33% ($P = .02$) and 78% vs 43% ($P = .02$, respectively).[52] Gohel et al[39] (Comparison of Surgery and Compression with Compression Alone in Chronic Venous Ulceration [ESCHAR] trial) monitored patients with open or recently healed leg ulcers and superficial venous reflux who were randomized to surgery with compression therapy vs compression therapy. Surgical correction of superficial venous reflux in addition to compression bandaging did not significantly improve ulcer healing at 4 years (93% for surgery vs 89% for the conservative management; $P = .73$) but reduced the recurrence of ulcers (31% for surgery vs 56% for the conservative management; $P < .01$) and resulted in a greater proportion of ulcer-free time at 3 years (78% vs 71%; $P = .007$).

However, because compression abolishes saphenous reflux in a nonsurgical way, it should not be surprising that surgery in addition to compression did not shorten healing times. If surgery only, without compression, had been included in the trial, it would be plausible that the healing time would have been similar to that shown in observational studies.[53,60] In an era when surgery has become an outpatient procedure, it is unclear whether lengthy compression is needed; particularly, because the effect of compression on cost or quality of life outcomes is not well documented.

Two studies only reported laboratory and physiologic measurements and did not report the clinical outcomes of interest. In the first study, patients with chronic venous insufficiency and healed venous ulcers were randomized to surgery (ligation of incompetent lower leg communicating veins, ablation of incompetent superficial veins, and below knee graduated compression elastic stocking) or to a control group that only received compression therapy. Calf function measurements did not improve by surgery.[50] In the second study, selective saphenous vein repair with plication for patients with superficial venous incompetence increased refilling time and decreased incompetent sites compared with conservative management with stockings.[29]

Two of the RCTs protected randomization by concealing allocation and their rates of loss to follow-up were small,[39,52] but none of them blinded outcome assessors. Hence, the overall quality of evidence in this comparison supporting surgery is moderate.

Surgery vs foam therapy. In a noninferiority, 1-year RCT, Wright, et al[55] compared the efficacy of a microfoam preparation injected under ultrasound guidance in patients with varicose veins and/or SSV incompetence vs sclerotherapy or surgery, consisting of high ligation (91.5%); stripping (88.3%), and avulsion phlebectomy (53.2%). When the end point of ultrasound-determined occlusion of trunk vein and resolution of reflux was considered, foam therapy was noninferior to the comparator therapies and was associated with less pain and faster return to work. The study had a short follow-up time of 1 year.

Table II. Commonly reported adverse events

Surgery	*Sclerotherapy*	*Laser ablation*	*Radiofrequency ablation*	*Foam therapy*
• Wound infection, 3%-6%	• Skin staining or necrosis, 3%	• Purpura/bruising, 11%-23%	• Saphenous nerve paresthesia, 13%	• Contusion, bruising, hematoma, 61%
• Sural or saphenous nerve injury, 10%-23%	• Superficial phlebitis, 22%-27%	• Erythema, 33%	• Superficial phlebitis, 0%-20%	• Skin pigmentation, 51%
• Hematoma, 31%		• Hyperpigmentation, 57%	• Hematoma, 7%	• Headache, 11%
• Superficial phlebitis, 0%-12%		• Hypopigmentation, 2%	• Thermal skin injury, 7%	
		• Blistering/sloughing, 7%	• Paresthesia, <1%	
		• Scaring, 13%	• Leg edema, <1%	
		• Telangiectatic matting, 28%		
		• Edema, 15%		
		• Paresthesia, 1%-2%		
		• Superficial phlebitis, 6%		

Bountouroglou et al[32] randomized patients to SFJ ligation and GSV stripping and phlebectomies, or to SFJ ligation under local anesthetics and foam sclerotherapy to the GSV. At 3 months, both groups had similar reduction in the median CEAP class from preoperative value of C_4 to a value of C_1. Sclerotherapy however, was associated with faster return to normal activities (2 vs 8 days), better reduction of VCSS (sclerotherapy group median VCSS dropped from 5 to 1 and surgery median dropped from 7 to 3; $P < .001$), and reduced overall cost by almost 50%.[32]

Allocation was concealed in both of these RCTs; however, the short duration of follow-up renders the assessment of outcomes of interest less valid and the quality of evidence is low. These studies were sponsored by commercial funding sources (foam manufacturers). The quality of evidence supporting equivalence is considered low.

