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The 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part II

Endorsed by the Society of Interventional Radiology and the Society for Vascular Medicine

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ABSTRACT

The Society for Vascular Surgery, the American Venous Forum, and the American Vein and Lymphatic Society recently published Part I of the 2022 clinical practice guidelines on varicose veins. Recommendations were based on the latest scientific evidence researched following an independent systematic review and meta-analysis of five critical issues affecting the management of patients with lower extremity varicose veins, using the patients, interventions, comparators, and outcome system to answer critical questions. Part I discussed the role of duplex ultrasound scanning in the evaluation of varicose veins and treatment of superficial truncal reflux. Part II focuses on evidence supporting the prevention and management of varicose vein patients with compression, on treatment with drugs and nutritional supplements, on evaluation and treatment of varicose tributaries, on superficial venous aneurysms, and on the management of complications of varicose veins and their treatment. All guidelines were based on systematic reviews, and they were graded according to the level of evidence and the strength of recommendations, using the GRADE method. All ungraded Consensus Statements were supported by an extensive literature review and the unanimous agreement of an expert, multidisciplinary panel. Ungraded Good Practice Statements are recommendations that are supported only by indirect evidence. The topic, however, is usually noncontroversial and agreed upon by most stakeholders. The Implementation Remarks contain technical information that supports the implementation of specific recommendations. This

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comprehensive document includes a list of all recommendations (Parts I-II), ungraded consensus statements, implementation remarks, and best practice statements to aid practitioners with appropriate, up-to-date management of patients with lower extremity varicose veins. (J Vasc Surg Venous Lymphat Disord 2024;12:101670.)

Keywords: Ablation; Compression; Cyanoacrylate; Chronic venous disease; Mechanochemical; Endovascular; Endovenous; Foam; Guidelines; Thrombosis; Thrombophlebitis; Venoactive drugs; Laser; Radiofrequency; Sclerotherapy; Saphenous vein; Varicose veins; Venous insufficiency

Summary of recommendations and statements

1. Evaluation of patients with varicose veins			
1.1. Classification and grading of clinical severity of chronic venous disorders			
Good Practice Statements			
1.1.1.	We recommend the use of the 2020 updated clinical stage, etiology, anatomy, pathology (CEAP) classification system for chronic venous disorders. The clinical or basic CEAP classification can be used for clinical practice, and the full CEAP classification system should be used for clinical research.		
1.1.2.	We recommend the use of the revised Venous Clinical Severity Score (VCSS) for patients with chronic venous disorders for grading of clinical severity and for assessment of post treatment outcome.		
1.2-1.5. Doppler ultrasound scanning (DUS)			
Guideline		Grade of Recommendation	Quality of Evidence
1.2.1.	For patients with chronic venous disease of the lower extremities, we recommend DUS as the diagnostic test of choice to evaluate for venous reflux.	1 (strong)	B (moderate)
Implementation remarks			
1.3.1.	Reflux is defined as a minimum value >500 ms of reversed flow in the superficial truncal veins (great saphenous vein [GSV], small saphenous vein [SSV], anterior accessory great saphenous vein [AAGSV], and posterior accessory great saphenous vein [PAGSV]) and in the tibial, deep femoral, and perforating veins. A minimum value of >1 second of reversed flow is diagnostic of reflux in the common femoral, femoral, and popliteal veins. There is no minimum diameter required to have pathologic reflux.		
1.3.2.	Axial reflux of the GSV is defined as uninterrupted retrograde venous flow from the groin to the upper calf. Axial reflux in the SSV is defined as being from the knee to the ankle. Axial reflux in the AAGSV and PAGSV is retrograde flow between two measurements, at least five cm apart. Retrograde flow can occur in the superficial or deep veins, with or without perforating veins. Junctional reflux is limited to the saphenofemoral (SFJ) or saphenopopliteal junction (SPJ). Segmental reflux occurs in only a portion of a superficial or deep truncal vein.		
1.3.3.	A definition of "pathologic" perforating veins in patients with varicose veins (CEAP) clinical class C2 includes those with an outward flow duration of >500 ms and a diameter of >3.5 mm on DUS.		
Good Practice Statements			
1.4.1.	We recommend that evaluation of reflux with DUS be performed in an Intersocietal Accreditation Commission or American College of Radiology accredited vascular laboratory by a credentialed ultrasonographer, with the patient standing whenever possible. A sitting or reverse Trendelenburg position can be used if the patient cannot stand.		
1.4.2.	We recommend that for evaluation of reflux with DUS, the sonographer use either a Valsalva maneuver or augmentation to assess the common femoral vein and SFJ and distal augmentation with either manual compression or cuff deflation for evaluation of more distal segments. Superficial reflux must be traced to its source, including the saphenous junctions, truncal or perforating veins, or pelvic origin varicose veins. The study should be interpreted by a physician trained in venous DUS interpretation.		
1.4.3.	We recommend that a complete DUS examination for venous reflux in the lower extremities include transverse gray scale images without and with transducer compression of the common femoral, proximal, mid, and distal femoral and popliteal veins, SFJ, and at least two segments along the GSV and SSV.		
1.4.4.	We recommend that a complete DUS examination for venous reflux in the lower extremities include measurement of the spectral Doppler waveform using calipers. Reflux at baseline and in response to a Valsalva maneuver or distal augmentation in the common femoral vein and at the SFJ and in response to distal augmentation in the midfemoral and popliteal vein should be documented. Reflux in the GSV at the proximal thigh and knee, in the AAGSV or PAGSV at the SFJ and at the proximal thigh and in the SSV at SPJ and at the proximal calf should be documented.		
1.4.5.	We recommend that a complete DUS examination for venous reflux in the lower extremities include diameter measurements in patients with the leg in the dependent position, from the anterior to the posterior wall, in the GSV 1 cm distal to the SFJ, at the proximal thigh and at the knee, in the AAGSV and PAGSV in the proximal thigh, and in the SSV at the SPJ and the proximal calf. Images of both normal and abnormal findings should be documented in the records of the patient.		

