Cynthia K. Shortell, MD, SECTION EDITOR

# A systematic review of the efficacy and limitations of venous intervention in stasis ulceration

Myriam L. Montminy, MD, MSc, FRCSC, Arjun Jayaraj, MD, *and* Seshadri Raju, MD, FACS, *Jackson, Miss*

## ABSTRACT

**Background:** Surgical techniques to address various components of chronic venous disease are rapidly evolving. Their efficacy and generally good results in treating superficial venous reflux (SVR) have been documented and compared in patients presenting with pain and swelling. A growing amount of literature is now available suggesting their efficacy in patients with venous leg ulcer (VLU). This review attempts to summarize the efficacy and limitations of commonly used venous interventions in the treatment of SVR and incompetent perforator veins (IPVs) in patients with VLU.

**Methods:** A systematic review of the published literature was performed. Two different searches were conducted in MEDLINE, Embase, and EBSCOhost to identify studies that examined the efficacy of SVR ablation and IPV ablation on healing rate and recurrence rate of VLU.

**Results:** In the whole review, 1940 articles were screened. Of those, 45 were included in the SVR ablation review and 4 in the IPV ablation review. Data were too heterogeneous to perform an adequate meta-analysis. The quality of evidence assessed by the Grading of Recommendations Assessment, Development, and Evaluation for the two outcomes varied from very low to moderate. Ulcer healing rate and recurrence rate were between 70% and 100% and 0% and 49% in the SVR ablation review and between 59% and 93% and 4% and 33% in the IPV ablation review, respectively. To explain those variable results, limitations such as inadequate diagnostic techniques, saphenous size, concomitant calf pump dysfunction, and associated deep venous reflux are discussed.

**Conclusions:** Currently available minimally invasive techniques correct most venous pathologic processes in chronic venous disease with a good sustainable healing rate. There are still specific diagnostic and efficacy limitations that mandate proper match of individual patients with the planned approach. (J Vasc Surg: Venous and Lym Dis 2018;6:376-98.)

Chronic venous disease (CVD) is a common medical condition. Venous leg ulcer (VLU) is the most severe clinical presentation of CVD. Active VLUs are present in up to 0.5% of the adult Western population, whereas healed VLUs are seen in 0.6% to 1.4%.[1] In the United States, >2 million adults have advanced CVD, and at least 20,556 patients receive a new diagnosis of VLU each year. Delay in ulcer healing and ulcer recurrence are often seen and most often require prolonged therapy.

The underlying pathologic process contributing to the occurrence of CVD includes varying degrees of superficial venous insufficiency, deep venous insufficiency, deep venous obstruction, and calf muscle pump dysfunction.[2-5] Both superficial reflux and deep reflux are common in patients with VLU. In 264 patients with venous ulceration, the anatomic distribution of reflux was noted as follows: deep venous reflux (DVR; 71%), superficial venous reflux (SVR; 57%), and incompetent perforator veins (IPVs; 17%).[5] Reflux in more than one venous compartment is extremely common, occurring in as many as two-thirds of patients with healed or active ulceration.[2,5] Isolated perforator insufficiency is extremely rare as a basis of VLU; most are instead associated with reflux in other territories (secondary perforator insufficiency).[3]

In the last two decades, technology has rapidly evolved from open to minimally invasive techniques to correct these pathologic processes. All open and minimally invasive techniques have shown good results in patients with leg pain and swelling. Less well documented are their efficacy and limitations in patients with VLU. A logical algorithm as to how the various techniques should be used, in what sequence and in what combinations, for optimal results also has yet to be established. The purpose of this article was first to summarize in a systematic review the efficacy of commonly used open and minimally invasive techniques and then to highlight their limitations. A stepwise approach combining those techniques in the management of VLU is suggested on the basis of our estimate of efficacy, limitations, and relative risk of the various techniques.

From The RANE Center at St. Dominic's Memorial Hospital.

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Correspondence: Seshadri Raju, MD, FACS, The RANE Center, St. Dominic's Memorial Hospital, 971 Lakeland Dr, Ste 401, Jackson, MS 39216 (e-mail: rajumd@earthlink.net).

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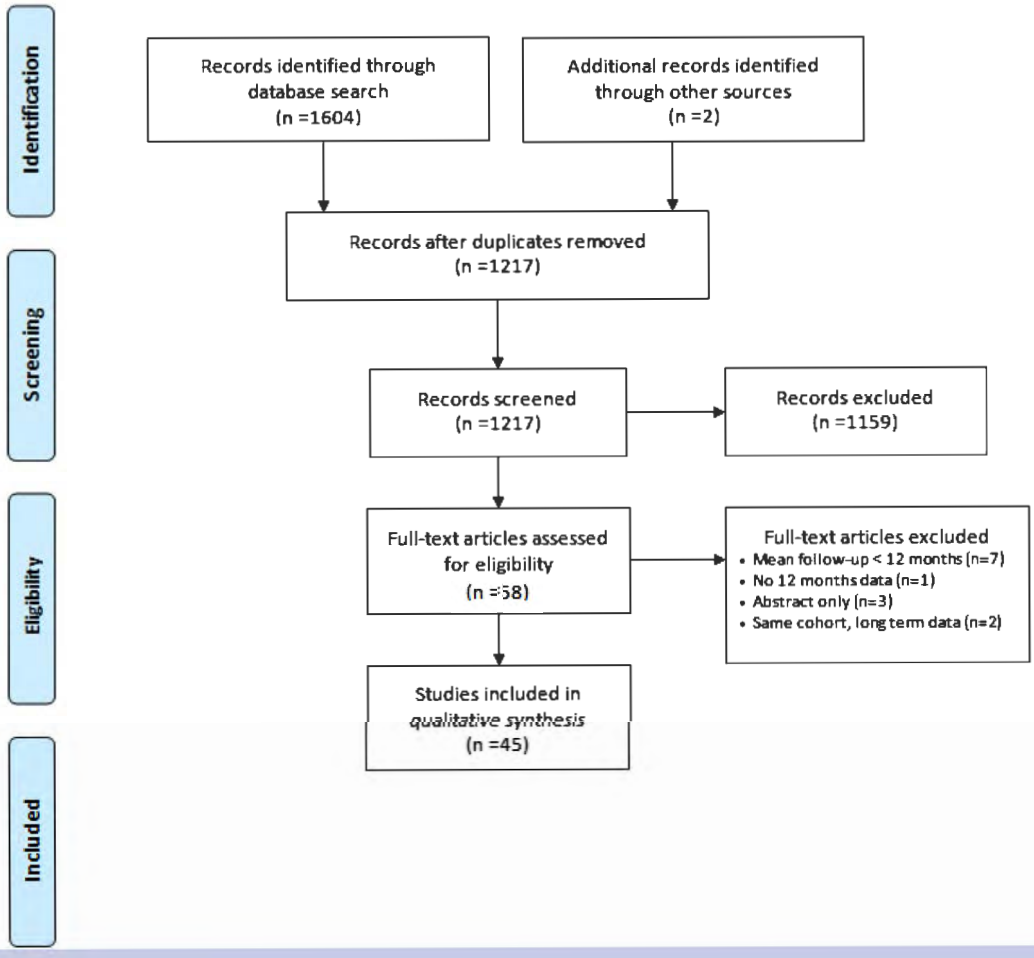


**Fig 1.** Superficial venous reflux (SVR) ablation.

## METHODS

A systematic review of the literature, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations, was performed.[6] The aim of the study, eligibility criteria, and outcomes were predefined. Two different searches were conducted to identify studies that examined the efficacy of SVR ablation and IPV ablation in patients with VLU.

### Study eligibility

**Type of studies.** All observational studies and randomized controlled trials (RCTs) were eligible. Review articles were searched to identify additional relevant publications. Articles not yet published were excluded. No time limit was set for inclusion or exclusion. Despite changing technology over time, effects of correcting specific disease (eg, superficial reflux) appear to be the same as detailed herein regardless of specific technique used.

**Type of patients.** Participants of all ages with a healed or active medial VLU (C5-C6) were included. A minimum of 20 patients with Clinical, Etiology, Anatomy, and Pathophysiology clinical class C5 to C6 score were required. The SVR ablation search included all techniques of great saphenous vein (GSV), small saphenous vein (SSV), and varicose vein ablation. Studies with both SVR ablation and IPV ablation were included in that search. The IPV ablation search considered articles in which IPV ablation was the only intervention, either because no SVR was present or because SVR had been previously ablated.

**Outcomes.** The primary outcomes were ulcer healing and ulcer recurrence. Outcome measurement at 12 months or a mean follow-up of 12 months was determined to be the minimal requirement to assess the chosen outcomes.

### Search strategy

An electronic search was conducted in January 2017. MEDLINE, Embase, and EBSCOhost databases were searched with English-language restraint and without publication date limitation. The references of included studies and of relevant review articles were manually searched for additional publications. Key words used for each search are shown in the Appendix (online only).