Other surgical studies. Jakobsen[42] compared radical surgery, including saphenofemoral and/or saphenopopliteal ligation, GSV and/or SSV stripping, ligation of incompetent perforating veins located by clinical examination, and avulsion of tributaries, with minimally-invasive surgery (ligation under local anesthesia) and sclerotherapy. At 3 years, radical surgery was associated with better esthetic and symptomatic results.

Rutgers et al[49] compared stripping and local avulsions of varicose veins vs high ligation of the saphenofemoral junction and sclerotherapy. Cosmetic results, judged by both the patient and the surgeon, and clinical and Doppler ultrasound results, were significantly better after the stripping operation.

Dwerryhouse et al[37,61] compared flush ligation of the saphenofemoral junction with subsequent diathermy avulsion of all the visible varicose tributaries vs a combination of ligation and GSV stripping to the knee. After 5 years of follow-up, they found that stripping had significantly decreased the need for reoperation (RR, 0.28; 95% CI, 0.13-0.59).

When surgery is compared with all endoluminal ablation therapies (laser, radiofrequency, and foam), meta-analysis shows that surgery led to a nonsignificant reduction in the risk of varicose vein recurrence (RR, 0.63; 95% CI, 0.37-1.07; $I^2 = 90\%$; 16 studies).

Adverse effects

In general, all treatments for varicose veins were well tolerated, without significant periprocedural adverse effects; particularly, DVT and PE in these studies were very infrequently reported. Local complications were common but were generally minor. Table II summarizes the reported frequency of local complications associated with surgery, liquid sclerotherapy, laser ablation, radiofrequency ablation, and foam therapy. Laser and radiofrequency ablation studies reported more side effects than sclerotherapy and surgery studies, which could be attributed to differential reporting of minor side effects.

DISCUSSION

Our findings. In the systematic review, we searched the literature for studies that compared different treatment modalities for varicose veins. We found 38 studies that met eligibility criteria and compared different permutations of the available approaches to treating varicose veins and the incompetent saphenous veins. In general, invasive treatments (surgical and endoluminal) were superior to conservative management in elimination of varicose veins and decreasing ulcer recurrence rates. Studies of liquid sclerotherapy, foam, and endoluminal thermal ablation therapies had short follow-up time, making them unsuitable to assess long-term outcomes.

Surgery appears to have low- to moderate-quality evidence demonstrating less recurrence and better long-term results. Compared with surgery, however, liquid or foam sclerotherapy and endoluminal thermal ablation therapies (laser and radiofrequency) were associated with faster re-

turn to work, shorter duration of disability, and less pain. The evidence on quality of life was sparse and inconclusive. Data on outcomes of DVT and PE were sparse and poorly reported. There were insufficient data to conduct many planned meta-analyses and subgroup analyses, particularly analysis based on CEAP class.

The quality of evidence in this review is low to very low. Although the evidence is mainly derived from randomized trials, it was downgraded[12] because the subjective outcomes in these studies were not assessed by blinded assessors, the number of events was low, which led to imprecision (ie, wide CIs, high *P* values for comparisons in which large differences could not be excluded), and there was great inconsistency in patients, interventions, and results across studies. Furthermore, many studies designated surrogate markers as end points, such as refilling time and other ultrasonographic measures, that indirectly apply to the outcomes of interest, further weaken clinical inferences, and therefore lower the overall quality of evidence.

The strengths of our review stem from the comprehensive literature search strategy that had no language restrictions and included randomized and observational, comparative (controlled) studies. We also attempted to reduce bias by reviewing articles, extracting data, and appraising the literature by pairs of blinded reviewers with adequate interobserver agreement.