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1. Evaluation of patients with varicose veins		
Consensus statements		
1.5.1. In asymptomatic patients with telangiectasias or reticular veins (CEAP Class C1) DUS evaluation of the lower extremity veins should not be routinely performed, since testing could result in unnecessary saphenous vein ablation procedures.		
1.5.2. In symptomatic CEAP Class C1 patients with bleeding or with severe symptoms of pain or burning due to moderate to severe telangiectasias or reticular veins, DUS evaluation may be performed to exclude associated venous incompetence; however, saphenous ablation for C1 disease without bleeding is rarely required.		
1.5.3. In symptomatic patients with varicose veins (CEAP Class C2) the deep venous system should be routinely evaluated for infrainguinal obstruction or valvular incompetence		
1.5.4. In symptomatic patients with varicose veins (CEAP Class C2) evaluation for iliofemoral venous obstruction with DUS or with other imaging studies should be performed if suprapubic or abdominal wall varicosities are present and in patients with symptoms of proximal obstruction, including thigh and leg fullness, heaviness, swelling and venous claudication. CEAP Classes 3-6 warrant DUS or other imaging studies to evaluate for iliofemoral obstruction.		
1.5.5. In patients with medial thigh or vulvar varicosities evaluation of pelvic venous pathology with DUS or other imaging studies is not indicated if they have no symptoms of pelvic venous disease.		
2. Compression therapy		
2.1 Compression therapy vs. intervention		
Guidelines	Grade of recommendation	Quality of Evidence
2.1.1. For patients with symptomatic varicose veins and axial reflux in the superficial truncal veins, we suggest compression therapy for primary treatment if the patient's ambulatory status and/or underlying medical conditions warrant a conservative approach, or if the patient prefers conservative treatment for either a trial period or definitive management.	2 (weak)	C (low to very low)
2.1.2. For patients with symptomatic varicose veins and axial reflux in the GSV or SSV who are candidates for intervention, we recommend superficial venous intervention over long-term compression stockings.	1 (strong)	B (moderate)
2.1.3. For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, who are candidates for intervention, we suggest superficial venous intervention over long-term compression stockings.	2 (weak)	C (low to very low)
2.1.4. In patients with symptomatic varicose veins who are candidates for endovenous therapy and wish to proceed with treatment, we suggest against a 3-month trial of compression therapy before intervention.	2 (weak)	B (moderate)
2.2 Compression therapy after intervention		
2.2.1. In patients undergoing thermal ablation for saphenous incompetence, with or without concomitant phlebectomy, we suggest postprocedure compression therapy for a minimum of 1 week for pain reduction.	2 (weak)	B (moderate)
3. Pharmacological treatment		
Guidelines	Grade of recommendation	Quality of Evidence
3.1. In symptomatic patients with varicose veins who are not candidates for intervention, or who are waiting for intervention or have symptoms after intervention, we suggest micronized purified flavonoid fraction or Ruscus extracts for treatment of vein related pain, leg heaviness and/or sensation of swelling. [a]	2 (weak)	B (moderate)
3.2. In symptomatic patients with varicose veins who are not candidates for intervention, or who are waiting for intervention or have symptoms after intervention, we suggest hydroxyethylrutosides, calcium dobesilate, horse chestnut extract, red vine leaf extract, or sulodexide for treatment of vein-related pain, leg heaviness, night cramps and/or sensation of swelling.[a]	2 (weak)	C (low to very low)
[a]These products are not approved drugs by the U.S. Food and Drug Administration (FDA). The FDA does not approve medical food or nutritional supplements (https://www.fda.gov/).		
4.1. Endovenous ablation vs high ligation and stripping (HL&S)		
Guidelines	Grade of recommendation	Quality of Evidence
4.1.1. For patients with symptomatic varicose veins and axial reflux in the GSV, who are candidates for intervention, we recommend treatment with endovenous ablation over HL&S of the GSV.	1 (strong)	B (moderate)