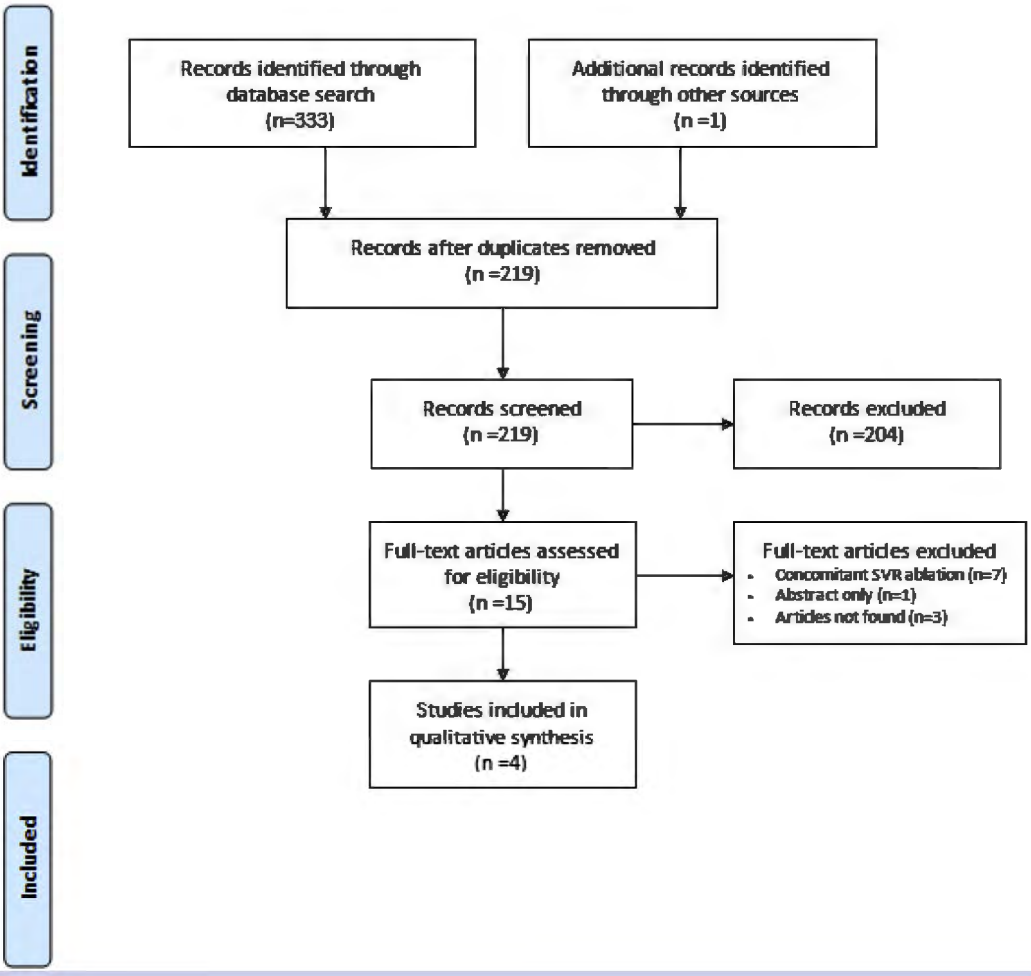


**Fig 2.** Incompetent perforator vein (IPV) ablation. *SVR,* Superficial venous reflux.

### Data extraction and analysis

All articles located with the search strategy were screened by abstract and title by one author (M.L.M). The same author subsequently reviewed the selected full article and discussed and confirmed the selection and exclusion (and the reason) with S.R. and A.J., reaching a consensus. References from selected articles were then searched manually. If only an abstract had been published, the study was excluded.

The following data were extracted in a predesigned table: study design, inclusion/exclusion criteria, diagnostic criteria, age, sample size, etiology and pathophysiology of chronic venous insufficiency, ulcer time before intervention, mean follow-up, intervention, outcomes, and predictive factors.

Risk bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[7] The studies were assessed for key bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Biases were also evaluated at outcome level with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment of evidence.[8]

## RESULTS

### Study selection

**SVR ablation.** The SVR ablation search strategy yielded 1604 articles. Two articles were added from references search. Once duplicates were removed, 1217 articles were reviewed for title and abstract. Fifty-eight articles were selected for full-text reading; of these, 45 were deemed eligible (Fig 1). Studies were divided into four categories according to intervention type: surgical ablation, foam sclerotherapy, endovenous laser ablation therapy (EVLT), and radiofrequency ablation (RFA).

**IPV ablation.** The IPV ablation search strategy yielded 333 articles. After duplicates were removed, 219 articles were reviewed for title and abstract. Fifteen articles were selected for full-text reading; of these, four met the eligibility criteria (Fig 2).

### Study characteristics

**Surgical ablation.** Twenty-seven studies met the inclusion criteria.[9-35] Of these, two were long-term publications of already included RCTs and were not counted as additional articles. Five were RCTs and 20 were case series. Supplementary Table, online only summarizes study characteristics.

**Foam sclerotherapy ablation.** Ten studies met the inclusion criteria.[36-45] One was an RCT and nine were case series. Table I summarizes study characteristics.

**EVLT.** Six studies met the inclusion criteria.[46-51] One was an RCT and five were case series. Table II summarizes study characteristics.

**RFA.** Four studies met the inclusion criteria.[52-55] Three were case series and one was a retrospective cohort study. Table III summarizes study characteristics.

**IPV ablation.** Four studies, all case series, met the inclusion criteria. Table IV summarizes study characteristics.

### Quality assessment of the studies

**SVR ablation.** The general quality of the included studies, mostly case series, was weak. Figs 3 to 6 and Table V summarize the bias assessment. Using the GRADE approach, the quality of evidence was rated moderate for surgical ablation, low for foam sclerotherapy and EVLT, and very low for RFA; this was true for outcomes of both ulcer healing and ulcer recurrence (Table VI).

**IPV ablation.** The overall quality of the studies included was weak. Fig 7 and Table V summarize the bias assessment. Using the GRADE approach, the quality of evidence was rated very low for outcomes of both ulcer healing and ulcer recurrence (Table VI).

### Efficacy

**Surgical ablation. Surgical ablation vs compression.** In RCTs comparing surgical ablation with compression, ulcer healing rates and recurrence were, respectively, 83% to 100% and 9% to 49% in the surgical group and 73% to 96% and 23% to 94% in the compression group.[12,21,25,26,32,34,35] The Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) trial, including 500 patients having either surgical ablation of SVR and compression or compression alone, showed no significant difference in ulcer healing rate between groups ($P = .73$). The trial design did not include surgery alone without compression as a test group. A significantly higher ulcer-free time was seen in the compression/surgery group compared with the compression group ($P = .007$).[25,26] Recurrence rate was significantly lower in the compression/surgery group, and that effect persisted in the long-term (4 years) data of the trial.[26] Subgroup analysis showed that at both 12 months and 4 years, the recurrence rate was significantly lower in the compression/surgery group in patients with isolated SVR or mixed SVR and segmental DVR but not in patients with mixed SVR and total DVR. van Gent et al[34] compared subfascial endoscopic perforator surgery (SEPS) with or without surgical SVR ablation with compression, and no significant difference in ulcer healing rate or recurrence rate was noted between groups. However, these were both secondary outcomes and might not have been adequately powered. Factors identified as negatively affecting ulcer healing rate in both groups included a recurrent ulceration, ulcer duration for >4 months, larger ulcer, concomitant DVR, and history of deep venous thrombosis (DVT). First-time ulcers had significantly lower recurrence rate than recurrent ulcer ($P < .01$). Ulcer-free rate at mean follow-up was not significantly different between groups and, unlike ulcer healing rate, was not affected by the presence of concomitant DVR. However, both recurrent ulceration and a medially located ulceration were factors identified as positively affecting the ulcer-free period in the surgical group compared with the conservative group ($P = .02$). On a longer term follow-up of 97 months, with only 41% of the patients included in the analysis, ulcer-free rate was significantly higher in the surgical group (58.9%) than in the conservative group (39.6%; $P = .007$).[35] Ulcer recurrence rate was also 49% for the surgical group and 94% for the conservative group. Zamboni et al[21] compared Cure Conservatrice et Hémodynamique de L'insuffisance Veineuse en Ambulatoire (CHIVA) technique (saphenous-sparing intervention in which only incompetent tributaries are ligated and varicosities are removed) with compression and showed both significantly higher ulcer healing rate (100% vs 96%; $P < .02$) and lower recurrence rate (9% vs 38%; $P < .05$) in the surgical group.

**Surgical SVR ablation with or without IPV ablation.** Nelzén et al[32] recruited only 75 of the 200 patients originally planned in their RCT and were unable to show any significant difference in terms of ulcer healing rate or recurrence rate for surgical SVR ablation with or without concomitant SEPS.

Other case series examining surgical ablation of SVR with or without IPV ablation reported an ulcer healing rate between 70% and 92%.[10,13,17,23,24,27,28,33] Size of the ulcer was a factor associated with ulcer healing. Smaller ulcers showed higher ulcer healing rate than medium-sized and large ulcers in the case series of Bello et al[13] ($P < .005$). Effect of SVR ablation on IPV was variable in the included studies. Al-Mulhim et al[24] found that 74.5% of IPVs seen preoperatively regained their competence postoperatively; this was associated with a significant diminution in their diameter after SVR ablation ($P < .001$). On the contrary, Nelzén et al[32] found that only 19% of IPVs seen preoperatively in their SVR ablation only group regained their competence postoperatively.