Comparison with other reviews. Van de Bos et al[62] compared the different treatments available for varicosities and concluded that they all had a high success rate (>70%), with better results with endovenous laser therapy. These conclusions were based only on ultrasonographic outcomes, and many of the included studies were noncomparative; hence, the quality of evidence presented in that review was affected by the indirectness of outcomes and the methodologic limitations of the primary evidence. Rigby et al[63] qualitatively summarized RCTs that compared sclerotherapy and surgery and did not offer a meta-analytic estimate. They concluded that sclerotherapy is associated with a favorable recurrence rate in the first year but that surgery has better long-term outcomes, a finding consistent with our review.

Bamigboye et al[64] summarized varicose veins treatments in pregnancy and only found one RCT that demonstrated modest beneficial effects of a phlebotonic drug (rutoside) in reducing symptoms of varicose veins (nocturnal cramps, feelings of tiredness, paresthesia). Jia et al[8] summarized studies of foam therapy, including noncomparative studies, and concluded that serious side effects were rare (DVT and PE <1%; visual disturbances, headache and thrombophlebitis <5%); however, data were inconclusive regarding effectiveness.

Similarly, Mundy et al[6] summarized studies of laser therapy, including noncomparative studies, and concluded that serious periprocedural adverse effects such as DVT and incorrect placement of the laser in blood vessels were uncommon. They were also unable to draw inferences regarding effectiveness and varicose veins recurrence rates because of the paucity of comparative studies with long-term follow-up.

Luebke and Brunkwall[65] summarized studies of endoluminal thermal ablation and foam therapy, including noncomparative studies, and concluded that all three were fairly safe with good short-term and midterm results.

Implications for practice and research. The clinical and practical implications of this review are explained in the accompanying clinical practice guidelines from the venous committee from the SVS and the AVF. In terms of implications for future research, there is apparent need for randomized trials of newer and less invasive therapies, such as laser, radiofrequency ablation, and foam therapy, to compare their efficacy and safety with that of the standard procedure of ligation, stripping, and multiple phlebectomies. These studies need to stratify participants by the severity of symptoms, such as by the VCSS, and/or other measures of disease severity, including physical examination or imaging findings. This is particularly important because advanced stages of chronic venous insufficiency (CEAP C_4, C_5, and C_6) may be associated with limitations or contraindications to surgical treatment by conventional vein stripping, including extensive dermatosclerosis, fibrosis, ulcer scarring sequelae, active ulcers, edema, or lymphedema, thus making the use of alternative methods of treatment necessary.[53]

In addition, future studies should have a long follow-up duration (possibly 5 years or longer), assess patient-important outcomes, such as varicose vein recurrence, patient satisfaction, disability, and quality of life; and use standardized disease-specific scales for these outcomes, such as the VCSS and the Venous Disability Score.

The expertise-based RCT is likely the optimal design for future studies: in traditional RCTs, patients are randomized to treatment A or treatment B, administered by the same clinician, whereas in expertise-based RCTs, patients are randomized to clinician A or clinician B, and each clinician administers the procedure in which they have the best expertise.[66] Indeed, we found examples in this review of studies in which treatment groups were imbalanced in size, suggesting expertise or preference biased toward a particular treatment.[20]

Lastly, there is general paucity of data on the cost-effectiveness of these procedures.[2,63] This is another area that requires careful assessment considering that procedures are done for a wide range of indications that include cosmesis.

CONCLUSION

Very low quality evidence suggests that the available treatments for varicose veins (surgery, sclerotherapy, foam therapy, laser endoluminal ablation and radiofrequency endoluminal ablation) appear to be safe with rare side effects. Surgery is the only treatment with long-term effectiveness data. The other less invasive treatments are associated with shorter disability and less pain, but only short-term effectiveness data.

AUTHOR CONTRIBUTIONS

Conception and design: MM, VM, PG
Analysis and interpretation: MM, VM, PG
Data collection: MM, FC, MZ, ME, MD, PE
Writing the article: MM, VM, PG
Critical revision of the article: MM, FC, MZ, ME, MD, PE, VM, PG
Final approval of the article: MM, FC, MZ, ME, MD, PE, VM, PG
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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