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4.1. Endovenous ablation vs high ligation and stripping (HL&S)			
4.1.2.	For patients with symptomatic varicose veins and axial reflux in the SSV, who are candidates for intervention, we recommend treatment with endovenous ablation over ligation and stripping of the SSV.	1 (strong)	C (low to very low)
4.1.3.	For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, who are candidates for intervention, we suggest treatment with endovenous ablation, with additional phlebectomy, if needed, over ligation and stripping of the accessory vein.	2 (weak)	C (low to very low)
4.1.4.	For patients with symptomatic varicose veins and axial reflux in the GSV or SSV, we recommend treatment with HL&S of the saphenous vein if technology or expertise in endovenous ablation is not available or if the venous anatomy precludes endovenous treatment.	1 (strong)	B (moderate)
4.1.5.	For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, we suggest treatment with ligation and stripping of the accessory saphenous vein, with additional phlebectomy, if needed, if technology or expertise in endovenous ablations is not available or if the venous anatomy precludes endovenous treatment.	2 (weak)	C (low to very low)
4.1.6.	For patients with symptomatic varicose veins and axial reflux in the GSV who place a high priority on the long-term outcomes of treatment (quality of life [QOL] and recurrence), we suggest treatment with endovenous laser ablation (EVLA), radiofrequency ablation (RFA), or HL&S over physician-compounded ultrasound-guided foam sclerotherapy (UGFS), because of long-term improvement of QOL and reduced recurrence	2 (weak)	B (moderate)
4.1.7.	For patients with symptomatic varicose veins and axial reflux in the SSV, we suggest treatment with EVLA, RFA, or ligation and stripping from the knee to the upper or midcalf over physician-compounded UGFS because of long-term improvement of QOL and reduced recurrence	2 (weak)	C (low to very low)
4.1.8.	For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV who place a high priority on the long-term outcomes of treatment (QOL and recurrence), we suggest treatment of the refluxing superficial trunk with endovenous laser ablation, RFA, or HL&S, with additional phlebectomy, if needed, over physician-compounded UGFS because of long-term improvement of QOL and reduced recurrence	2 (weak)	C (low to very low)
4.2. Thermal vs nonthermal ablation of superficial truncal veins			
Guidelines		Grade of recommendation	Quality of Evidence
4.2.1.	For patients with symptomatic axial reflux of the GSV, we recommend either thermal or nonthermal ablation from the groin to below the knee, depending on the available expertise of the treating physician and the preference of the patient.	1 (strong)	B (moderate)
4.2.2.	For patients with symptomatic axial reflux of the SSV, we recommend either thermal or nonthermal ablation from the knee to the upper or midcalf, depending on the available expertise of the treating physician and the preference of the patient	1 (strong)	C (low to very low)
4.2.3.	For patients with symptomatic axial reflux of the AAGSV or PAGSV, we suggest either thermal or nonthermal ablation, with additional phlebectomy, if needed, depending on the available expertise of the treating physician and the preference of the patient.	2 (weak)	C (low to very low)
5. Factors affecting choice of superficial truncal ablation and outcome			
Guidelines		Grade of recommendation	Quality of Evidence
5.1.1.	In symptomatic patients with C2 disease we suggest against using truncal vein diameter to determine which patients need venous ablation	2 (weak)	B (moderate)
Consensus statements			
5.2.1.	In asymptomatic patients with C2 disease, prophylactic intervention does not prevent progression of venous disease. Weight control, compression stockings, and avoiding prolonged standing may be beneficial.		
5.2.2.	Interventions to treat varicose veins can be performed in an office-based setting, surgery center, or hospital operating room, at the discretion of the physician, who is specialized in vein care. Better patient experience and lower cost was reported for procedures performed in an office-based setting.		
5.2.3.	In patients with symptomatic C2 disease, isolated SFJ incompetence does not justify ablation of an otherwise competent GSV.		
5.2.4.	In patients with symptomatic C2 disease, ablation of the incompetent GSV may be indicated, even if the axial reflux is not complete and the SFJ is competent. Ablation of isolated refluxing GSV segments, in the presence of competent segments proximally and distally, is rarely indicated. Shared decision-making with the patient is warranted.		