**Table I.** Summary of the included studies—Superficial venous reflux (*SVR*) foam sclerotherapy

| Study | Study design | Inclusion/exclusion | Sample size | Age, years |
|---|---|---|---|---|
| Darvall,[36] 2009 | Prospective consecutive case series | Inclusion<br>○ C6<br>○ SVR<br>Exclusion<br>○ ABI <0.8<br>○ Patient refusing to undergo UGFS | 27 patients<br>28 legs<br>DVR + | Median, 69 (54-79) |
| Pang,[37] 2010 | Consecutive case series | Inclusion<br>○ C5/C6<br>○ SVR<br>Exclusion<br>○ ABI <0.8<br>○ PTS, DVR, or obstruction<br>Dx<br>○ Reflux >0.5 second | 130 patients<br>132 limbs<br>49 C5/83 C6<br>DVR + | Median, 70 (56-76) |
| Figueiredo,[38] 2012 | Prospective case series | Inclusion<br>○ C6<br>Exclusion<br>○ Severe systemic diseases<br>○ Allergy to polidocanol<br>○ DVT<br>○ ABI <0.8 | 35 patients<br>35 limbs | 35-87 |
| Kulkarni,[39] 2013 | Case series | Inclusion<br>○ C5 (healed in the last 6 months) or C6 (>4 weeks)<br>○ SVR<br>Exclusion<br>○ ABI >0.85<br>○ Total DVR | 186 patients<br>200 limbs<br>163 C5/37 C6<br>DVR + Segmental | — |
| Williamsson,[40] 2014 | Case series | Inclusion<br>○ C6<br>○ Compression minimum of 3 months<br>Exclusion<br>○ Allergy<br>○ Tortuous vein<br>○ ABI <0.8<br>○ DVR<br>Dx<br>○ Reflux >0.5 second<br>○ Diameter >3 mm | 31 patients<br>32 limbs<br>DVR − | Median, 77 (39-94) |
| Lloret,[41] 2015 | Prospective consecutive case series | Inclusion<br>○ C6 >4 weeks<br>○ ABI >0.85<br>○ SVR, DVR, or IPV<br>Exclusion<br>○ Unable to give informed consent<br>○ Allergic response to polidocanol<br>○ Unable to walk a minimum of 5 min/h/d<br>Dx<br>○ Reflux >1 second for truncal veins, >0.5 second for IPV | 180 patients<br>DVR + | Median, 65 (25-85) |

*AASV,* Anterior accessory saphenous vein; *ABI,* ankle-brachial index; *CVI,* chronic venous insufficiency; *DVR,* deep venous reflux; *DVT,* deep venous thrombosis; *Dx,* diagnosis; *GSV,* great saphenous vein; *IPV,* incompetent perforator vein; *OR,* odds ratio; *PTS,* post-thrombotic syndrome; *RCT,* randomized controlled trial; *SSV,* small saphenous vein; *UGFS,* ultrasound-guided foam sclerotherapy.

**Table I.** Continued.

| Ulcer duration | Mean follow-up | Intervention | Results | Predictive factors |
|---|---|---|---|---|
| — | | UGFS of GSV and varicose veins | 70% occlusion rate at 12 months<br>Ulcer healing rate<br>○ 96% at 6 months<br>Recurrence rate<br>○ 7.4% at 12 months | — |
| | 16 months (12-32) | UGFS of GSV, SSV, AASV | 92% occlusion rate<br>Ulcer healing 81% at 6 months<br>Recurrence rate at 2 years 4.9% | — |
| 18 years | 56.5 months (4-68) | GSV/SSV ligation and UGFS | 46% occlusion rate<br>Ulcer healing rate 75%<br>Mean ulcer-free time 48.73 months | — |
| — | — | GSV or SSV UGFS | 92.5% occlusion rate<br>Cumulative rate of ulcer healing at 1 year 91.2%<br>Cumulative recurrence rates at 1 year and 4 years were 4.7% and 28.1%, respectively | — |
| — | — | GSV or SSV catheter-directed foam sclerotherapy | 86% occlusion rate at 1 year<br>Total ulcer healing rate 70%<br>Recurrence rate at 1 year 6.5% | Nonhealed ulcer<br>○ Three developed arterial disease with an ABI <0.8<br>○ One had a recanalized GSV<br>○ One had a partly occluded GSV<br>○ One had a recanalized SSV |
| 7 months (1-134) | 30 months (17-40) | UGFS GSV ± perforators | Ulcer healing rate 95.6%<br>Recurrence rates at 1, 2, and 3 years were 8.1%, 14.9%, and 20.8%, respectively | Identified factors of impaired healing<br>○ Chronicity >12 months (OR, 7.69)<br>○ Area >6 $cm^2$ (OR, 4.24)<br>○ Lipodermatosclerosis (OR, 12.22)<br>○ History of three or more previous ulcers (OR, 5.57)<br>○ History of DVT (OR, 6.18)<br>Identified factors associated with higher recurrence rate<br>○ Isolated perforator incompetence<br>○ History of venous surgery ($P = .03$)<br>Larger and more chronic ulcers as well as DVR were associated, but not significantly, with the appearance of recurrences |

**Table I.** Summary of the included studies—Superficial venous reflux (*SVR*) foam sclerotherapy

| Study | Study design | Inclusion/exclusion | Sample size | Age, years |
|---|---|---|---|---|
| Campos,[42] 2015 | RCT | Inclusion<br>○ Primary CVI<br>○ SVR<br>○ GSV diameter of 0.7-1.4<br>○ Active ulcer (maximum 5-cm diameter)<br>○ ABI 0.9-1.3<br>Exclusion<br>○ History or DVT<br>○ DVR<br>○ Superficial thrombosis<br>○ Diabetes<br>○ Thrombophilia<br>○ Pregnancy<br>○ Allergy to polidocanol<br>Dx<br>○ Reflux >0.5 second | 56 patients<br>58 limbs<br>C6 only<br>Group 1: surgery, 29 limbs<br>Group 2: UGFS, 29 limbs | Group 1: 47 ± 10<br>Group 2: 52 ± 5 |
| Garcarek,[43] 2015 | Case series | Inclusion<br>○ C6 related to SVR and IPV<br>○ Failed compression<br>○ Not candidate for surgery<br>Exclusion<br>○ Obstruction of the deep veins or main superficial veins<br>○ Thrombophlebitis<br>○ Following stripping procedure<br>○ Allergy to contrast medium | 35 patients<br>38 limbs<br>Group 1: 17 PTS<br>Group 2: 21 no PTS | Mean, 62 (34-77) |
| Howard,[44] 2016 | Consecutive case series | Inclusion<br>○ Active or recently (within 6 months) healed ulcer<br>○ SVR<br>○ ABI >0.85<br>Exclusion<br>○ Deep venous occlusion<br>Dx<br>○ Reflux >1 second | 92 patients<br>100 limbs<br>86 C5 /14 C6<br>DVR + | Median, 74 (40-90) |
| Grover,[45] 2016 | Retrospective review of prospective database | Inclusion —<br>○ C6 > 4 weeks<br>Exclusion<br>○ Concurrent arterial disease<br>○ Ulcers with alternative etiology | 54 patients<br>57 limbs<br>DVR + | Median, 68 |

Recurrence rate was between 0% and 22%.[10,23,24,28,32,33] The lowest recurrence rate was found in studies with outcome reported at 12 months, and the highest recurrence rate was found in studies with outcome reported after follow-up of up to 6 years.[23,24,33] Magnusson et al[28] identified duration of ulcer disease at the index operation as a factor predicting recurrence both preoperatively and postoperatively ($P = .0000$). Axial reflux ($P = .0033$), high postoperative ambulatory venous pressure ($P = .0095$), and current time since index operation ($P = .0161$) were identified as also predictive of ulcer recurrence. Isolated residual reflux of superficial, deep, or mixed reflux was not found to be significantly associated with ulcer recurrence.

**Conflicting results of IPV ablation with or without surgical SVR ablation.** Comparing modified Linton procedure with SEPS with or without surgical SVR ablation in an RCT, Pierik et al[12] did not show any difference in ulcer healing rate or recurrence rate between the two techniques. The effect of concomitant ablation of SVR with IPV ablation was not reported it that publication. The recruitment was stopped early after an interim analysis that showed significantly more complications in the modified Linton group compared with the SEPS group.

Case series examining the effect of SEPS with or without SVR ablation by means of stripping or ligation reported an ulcer healing rate between 74% and 95% and recurrence rate between 0% and 28%.[9,11,14-16,18-20,22,29-31] Data on the effect of concomitant ablation of SVR with IPV ablation are conflicting in the case series reported here. One registry identified it as a factor predicting ulcer healing.[14] Moreover, Iafrati et al[18] found the absence of concomitant GSV stripping with SEPS to be associated with delayed ulcer

**Table I.** Continued.

| Ulcer duration | Mean follow-up | Intervention | Results | Predictive factors |
|---|---|---|---|---|
| — | 502 ± 220 days | GSV stripping, phlebectomy, perforator ligation vs GSV UGFS | Ulcer healing rate<br>○ 100% group 1<br>○ 91.3% group 2<br>○ ($P = .19$)<br>The mean time to ulcer healing was 37.1 ± 22.1 days in the surgical treatment group and 56.4 ± 39.4 days in the foam sclerotherapy group ($P = .008$)<br>Recurrence rate<br>○ 6.9% group 1<br>○ 4.3% group 2 | — |
| 28 months | — | Fluoroscopy-guided foam sclerotherapy of IPV and proximal GSV | Ulcer healing rate 84%<br>○ Group 1: 76.5%<br>○ Group 2: 90.5%<br>Recurrence rate 26.3%<br>○ Group 1: 35.3%<br>○ Group 2: 19% | New insufficient superficial and perforating veins developed in all 10 patients with ulcer recurrence |
| 5 months (2-36) | Up to 2 years | GSV and tributaries UGFS | Occlusion rate at 2 weeks of 99%, at 1 year of 50%<br>Ulcer healing rate 86% at 1 year<br>Recurrence rates at 1 and 2 years of 2.3% and 5.1% | Despite recanalization rate of 24%, ulcer recurrence rates were low, and recanalization failed to predict recurrence |
| Median, 15 months (5 months-17 years) | 23 months (16-31) | UGFS of GSV, SSV, AASV, four perforators | 90% truncal occlusion at 2.7 months<br>Ulcer healing 88%<br>Recurrence was seen in 8% at 12 months | — |

healing. On the other hand, an added procedure to SEPS was found to have no influence in the case series of Murray et al.[15] Other factors identified as associated with delayed healing or nonhealing of ulcer included persistence of IPV ($P = .004$),[11] ulcer >2 cm in diameter ($P < .05$), post-thrombotic etiology ($P < .05$),[18] previous limb trauma ($P = .011$),[22] and age at the time of the operation.[29] Factors associated with increased recurrence were SSV reflux,[18] age, severe edema,[29] and post-thrombotic etiology.[14,19] Case series were unable to identify concomitant DVR as a factor significantly associated with delayed ulcer healing or recurrence rate. Only one case series reported 33% of active ulcer in patients with residual DVR compared with 13% in patients with only residual SVR after the intervention.[16]

**Foam sclerotherapy for SVR ablation.** One RCT looking at ultrasound-guided foam sclerotherapy (UGFS) vs surgical ablation was included and showed no significant difference between groups in terms of ulcer healing (91% vs 100%; $P = .19$) or ulcer recurrence (7% vs 4%).[42] However, the time required for ulcer healing was shorter in the surgical group than in the UGFS group ($P = .008$).

In the case series included, ulcer healing rate was between 70% and 96%. Occlusion rate was between 46% and 92%.[36-41,43-45] Factors identified as impairing healing were chronicity for >12 months (odds ratio [OR], 7.69), area >6 $cm^2$ (OR, 4.24), lipodermatosclerosis (OR, 1.22), history of more than three previous ulcers (OR, 5.57), and history of DVT (OR, 6.18).[41]

Recurrence rate was between 4% and 28%.[36,37,39-41,43-45] In 2012, Lloret et al[41] identified an isolated perforator

**Table II.** Summary of the included studies—Superficial venous reflux (*SVR*) endovenous laser ablation therapy (*EVLT*)

| Study | Study design | Inclusion/exclusion | Sample size |
|---|---|---|---|
| Viarengo,[46] 2007 | RCT | Inclusion<br>○ C6<br>○ Varicose veins<br>Exclusion<br>○ Previous GSV ablation<br>○ Acute DVT or superficial thrombophlebitis<br>○ Occlusion of the femoral or iliac vein presenting with PTS<br>○ Coagulation disorders<br>○ PAD<br>○ Degenerative systemic diseases<br>○ Pregnancy<br>○ Unable to ambulate | 52 patients<br>Group 1: compression, 25<br>Group 2: EVLT GSV, SSV, 27 |
| Sharif,[47] 2007 | Prospective case series | Inclusion<br>○ C5-C6<br>○ SVR<br>Exclusion<br>○ ABI <0.8<br>○ DVR<br>Dx<br>○ Reflux >0.5 second | 20 patients<br>23 limbs<br>16 C5/7 C6<br>DVR − |
| Rathod,[48] 2010 | Prospective consecutive case series | Inclusion<br>○ Symptomatic varicose veins<br>○ C2-C6<br>Dx<br>○ Reflux >0.5 second<br>○ IPV diameter >4 mm | 72 patients<br>76 limbs<br>6 C5/20 C6 |
| Teo,[49] 2010 | Prospective consecutive case series | Inclusion<br>○ C5-C6<br>Exclusion<br>○ Unable to ambulate<br>○ DVT in the unilateral lower limb<br>○ Women who were pregnant, nursing, or planning to become pregnant | 44 patients<br>44 limbs<br>DVR + |
| Murli,[50] 2013 | Case series | Inclusion<br>○ C5-C6<br>○ SVR<br>Exclusion<br>○ PAD<br>○ Inability to ambulate<br>○ DVT<br>○ Poor health<br>○ Pregnancy<br>○ Torturous GSV | 145 limbs<br>20 C5/125 C6 |
| Shi,[51] 2015 | Retrospective review of a prospectively maintained database | Inclusion<br>○ C2-C6<br>○ SVR and IPV ± DVR<br>Exclusion<br>○ Previous varicose vein surgery<br>○ Vascular malformation<br>○ PTS<br>○ May-Thurner syndrome<br>○ Venous obstructive disease<br>○ ABI <0.9<br>○ SSV reflux<br>○ Nonmedial calf ulcers<br>Dx<br>○ Reflux >0.5 second | 311 patients<br>376 limbs<br>Group 1: 132 patients, 156 limbs; 30 C5/43 C6<br>Group 2: 179 patients, 220 limbs; 57 C5/49 C6 |

*AASV,* Anterior accessory saphenous vein; *ABI,* ankle-brachial index; *DVR,* deep venous reflux; *DVT,* deep venous thrombosis; *Dx,* diagnosis; *GSV,* great saphenous vein; *IPV,* incompetent perforator vein; *PAD,* peripheral arterial disease; *PTS,* post-thrombotic syndrome; *RCT,* randomized controlled trial; *SSV,* small saphenous vein.

**Table II.** Continued.

| Age, years | Ulcer duration | Mean follow-up | Intervention | Results | Predictive factors |
|---|---|---|---|---|---|
| Group 1: mean, 61<br>Group 2: mean, 57 | — | — | Compression vs EVLT and compression | Ulcer healing rate at 12 months<br>○ 36% in group 1<br>○ 81.5% in group 2<br>○ ($P = .0001$)<br>Recurrence rate<br>○ 44% in group 1<br>○ 0% in group 2 | — |
| Mean, 59 (32-76) | 31 months (6-95) | — | GSV EVLT | 90% occlusion rate at 12 months<br>Ulcer healing rate 100% at 12 months<br>Recurrence rate 4.5% at 22 months | One patient had recurrent ulceration attributed to significant calf perforator incompetence along with recanalized GSV |
| 44 | — | — | EVLT of GSV, SSV, AASV ± IPV<br>Mean GSV size 8.8 mm | 98.6% total occlusion 12 months<br>Ulcer healing rate 85% at 12 months | Factor positively affecting the ulcer healing rate: ulcer area $<5$ cm$^2$ vs ulcer area $>5$ cm$^2$ at 1 month ($P = .008$), 6 months ($P = .009$), and 12 months ($P = .009$) |
| Mean, 63 (38-90) | — | 36 months (8-59) | GSV EVLT<br>Mean GSV size 9.9 mm | Cumulative healing rate at 12 months was 97.4%<br>Recurrence rate 11.4% between 14 and 52 months after EVLT | Of the patients with concomitant DVR, 91% demonstrated ulcer healing within 3 months |
| 54 (20-89) | — | — | EVLT GSV or SSV ± IPV | 97.7% occlusion rate<br>Ulcer healing rate 89.8% at 2 years<br>Recurrence rate 10% at 2 years | Recurrence of venous ulcers was not related to the limbs with incomplete obliteration of GSV or SSV |
| Group 1: 61 (41-75)<br>Group 2: 58 (38-79) | — | — | Group 1<br>○ GSV ligation and EVLT<br>○ IPV EVLT<br>Group 2<br>○ GSV ligation and EVLT | Ulcer healing rate at 12 months<br>○ 93% group 1<br>○ 89.8% group 2<br>○ ($P = .584$)<br>Median ulcer healing time<br>○ 1.4 months group 1<br>○ 3.3 months group 2<br>○ ($P = .001$) | — |

**Table III.** Summary of the included studies—Superficial venous reflux (*SVR*) radiofrequency ablation (*RFA*)

| Study | Study design | Inclusion/exclusion | Sample size | Age, years |
|---|---|---|---|---|
| Harlander-Locke,[52] 2012 | Consecutive case series | Inclusion<br>○ No healing venous ulcer after conservative treatment for a minimum of 5 weeks—C6<br>Dx<br>○ GSV or SSV or IPV reflux >1 second and diameter >3 mm<br>○ Large tributary veins with reflux >1 second and diameter >3 mm extending directly into the area of ulceration | 72 patients<br>88 limbs<br>110 VLU<br>DVR +<br>Occlusion + | Mean, 71 (32-40) |
| Harlander-Locke,[53] 2012 | Case series | Inclusion<br>○ Progressive skin changes or malleolar pain after 3 months of compressive therapy—C5<br>Dx<br>○ GSV or SSV or IPV reflux >1 second and diameter >3 mm<br>○ Large tributary veins with reflux >1 second and diameter >3 mm extending directly into the area of ulceration | 21 patients<br>28 procedures<br>DVR +<br>No occlusion | Mean, 73 (45-93) |
| Rueda,[54] 2013 | Retrospective review of a prospectively maintained database | Inclusion<br>○ C5-C6<br>Dx<br>○ Reflux >0.5 second or diameter >3.5 mm | 64 patients<br>26 C5/38 C6<br>DVR + | SEPS: mean, 59 (30-83)<br>RFA: mean, 60 (35-87) |
| Alden,[55] 2013 | Retrospective cohort study | Inclusion<br>○ C6<br>○ At least two visits with adequate data<br>Dx<br>○ Reflux >1 second | 86 patients<br>95 ulcers<br>Group 1: intervention, 48<br>Group 2: compression, 47<br>DVR + in group 2 only | Group 1: mean, 67 (±14)<br>Group 2: mean, 71 years (±13) |

*DVR,* Deep venous reflux; *Dx,* diagnosis; *GSV,* great saphenous vein; *IPV,* incompetent perforator vein; *NS,* not significant; *SEPS,* subfascial endoscopic perforator surgery; *SSV,* small saphenous vein; *VLU,* venous leg ulcer; *UGFS,* ultrasound-guided foam sclerotherapy.

incompetence ($P = .03$) and a previous history of venous surgery ($P = .03$) as factors associated with ulcer recurrence. Larger ulcer, chronic ulcer, and presence of concomitant DVR were associated, but not significantly, with recurrence. Association between recanalization and ulcer recurrence was not significantly shown in any included study. Moreover, Howard et al[44] found that despite their high rate of recanalization (50%), ulcer recurrence was low and recanalization failed to predict recurrence.