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5. Factors affecting choice of superficial truncal ablation and outcome			
5.2.5.	In patients with reflux in the below-knee GSV, ablation to the lowest point of reflux resulted in better early outcome. Nonthermal techniques are better for ablation of refluxing distal calf saphenous veins, to avoid thermal nerve injury.		
5.2.6.	In patients with an epifascial or superficial saphenous vein, thermal ablation may result in skin burns, hyperpigmentation, or induration, while nonthermal techniques may cause hyperpigmentation or induration. Miniphlebectomy or limited stripping is safe and effective if the saphenous vein is close to the skin (<0.5 cm).		
5.2.7.	For patients with large (>10 mm), nonaneurysmal saphenous veins, thermal ablation with EVLA or RFA should be performed rather than using nonthermal ablation techniques.		
5.2.8.	The incidence of superficial thrombophlebitis has been reported to be similar for thermal and nonthermal ablations.		
5.2.9.	In patients with uncomplicated C2 disease (no venous claudication, thigh swelling, suprapubic or abdominal wall varicosities) due to concurrent superficial incompetence and iliac or iliofemoral venous obstruction, treatment of superficial incompetence first is indicated.		
6. Interventions to preserve the GSV			
Guideline		Grade of recommendation	Quality of Evidence
6.1.1.	For patients with the early stages of symptomatic varicose veins we suggest preserving the GSV using the ambulatory selective variceal ablation under local anesthesia (ASVAL) technique, if performed by a physician who is familiar with the strategy.	2 (weak)	B (moderate)
6.1.2.	For patients with symptomatic varicose veins, we suggest preserving the GSV using the ambulatory conservative hemodynamic correction of venous insufficiency (CHIVA) technique, if performed by physician who is familiar with the strategy.	2 (weak)	B (moderate)
7. Treatment of venous tributaries			
7.1. Telangiectasias and reticular veins			
Guidelines		Grade of recommendation	Quality of Evidence
7.1.1.	For patients with symptomatic telangiectasias and reticular veins, we recommend sclerotherapy with liquid or foam.	1 (strong)	B (moderate)
7.1.2	For patients with symptomatic telangiectasias or reticular veins, we suggest transcutaneous laser treatment if the patient has sclerosant allergy, needle phobia, sclerotherapy ,failure or small veins (<1 mm) with telangiectatic matting.	2 (weak)	B (moderate)
7.2. Varicose tributaries			
Guidelines		Grade of recommendation	Quality of Evidence
7.2.1.	For treatment of symptomatic varicose tributaries, we recommend miniphlebectomy or ultrasound guided sclerotherapy using physician-compounded foam (PCF) or polidocanol endovenous microfoam (PEM).	1 (strong)	B (moderate)
7.2.2.	For treatment of symptomatic varicose tributaries, we suggest transilluminated powered phlebectomy as an alternative treatment for patients with clusters of varicosities by a physician who is trained in the procedure.	2 (weak)	C (low to very low)
Consensus statements			
7.2.3.	For patients with symptomatic varicose tributaries, treatment of the tributaries should be performed, even if the superficial trunks are competent.		
7.2.4.	There is no clinical evidence that FS using room air is less safe and effective than using CO_2 gas mixture.		
7.2.5.	There is currently no clinical study of sclerotherapy with PCF, prepared using the Tessari method, that shows that it is less safe or effective than PEM.		
8. Treatment of varicose tributaries concomitant or staged with superficial truncal ablation			
Guidelines		Grade of recommendation	Quality of Evidence
8.1.1.	For patients with symptomatic reflux in the GSV or SSV and associated varicosities, we recommend ablation of the refluxing venous trunk and concomitant phlebectomy or ultrasound- guided FS of the varicosities with PCF or PEM.	1 (strong)	C (low to very low)
8.1.2.	For patients with symptomatic reflux in the AAGSV or PAGSV, we suggest simultaneous ablation of the refluxing venous trunk and phlebectomy or UGFS of the varicosities with PCF or PEM.	2 (weak)	C (low to very low)

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8. Treatment of varicose tributaries concomitant or staged with superficial truncal ablation			
8.1.3	For patients with symptomatic reflux in the GSV or SSV, we suggest ablation of the refluxing venous trunk and staged phlebectomy or UGFS of the varicosities only if anatomical or medical reasons are present. We suggest shared decision-making with the patient regarding the timing of the procedure.	2 (weak)	C (low to very low)
8.1.4.	For patients with symptomatic reflux in the AAGSV or PAGSV, we suggest ablation of the refluxing venous trunk and staged phlebectomy or UGFS of the varicosities only if anatomical or medical reasons present. We suggest shared decision-making with the patient regarding the timing of the procedure.	2 (weak)	C (low to very low)
Good clinical practice statement			
8.2.	For patients with symptomatic reflux in the major superficial venous trunks and associated varicosities undergoing initial ablation alone, we recommend follow-up for >3 months to assess the need for staged phlebectomy or ultrasound- guided sclerotherapy for persistent or recurrent symptoms. Longer follow-up is recommended for those with recurrence or more advanced CEAP class.		
9. Management of recurrent varicosities			
Consensus statements			
9.1.1.	For patients with symptomatic recurrent varicosities, clinical evaluation and DUS should be performed before treatment to determine the potential source of recurrence.		
9.1.2	For patients with symptomatic recurrent varicosities due to persistent or recurrent reflux of the GSV or AAGSV, treatment either with open surgical or endovascular techniques may be performed, with good outcomes expected.		
9.1.3.	For patients with symptomatic recurrent varicosities due to persistent or recurrent reflux at the groin, either EVLA or RFA can be used if there is a straight GSV stump, long enough for thermal ablation. Sclerotherapy or phlebectomy should be performed for recurrence due to neovascularization.		
9.1.4.	For patients with symptomatic recurrent varicosities due to persistent or recurrent reflux of the SSV, UGFS should be performed.		
9.1.5.	For patients with residual or recurrent varicosities due to incompetent perforator veins, treatment with both open and endovascular techniques may be used depending on the physician's experience, patient choice and availability of technology.		
10. Ablation of incompetent perforating veins			
Guidelines		Grade of recommendation	Quality of Evidence
10.1.1.	For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the GSV or SSV, we recommend against treatment of incompetent perforating veins concomitant with initial ablation of the saphenous veins.	1 (strong)	C (low to very low)
10.1.2.	For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the AAGSV or PAGSV, we suggest against treatment of incompetent perforating veins concomitant with initial ablation of the superficial truncal veins.	2 (weak)	C (low to very low)
Consensus statement			
10.2.	For patients with incompetent pathologic perforators associated with symptomatic residual, recurrent, and rarely primary varicosities, without associated saphenous incompetence, either open or endovascular techniques can be used to treat the perforator veins.		
11. Management of ablation-related thrombus extension (ARTE) and deep vein thrombosis (DVT) after endovenous ablations			
11.1. Postprocedure duplex ultrasound scanning (DUS)			
Guideline		Grade of recommendation	Quality of Evidence
11.1.1.	In an average-risk patient who is asymptomatic following thermal ablation of the saphenous vein, we recommend against routine early postprocedural DUS to detect ARTE (ARTE, formerly known as endovenous heat-induced thrombosis [EHIT]) or DVT.	1 (strong)	B (moderate)
Consensus statement			
11.1.2.	In an average-risk patients who is asymptomatic following nonthermal ablation of the saphenous vein, routine early postprocedural DUS may be performed to detect ARTE or DVT.		