**EVLT.** The only RCT included compared compression with EVLT.[46] At 12 months, ulcer healing rate was 82% in the EVLT group compared with 36% in the compression group ($P = .0001$). Recurrence was 44% in the compression group. In case series, with an occlusion rate between 90% and 99%, the ulcer healing rate was between 85% and 100%.[47-51] Rathod et al[48] identified an ulcer area of $<5.2$ cm$^2$ as a positive factor for ulcer healing. Teo et al[49] found a 91% ulcer healing rate in their patients with concomitant untreated DVR. Recurrence rates from 4% to 11% were reported in case series. In their publication examining 145 C5 to C6 limbs, Murli et al[50] found no relation between ulcer recurrence and incomplete obliteration of GSV or SSV.

**RFA.** In examining C6 patients, with a mean follow-up of 12 months, Harlander-Locke et al[53] reported an occlusion rate of 100%, an ulcer healing rate of 76%, and a recurrence rate of 7%. In another of their publications examining C5 patients, they reported an occlusion rate of 96% and a recurrence rate of 5% at 12 and 18 months.[52] Rueda et al[54] reviewed their case series of C5 and C6 patients treated by RFA and compared them with their

**Table III.** Continued.

| Ulcer duration | Mean follow-up | Intervention | Results | Predictive factors |
|---|---|---|---|---|
| 71 months (2-432) | 12 ± 1.25 months | RFA<br>○ SVR ablation first<br>○ IPV ablation if nonhealing at 4 weeks<br>Mean GSV size 7.4 mm | 100% occlusion rate<br>Ulcer healing rate 76.3%<br>Recurrence rate 7.1% | — |
| — | 25 months (18-51) | RFA<br>○ SVR ablation first<br>○ IPV ablation if nonhealing at 3 months<br>Mean GSV size 6.9 mm | 96.4% occlusion rate<br>Ulcer recurrence rates<br>○ 0% at 6 months<br>○ 4.8% at 12 and 18 months | — |
| — | 37 months | SEPS and GSV ablation *or* RFA IPV and RFA GSV Compression | Ulcer healing rate<br>○ 88% SEPS<br>○ 100% RFA IPV<br>○ ($P$ = NS)<br>Ulcer recurrence rate<br>○ 17% SEPS<br>○ 23% RFA IPV<br>○ ($P$ = NS) | — |
| Group 1: mean, 15 weeks<br>Group 2: mean, 12 weeks | — | Compression vs compression and SVR ablation (RFA, stripping, ligation) ± UGFS of IPV a second time | Ulcer healing rate<br>○ Faster in the intervention group compared with compression group (10% vs 4% per week; $P$ = .001)<br>Recurrence rate<br>○ Fewer recurrences at 1-year follow-up in the intervention group compared with the compression group (27.1% vs 48.9 %; $P$ < .015) | Use of intervention was the strongest determinant of healing ($P$ = .003) |

historical cohort of patients treated with surgical ablation. At a mean follow-up of 37 months, ulcer healing rates of surgical ablation and RFA groups were 88% and 100%, respectively ($P$ = NS), and the recurrence rates were 17% and 23% ($P$ = NS). Alden et al,[55] in their retrospective cohort study, reported faster ulcer healing ($P$ = .001) and fewer recurrences (27% vs 49%; $P$ < .015) in the compression/RFA compared with the compression group. Intervention was the strongest determinant of healing ($P$ = .0003).

**IPV ablation alone.** In studies in which IPV ablation was the only intervention performed, healing rates ranged from 59% to 93%. The lowest ulcer healing rates were reported in UGFS studies. Kiguchi et al,[57] using UGFS, obtained an IPV closure rate of 54% and an ulcer healing rate of 59%. The use of warfarin ($P$ = .01) and male gender ($P$ = .03) were factors negatively affecting IPV thrombosis. Masuda et al[59] obtained a 98% IPV closure at the time of treatment and a 68% ulcer healing rate with only one UGFS treatment. In the study of Lawrence et al[58] using RFA, IPV closure rate was 58% after one treatment and 71% after a second treatment. No ulcer healed without at least one perforator being closed, and an ulcer healing rate of 90% was obtained in patients with at least one successful perforator ablation. In the study of Wolters et al[56] using SEPS, no residual IPV was demonstrated at 1 month after surgery. An ulcer healing rate of 93% was reported at 3 months.

Recurrence rate was separately reported in three studies.[56,58,59] The recurrence rates ranged from 4% to 33%. The lowest recurrence rate was reported at the shortest follow-up of 13 months.[58] In their study, Masuda et al[59] reported that the recurrence rate dropped from

**Table IV.** Summary of the included studies—Incompetent perforator vein (*IPV*) ablation

| Study | Study design | Inclusion/exclusion | Sample size | Age, years | Ulcer duration |
|---|---|---|---|---|---|
| Wolters,[56] 1996 | Prospective case series | Inclusion<br>○ C6<br>○ IPV without truncal or collateral varicosity | 27 patients | Median, 58 (36-67) | Mean, 8 ±13 months |
| Kiguchi,[57] 2014 | Retrospective case series | Inclusion<br>○ Persistent ulceration and r efluxing perforators >3.5 mm after saphenous ablation | 62 patients<br>73 VLU<br>Etiology: 36% PTS<br>DVR + | Mean, 57 (22-85) | Mean, 28 months |
| Lawrence,[58] 2001 | Retrospective case series | Inclusion<br>○ Nonhealing VLU of >3 months or after SVR ablation<br>○ No SVR<br>○ PAD not excluded<br>Dx<br>○ Reflux >1 second<br>○ Diameter >3 mm | 45 patients<br>75 VLU<br>31% PTS<br>DVR + | Mean, 74 (35-93) | Mean, 93 months |
| Masuda,[59] 2006 | Case series | Inclusion<br>○ Presence of IPV without axial reflux in the saphenous or deep venous systems<br>○ If axial reflux present, patient not a surgical candidate<br>Exclusion<br>○ Any venous surgery 2 years preceding UGFS<br>Dx<br>○ Reflux >0.5 second | 68 patients<br>80 limbs<br>1 C5/37 C6<br>DVR + | Mean, 62 (31-90) | — |

*DVR*, Deep venous reflux; *Dx*, diagnosis; *NA*, not available; *OR*, odds ratio; *PAD*, peripheral arterial disease; *PTS*, post-thrombotic syndrome; *SEPS*, subfascial endoscopic perforator surgery; *VLUs*, venous leg ulcer; *UGFS*, ultrasound-guided foam sclerotherapy.

33% to 14% after a second UGFS treatment. That same study showed a significant relation between ulcer recurrence and recurrent perforators (OR, 6.2; $P = .014$) and post-thrombotic syndrome (OR, 4.4; $P = .036$). Kiguchi et al[57] reported a recurrence or nonhealing rate of 41%. Increased age ($P = .05$) was identified as a predictor of decreased ulcer recurrence, whereas hypertension ($P = .04$) and increased follow-up time ($P = .02$) were predictors of increased ulcer recurrence. Wolters et al[56] reported a cumulative recurrence-free rate of 77% at 24 months.

Table VII summarizes factors associated with ulcer healing or ulcer recurrence identified in the systematic review of the literature.