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11. Management of ablation-related thrombus extension (ARTE) and deep vein thrombosis (DVT) after endovenous ablations		
11.1.3. In a high-risk patient who is asymptomatic following thermal or nonthermal saphenous ablation early DUS to exclude ARTE or DVT should be performed.		
Guideline	Grade of recommendation	Quality of Evidence
11.1.4. In patients who are symptomatic following thermal or nonthermal ablation, we recommend early DUS to exclude ARTE or DVT.	1 (strong)	A (high)
11.2. Pharmacological thromboprophylaxis		
Guideline	Grade of recommendation	Quality of Evidence
11.2.1. For high-risk patients undergoing endovenous ablation we suggest pharmacological thromboprophylaxis.	2 (weak)	C (low to very low)
Consensus statement		
11.2.2. For patients undergoing endovenous ablation routine risk stratification should be performed to assess the need for periprocedural thromboprophylaxis.		
11.3. Treatment of varicose vein procedure related DVT and ARTE		
Guideline[b]	Grade of recommendation	Quality of Evidence
11.3.1. For patients with acute isolated distal DVT after varicose vein procedure, without symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks.	2 (weak)	B (moderate)
11.3.2. For patients with isolated distal DVT after varicose vein procedure and symptoms or risk factors for extension we suggest anticoagulation.	2 (weak)	C (low to very low)
11.3.3. For patients with acute proximal DVT after varicose vein procedure, we recommend anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist).	1 (strong)	B (moderate)
11.3.4. For patients with symptomatic ARTE after endovenous ablation, we recommend anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist).	1 (strong)	C (low to very low)
[b]We endorsed the recommendations of Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021; 160(6):e545-e608. The evidence base for these guidelines was adopted without review.		
Consensus statements		
11.4.1. For patients with asymptomatic ARTE III and IV after endovenous ablation, anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist) should be performed.		
11.4.2. For patients who receive anticoagulation for ARTE following endovenous ablation, treatment should be continued until the thrombus retracts.		
12. Management of superficial vein thrombosis (SVT)		
Guideline 12. addresses the management of SVT in patients who have not recently undergone superficial venous interventions. The management of ARTE and other thrombotic complications of superficial venous interventions are addressed in Guideline 11.		
Guidelines	Grade of recommendation	Quality of Evidence
12.1.1. For patients with SVT of the main saphenous trunks and tributaries above the knee >3 cm from the SFJ and >5 cm in length, whether associated with varicose veins or not, we recommend fondaparinux 2.5 mg subcutaneously daily for 45 days. Alternatively, rivaroxaban 10 mg/d for 45 days may be appropriate for patients unwilling or unable to perform subcutaneous injections.	1 (strong)	A (high)
Consensus statement		
12.1.2. For patients with SVT of the main saphenous trunks ≤3 cm from the SFJ, treatment with full anticoagulation for a minimum of 6 weeks should be continued.		
Guidelines	Grade of recommendation	Quality of Evidence
12.1.3. For patients with SVT of the main saphenous trunks we recommend against using prophylactic or therapeutic dose low-molecular weight heparin and nonsteroid anti-inflammatory drugs (NSAIDs). Although both have been found to reduce SVT pain and extension, they have failed to prevent venous thromboembolism (VTE). If NSAIDs are used for treatment of short segment distal SVT, surveillance with DUS for VTE extension is recommended due to the high prevalence of concomitant DVT.	1 (strong)	A (high)