## Limitations of techniques in use

**Quantification of reflux.** To explain these variable results, many limitations must be borne in mind and discussed. First, duplex ultrasound is often the only diagnostic tool used in most centers for CVD assessment. The Society for Vascular Surgery guidelines suggest that a reflux duration of 0.5 second or more in the GSV is clinically significant. This qualitative measurement does not provide information as to whether reflux is quantitatively severe. This can be determined by measuring the velocity of reflux, its duration, and the size of the vein.[60,61] None of the studies included in our review defined a diameter criterion for SVR. Raju et al[61] showed that small-caliber saphenous veins, <5.5 mm, were invariably associated with trivial reflux and that their ablation was likely to be ineffective. Navarro et al[62] also showed that the GSV must be larger than 5.5 mm to harbor significant reflux. Consequently, saphenous vein ablation may not be effective because of small size but also because of technical failure in tortuous or very large saphenous veins or because of certain hemodynamic features. Large-caliber saphenous veins may not be easily ablated by thermal techniques, requiring special technical

**Table IV.** Continued.

| Mean follow-up | Intervention | Results | Predictive factors |
|---|---|---|---|
| NA | SEPS | No residual IPV at 1 month<br>Ulcer healing rate 93% at 3 months<br>Cumulative recurrence-free rate of ulcer<br>○ 92% at 3 months<br>○ 77% at 12 months<br>○ 77% at 24 months | — |
| 34 months | UGFS | IPV closure rate 54%<br>Ulcer healing rate at last follow-up 59%<br>Recurrence or nonhealing rate 41%<br>The IPV thrombosis rate was 69% in patients whose ulcers healed vs 38% in patients whose ulcers did not heal ($P < .001$) | Factors negatively predicting thrombosis of IPVs<br>○ Male gender ($P = .03$)<br>○ Warfarin use ($P = .01$)<br>Positive predictor of ulcer healing: complete IPV thrombosis ($P = .02$)<br>Negative predictor of ulcer healing: large initial ulcer area ($P = .08$)<br>Positive predictor of ulcer recurrence: advanced age ($P = .05$)<br>Negative predictors of ulcer recurrence<br>○ Hypertension ($P = .04$)<br>○ Increased follow-up time ($P = .02$) |
| 13 months | RFA | IPV closure rate 58% after first treatment, 71% after second treatment<br>Ulcers healed in patients with successful ablation of at least one perforator in 90%<br>Recurrence rate 4% | Ablation of 1.5 IPV/ulcer was required for healing<br>No ulcer healed without closure of at least one perforator |
| 20 months | UGFS | IPV closure rate 98% at first treatment<br>Ulcer healing rate with only one treatment 67.6%<br>Recurrence rate<br>○ 32.4% dropped to 13.5% after second treatment | A statistically significant relationship was shown<br>○ Between ulcer recurrence and recurrent perforators (OR, 6.2; $P = .014$)<br>○ Between ulcer recurrence and PTS (OR, 4.4; $P = .036$) |

modifications for a successful result.[63] An open saphenous stripping at the outset may be more appropriate in these cases and in others in which saphenous anatomy, such as tortuosity, poses hurdles to percutaneous ablation.

**Calf pump.** SVR has an impact on microcirculatory damage by two basic synergistic mechanisms—shear and venous hypertension. In VLU, venous hypertension is mediated through calf pump abnormalities (poor compliance, capacitance, or ejection fraction). A subnormal ejection volume is assessed by measuring ambulatory venous pressure (AVP) and air plethysmography, techniques that are seldom used even in academic centers today and that were not used in most

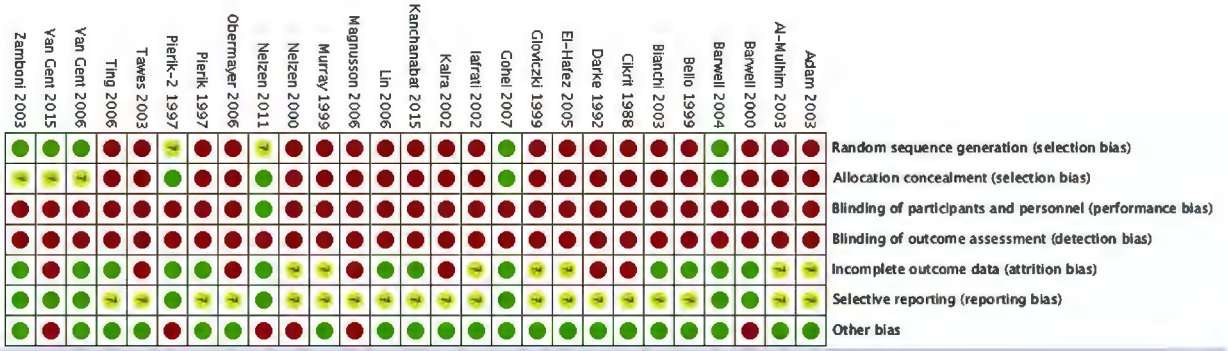


**Fig 3.** Risk of bias summary—surgical ablation; *green* is low risk, *red* is high risk, and *yellow* is unclear risk.

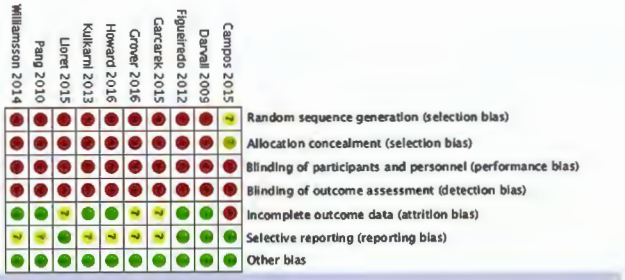


**Fig 4.** Risk of bias summary—foam sclerotherapy; *green* is low risk, *red* is high risk, and *yellow* is unclear risk.

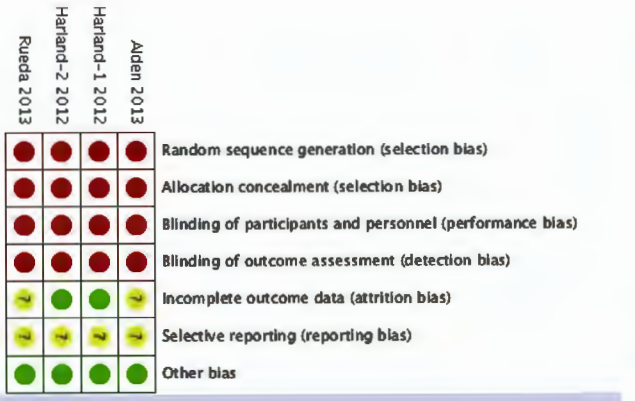


**Fig 6.** Risk of bias summary—radiofrequency ablation (RFA); *green* is low risk, *red* is high risk, and *yellow* is unclear risk.

of the included studies. Calf pump dysfunction in and of itself without saphenous reflux can lead to microvascular hypertension.[61] It is widely present in the CVD population, and such abnormalities often precede the onset of reflux and advanced skin changes.[61,64] Onset of reflux places additional stress on the calf pump. An undamaged calf pump can compensate for the additional load of saphenous reflux. A quantitative reflux of >30 mL has been suggested as a threshold that reflux must overpower to decompensate calf ejection (≈70 mL).[61] This is a useful threshold as even some large saphenous veins may harbor trivial reflux. The calf pump compensates for this reflux by increasing capacitance, compliance, ejection fraction, or a combination; so the ejection fraction appears to be a prime compensatory mechanism and is invariably compromised in advanced CVD.[61,64,65] In a hemodynamic study of saphenous reflux, AVP was maintained at normal levels by calf pump compensatory mechanisms in 12% of 119 limbs despite significant volumetric reflux.[61] Presumably, saphenous ablation would have yielded no clinical benefit in those patients with adequate calf pump compensation for the added reflux, although when calf pump is already significantly damaged, saphenous ablation may also be ineffective. This is particularly true when the saphenous reflux is trivial, the main problem being the calf pump dysfunction.[61,64]

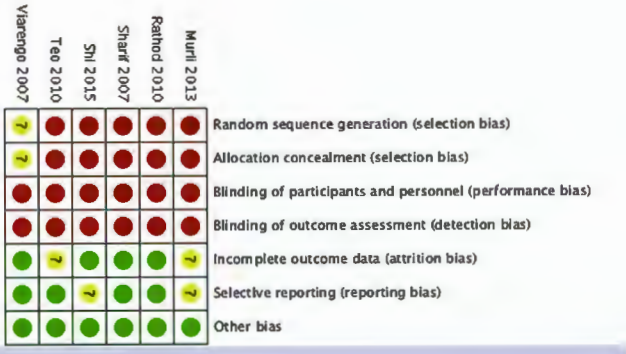


**Fig 5.** Risk of bias summary—endovenous laser ablation therapy (EVLT); *green* is low risk, *red* is high risk, and *yellow* is unclear risk.

**Concomitant DVR.** Moreover, regardless of the presence of superficial and perforator reflux, the presence of deep reflux has been associated with slower healing of venous ulceration.[5,66] Inclusion, exclusion, or even reporting of the presence of patients with concomitant DVR was variable in the studies included in this systematic review. Saphenous ablation may be less effective in ulcer healing and prevention of ulcer recurrence when there is associated DVR.[25,26,67,68] This is because deep reflux, particularly axial reflux (vs segmental reflux), dwarfs superficial reflux in quantity and impact on venous hypertension such that saphenous ablation does not lead to measurable improvement.[69] There have been attempts to differentially measure superficial and deep reflux by occluding the saphenous vein with a tourniquet. Recent work has shown that a tourniquet compresses not only superficial but also deep veins, negating the basic premise of this technique.[70] For the same reason, Perthes test, an old-time tourniquet technique used to detect concomitant deep venous obstruction, is no longer used. Digital compression of the incompetent saphenous vein is more selective but is limited in practical use because it is difficult to make ambulatory pressure or plethysmographic measurements with probe compression. Marston et al[71] have suggested a method of selection of patients for superficial ablation in cases of combined superficial and deep reflux. In 75 limbs (25% C5-C6), significant clinical and hemodynamic (air plethysmography) improvement was noticed when deep reflux had a maximum reflux velocity of 10 cm/s or less. The authors suggested that superficial ablation may be worthwhile when deep reflux is below this threshold, especially when associated DVR is segmental and is confined to the root segment at the origin of SVR (ie, femoral or popliteal in cases of GSV or SSV, respectively). This is in line with the observation of Ting et al,[30] which

**Table V.** Bias assessment

| Bias | Comments |
|---|---|
| SVR ablation—Surgical | |
| Random sequence generation (selection bias) | Two RCTs did not provide enough information on random sequence generation or allocation concealment.[14,34] |
| Allocation concealment (selection bias) | Two RCTs did not provide enough information on random sequence generation or allocation concealment.[23,36,37] |
| Blinding of participants and personnel (performance bias) | Blinding of participants in only one RCT[34] |
| Blinding of outcome assessment (detection bias) | No blinding |
| Incomplete outcome data (attrition bias) | Lost to follow-up from 0% to 28%, seven studies did not comment on lost to follow-up,[16-18,20,25,26,29] and one was unable to quantify lost to follow-up.[22] One case series was only an analysis of a subgroup of 72 of their 213 patients.[12] |
| Selective reporting (reporting bias) | Sixteen studies are retrospective without predefined outcomes. One of the prospective case series did not mention predefined outcomes. |
| Other bias | Two RCTs were significantly underpowered: one stopped recruitment after security interim analysis and the other did not meet the recruitment target.[14,34] Long-term publication of one RCT included only patients who agreed to come for a follow-up visit (volunteering bias), which was 47% of the initial cohort.[37] Two case series relied only on telephone interview (information bias) to assess long-term outcome.[18,30] The control group of a prospective cohort study consisted of patients who refused surgery, which might generate a volunteering bias.[19] |
| SVR ablation—Foam sclerotherapy | |
| Random sequence generation (selection bias) | One RCT included insufficient data on random sequence generation.[44] |
| Allocation concealment (selection bias) | One RCT included insufficient data on allocation concealment. |
| Blinding of participants and personnel (performance bias) | One RCT included no blinding. |
| Blinding of outcome assessment (detection bias) | One RCT included no blinding. |
| Incomplete outcome data (attrition bias) | 4% to 11% of lost to follow-up; three studies did not mention lost to follow-up.[43,45,47] |
| Selective reporting (reporting bias) | Three prospective studies[38,40,43] and one RCT with predefined outcomes,[44] six retrospective studies without predefined outcomes[39,41,42,45,47,46] |
| Other bias | In the only RCT, 21% of the sclerotherapy group did not receive sclerotherapy and were not considered in the analysis. |
| SVR ablation—EVLT | |
| Random sequence generation (selection bias) | One RCT included insufficient data on random sequence generation.[48] |
| Allocation concealment (selection bias) | One RCT included insufficient data on allocation concealment. |
| Blinding of participants and personnel (performance bias) | One RCT included no blinding. |
| Blinding of outcome assessment (detection bias) | One RCT included no blinding. |
| Incomplete outcome data (attrition bias) | 0%-6% lost to follow-up; two studies did not mention lost to follow-up.[51,52] |
| Selective reporting (reporting bias) | Three prospective studies[49-51] and one RCT with predefined outcomes[48] two retrospectives studies without predefined outcomes[52,53] |
| Other bias | — |
| SVR ablation—RFA | |
| Random sequence generation (selection bias) | All the studies were case series. |
| Allocation concealment (selection bias) | All the studies were case series. |
| Blinding of participants and personnel (performance bias) | All the studies were case series. |
| Blinding of outcome assessment (detection bias) | All the studies were case series. |

(Continued on next page)

**Table V.** Continued.

| Bias | Comments |
|---|---|
| Incomplete outcome data (attrition bias) | 0%-6% lost to follow-up; two studies did not mention lost to follow-up.[56,57] |
| Selective reporting (reporting bias) | All were retrospective studies with no predefined outcomes. |
| Other bias | — |
| IPV ablation | |
| Random sequence generation (selection bias) | All the studies were case series; none was consecutive case series. |
| Allocation concealment (selection bias) | All the studies were case series. |
| Blinding of participants and personnel (performance bias) | All the studies were case series. |
| Blinding of outcome assessment (detection bias) | All the studies were case series. |
| Incomplete outcome data (attrition bias) | Insufficient data on lost to follow-up. One case series had 16% of lost to follow-up in the whole group for duplex ultrasound study, but no information on the rate of lost to clinical follow-up in the C5-C6 subgroup was available.[59] |
| Selective reporting (reporting bias) | All the studies were case series with no predefined outcome. One was prospective, but predefined outcomes were not clear.[61] |
| Other bias | — |

*EVLT,* Endovenous laser ablation therapy; *IPV,* incompetent perforator vein; *RCTs,* randomized controlled trials; *RFA,* radiofrequency ablation; *SVR,* superficial venous reflux.

showed that common femoral vein incompetence decreased from 68% to 32% and the proportion of limbs with DVR at more than one site decreased from 42% to 12% at 1 year after ablation of IPV with or without SVR ablation. Saphenous ablation would abolish associated DVR in some patients, presumably by eliminating saphenous reflux load into the deep system. It has been suggested that this leads to less dilation of the deep veins and restoration of valve competence.[72-74] Several reports suggest that ulcer healing or hemodynamic improvement after superficial venous ablations is more likely when the associated deep reflux is segmental and not axial.[23,25,26,69,75] Adam et al[23] reported that 49% of segmental DVR had resolved 3 months after SVR ablation in their case series. It therefore appears reasonable to consider saphenous ablation, provided quantitative reflux in the saphenous vein is significant and the associated DVR is only segmental.

Long-standing dogma teaches that saphenous ablation is contraindicated in the presence of deep venous occlusion to avoid eliminating its collateral role. This notion has proved false in several series showing successful outcome without adverse clinical and hemodynamic sequelae.[76,77]

**Impact of IPV ablation.** For IPV diagnosis, laboratory testing is also usually limited to duplex ultrasound examination. The current guidelines recommend ablation of IPVs located under the bed of an ulcer when they are larger than 3.5 mm and have a reflux duration of >0.5 second.[78] Although useful in avoiding unwarranted interruption of small perforators with trivial reflux, this criterion is qualitative and yields little further functional information. Superficial pressure measurements near the entry point of the incompetent perforator have not been shown to be elevated.[78] Moreover, no hemodynamic improvement has been demonstrated after ligation of IPV. Diminution in shear stress in the adjacent veins could explain clinical improvement. Virtually no study has been done to identify, measure, and assess the effect of shear stress in veins.

SEPS has eliminated the high incidence of wound complications after prior open technique, and it can be performed on an outpatient basis.[12] Questions of specific efficacy remain because it is often carried out in combination with superficial saphenous ablations, thus confounding analysis.[79] Indeed, only one study looking at SEPS as an isolated procedure could be included in that review.[56] Furthermore, GSV ablation alone can reduce the size and number of perforators as reported in the previous section.[80,81]

Meanwhile, minimally invasive techniques to ablate identified perforators selectively have evolved. These techniques include perforator ligation through mini-incisions, laser ablation, or RFA and sclerotherapy. As shown in the included studies, the ulcer healing rate with the local approach appears to vary with the techniques used and the rate of IPV closure obtained. This has been confirmed by Hager et al,[82] who studied the closure rate of 296 local perforator interruption procedures using a variety of modalities in 112 patients. Perforator closure rates were significantly better (73% vs 57%) with radiofrequency than with sclerotherapy. The

**Table VI.** Grading of Recommendations Assessment, Development, and Evaluation (*GRADE*) assessment of the evidence

| Outcomes | Relative effect (95% CI) | No. of events | Quality of evidence (GRADE) | Comments |
|---|---|---|---|---|
| SVR ablation—Surgical | | | | |
| Ulcer healing | Not estimable | 3466 patients or limbs treated | ⊕⊕⊕⊖ Moderate | ○ Five RCTs were without adequate blinding.[14,23,27,28,36,37] Two did not provide enough information on random sequence generation[14,34] and two on allocation concealment.[21,22,24] Two were significantly underpowered: one stopped recruitment after security interim analysis[14] and the other did not meet the recruitment target.[34] Long-term publication of one RCT included only patients who agreed to come for a follow-up visit (volunteering bias), which was 47% of the initial cohort.[37]<br>○ Lost to follow-up from 0% to 28%. Seven studies did not comment on lost to follow-up,[16-18,20,25,26,29] and one was unable to quantify lost to follow-up.[23]<br>○ One case series analyzed only a subgroup of 72 of their 213 patients.[12]<br>○ Two case series relied only on telephone interview to assess long-term outcome, which might generate an information bias.[18,30]<br>○ The control group of a prospective cohort study was formed of patients who refused surgery, which might generate a volunteering bias. Moreover, groups were not compared for all factors that could affect the outcome.[19] |
| Ulcer recurrence | Not estimable | 3319 patients or limbs treated | ⊕⊕⊕⊖ Moderate | |
| SVR ablation—Foam therapy | | | | |
| Ulcer healing | Not estimable | 826 patients treated | ⊕⊕⊖⊖ Low | ○ One RCT included not enough data on random sequence generation and allocation concealment; no blinding; 21% of the sclerotherapy group did not receive sclerotherapy and were not considered in the analysis; small sample size.[44]<br>○ 4% to 11% lost to follow-up; three studies did not comment on follow-up.[43,45,47] |
| Ulcer recurrence | Not estimable | 791 patients treated | ⊕⊕⊖⊖ Low | |
| SVR ablation—EVLT | | | | |
| Ulcer healing | Not estimable | 644 patients or limbs treated | ⊕⊕⊖⊖ Low | ○ Only one RCT with not enough data on random sequence generation and allocation concealment and no blinding[48] |
| Ulcer recurrence | Not estimable | 261 patients or limbs treated | ⊕⊕⊖⊖ Low | |
| SVR ablation—RFA | | | | |
| Ulcer healing | Not estimable | 222 patients treated | ⊕⊖⊖⊖ Very low | ○ No RCT; retrospective case series only<br>○ 0%-6% lost to follow-up; two studies did not mention lost to follow-up[56,57] |
| Ulcer recurrence | Not estimable | 243 patients treated | ⊕⊖⊖⊖ Very low | |
| IPV ablation | | | | |
| Ulcer healing | Not estimable | 202 patients | ⊕⊖⊖⊖ Very low | ○ All studies were case series, none was consecutive.<br>○ Not enough information on lost to follow-up |
| Ulcer recurrence | Not estimable | 140 patients | ⊕⊖⊖⊖ Very low | |

*CI,* Confidence interval; *EVLT,* endovenous laser ablation therapy; *IPV,* incompetent perforator vein; *RCTs,* randomized controlled trials; *RFA,* radiofrequency ablation; *SVR,* superficial venous reflux.

main limitation of sclerotherapy appears to be the need for repeated sessions in some patients for technical success and clinical efficacy. Kiguchi et al[57] then demonstrated in their study the clinical impact of IPV closure rate by showing that a significantly higher rate of IPV thrombosis was present in patients with healed ulcer compared with patients whose ulcers did not heal (69% vs 38%; $P < .001$). Moreover, they identified complete IPV thrombosis as a positive factor for ulcer healing ($P = .02$). Also, recurrence of closed IPV has been associated with ulcer recurrence (OR, 6.2; $P = .014$).[59]

## DISCUSSION

**Study limitations.** A systematic review can be a powerful tool when there is substantial congruity of study


**Fig 7.** Risk of bias summary—incompetent perforator vein (IPV) ablation; *green* is low risk, *red* is high risk, and *yellow* is unclear risk.

population, disease, and methods. CVD is multivarious pathologic processes, and the techniques discussed here are applicable only when specific disease is present. Furthermore, severity metrics is largely qualitative, not quantitative. This limits the usefulness of meta-analysis, which we elected not to do. Whereas risk of bias can be weighted by the Cochrane method, inter-rater agreement of study quality can vary. Instruments such as Jadad and Schulze scores to assess trial quality have not diminished this problem.[83,84] We have chosen to use the Guyatt system to estimate study quality because it can be used in case series and RCTs. Most studies included here were estimated to be medium or low quality.

**Table VII.** Summary of factors associated with ulcer healing or recurrence

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|---|
| Factors associated with delayed ulcer healing |
| Recurrent ulcer[a] |
| Larger ulcer[a] |
| Chronicity of ulcer before intervention[a] |
| Concomitant DVR |
| History of DVT[a] |
| Persistent IPV (conflictual) |
| Age |
| Absence of SVR ablation with IPV ablation (conflictual) |
| Previous limb trauma |
| Lipodermatosclerosis |
| Factors associated with increased recurrence rate |
| Total DVR compared with segmental DVR |
| Recurrent ulcer |
| Chronicity of ulcer before intervention |
| History of DVT |
| Persistently elevated ambulatory venous pressure |
| Untreated SSV reflux |
| Time since intervention |
| Age |
| Severe edema |
| Persistence of axial reflux |
| Isolated perforator incompetence |
| Previous history of surgery |

*DVR,* Deep venous reflux; *DVT,* deep venous thrombosis; *IPV,* incompetent perforator vein; *SSV,* small saphenous vein; *SVR,* superficial venous reflux.
[a]Factors reported both in randomized controlled trials and in case series.

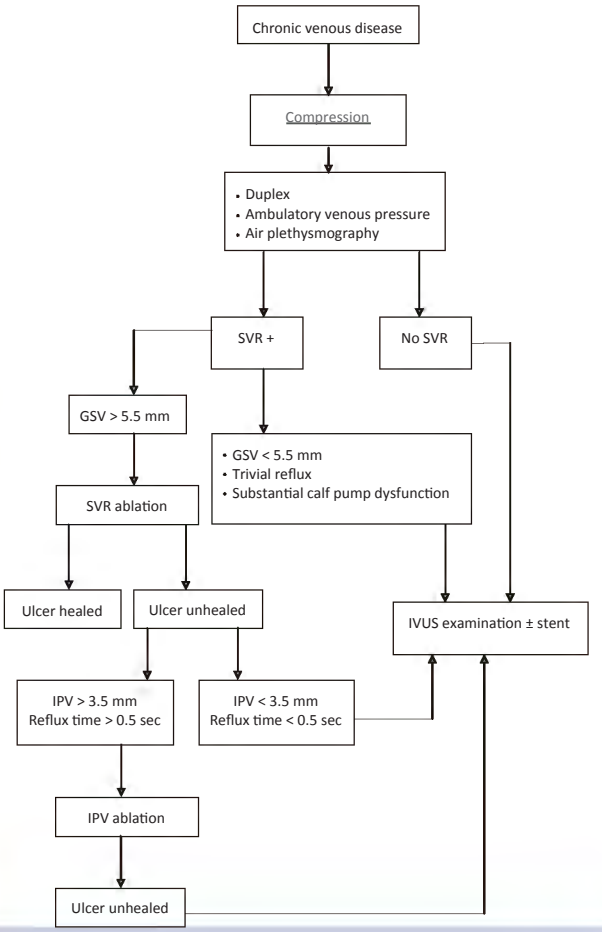


**Fig 8.** Algorithm. *GSV,* Great saphenous vein; *IPV,* incompetent perforator vein; *IVUS,* intravascular ultrasound; *SVR,* superficial venous reflux.

**Recommended approach.** Overall, good sustainable healing rates have been reported with various open or minimally invasive techniques, including saphenous ablation and perforator ablation. Since partial correction of complex multilevel disease can provide substantial and durable ulcer healing, a stepwise approach (Fig 8) to venous disease may be adopted.[85] Because of both procedural ease and lack of deleterious complications, we believe adding saphenous vein ablation to compression in the presence of SVR in VLU patients is an ideal place to start. However, saphenous ablation is

unlikely to be effective in certain subsets, such as when the saphenous vein is small, the reflux is trivial, or there is substantial calf pump dysfunction. Identification of these requires quantification of saphenous reflux and functional tests such as air plethysmography and AVP measurement. Significant leg swelling, pain disproportionate to reflux, presence of deep reflux only, and persistent ulcer despite saphenous ablation are good indicators to pursue intravascular ultrasound and possible iliac vein stents. Local perforator treatment is a salvage procedure in those patients whose ulcers remain recalcitrant despite adequate treatment of superficial reflux and deep obstruction if present. Continuous monitoring in this subset is required, and repeated perforator ablations are often necessary in addition to compliant compression therapy.

## CONCLUSIONS

Compression is the first-line treatment of venous ulcer disease; about 50% will fail to heal or recur because of inefficacy of or inability or unwillingness to use compression. Correction of underlying venous disease in these patients is the next step; it has fundamental appeal on its own as it is specific and not empirical like compression. Currently available minimally invasive techniques correct most venous pathologic processes in CVD with a good sustainable healing rate. Based on our experience, we discussed a stepwise approach. There are, however, diagnostic and treatment efficacy limitations that require proper match of the individual patient with the planned approach.

## AUTHOR CONTRIBUTIONS

Conception and design: MM, AJ, SR
Analysis and interpretation: MM, AJ, SR
Data collection: MM, AJ, SR
Writing the article: MM, AJ, SR
Critical revision of the article: MM, AJ, SR
Final approval of the article: MM, AJ, SR
Statistical analysis: MM, AJ, SR
Obtained funding: MM, AJ, SR
Overall responsibility: SR

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*Additional material for this article may be found online at www.jvsvenous.org.*

## APPENDIX (online only).

**Search strategy.**

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| ("Saphenous vein ablation") OR "superficial venous reflux") OR "ablative superficial venous surgery") OR "Endovenous radiofrequency") OR "Endovenous laser") OR "Endovenous intervention") OR "Endovenous laser ablation") OR "Endovenous radiofrequency ablation") OR "Endovenous ablation") OR "Radiofrequency ablation") OR "Laser ablation") OR EVLT) OR "Endovenous Laser therapy") OR "surgical treatment") OR sclerotherapy) OR "ultrasound guided sclerotherapy") OR "non-thermal non-tumescence ablation") OR "cyanoacrylate glue") OR "mechanochemical ablation") OR MOCA) OR "Great saphenous vein reflux") OR "small saphenous vein reflux") OR "great saphenous vein ablation") AND (((((((("venous leg ulcers") OR venous ulceration) OR "venous ulcer") OR "venous ulcers") OR "ulcer healing"))) AND Humans[Mesh] AND English[lang]) |
| "Perforator ablation") OR "Subfascial endoscopic perforator surgery") OR "incompetent perforating veins") OR "incompetent perforator veins") AND (((((((("venous leg ulcers") OR venous ulceration) OR "venous ulcer") OR "venous ulcers") OR "ulcer healing"))) AND Humans[Mesh] AND English[lang]) |