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12. Management of superficial vein thrombosis (SVT)			
12.1.4.	For selected patients with isolated thrombosis of varicose tributaries or limited involvement of the GSV, we suggest phlebectomy as a safe alternative.	2 (weak)	B (moderate)
Consensus statement			
12.1.5.	In patients with saphenous thrombophlebitis, ablation should be performed once the inflammation has resolved if there is evidence of pathologic reflux on DUS.		
13. Management of bleeding varicose veins			
Consensus statements			
13.1.	For patients presenting with acute bleeding from varicose veins, leg elevation, direct compression, and sclerotherapy should be attempted before suture ligation to control bleeding.		
13.2.	For patients with bleeding due to varicose veins, prompt referral to a venous specialist should be done.		
13.3.	For patients who presented with bleeding from varicose veins, after the bleeding has been controlled, evaluation for superficial venous incompetence and appropriate intervention on the responsible veins should be done to control venous hypertension and reduce the risk of recurrent hemorrhage.		
13.4.	Patients with varicose veins or venous ulcerations should be counseled on the possibility of venous bleeding and their families, caregivers, or friends educated regarding leg elevation and simple compression techniques to control severe bleeding.		
14. Management of superficial vein aneurysms			
Consensus statements			
14.1.	For patients with superficial truncal vein aneurysm, located within 3 cm of the SFJ or SPJ, open surgical excision, with high proximal and distal ligations should be performed. If symptomatic saphenous reflux is present, endovenous or open surgical ablation (phlebectomy or limited stripping) of the distal saphenous vein should be performed.		
14.2.	For patients with an asymptomatic superficial truncal vein aneurysm, located >3 cm distal to the SFJ, endovenous ablation alone should be performed. Thromboprophylaxis in these patients reduces the risk of VTE.		
14.3.	Patients with symptomatic, thrombosed or large (>3 cm) aneurysms in the superficial veins are best treated with surgical excision.		

DISCLAIMER

The Society for Vascular Surgery (SVS) develops evidenced-based clinical practice guidelines as a resource to assist members in the practice of vascular surgery. The guideline recommendations contained herein are based on a recent review of published evidence. They reflect the available body of evidence, and their applicability reflects the limitations of that data and are subject to reassessment and revision as new knowledge emerges. Given these limitations, clinical practice guidelines do not represent a statement of the standard of care, nor do they substitute for clinician judgment or supplant patient preference or shared decision-making. The Society of Vascular Surgery recognizes that departure from guidelines may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the clinical presentation of the patient, limitations of available resources, advances in knowledge or technology, or patient preference. The reader must rely solely on their own judgment to determine what practices and procedures, whether included in this practice guideline or not, are appropriate for them, their patient, their institution, or their practice.

INTRODUCTION

Varicose veins of the lower extremities are among the most frequent medical conditions affecting millions of people worldwide.[1-3] Chronic venous disease (CVD) may cause minimal symptoms, but varicose veins may often also be the source of discomfort, pain, swelling, thrombosis, bleeding, and ulcerations, causing disability and a negative impact on physical, psychological, and social functioning components of quality of life (QOL).[4] Patients with chronic venous insufficiency (CVI) may progress to phlebolymphedema, skin changes with chronic inflammation, and venous leg ulcerations.[5,6]

The Society for Vascular Surgery (SVS), the American Venous Forum (AVF), and the American Vein and Lymphatic Society have collaborated to update the 2011 SVS/AVF guidelines on CVD,[7] and recently published Part I of the 2022 clinical practice guidelines for the

management of varicose veins of the lower extremities.[8] All recommendations in Part I were based on a new, independent systematic review and meta-analysis[9] that provided the latest scientific evidence to support updated or completely new guidelines on evaluation with duplex scanning and on the management of superficial truncal reflux in patients with varicose veins. The writing committee recognized, however, that several additional important clinical issues need to be addressed, but many have varying levels of scientific evidence.[10-41] When a systematic review was not available, the writing committee based ungraded statements on a comprehensive review of the literature, combined with unanimous consensus of the expert panel.

Part II of the guidelines focuses on the rationale and scientific evidence for prevention and management of varicose veins with compression, medications, and nutritional supplements, as well as on evaluation and treatment of varicose tributaries, factors affecting treatment outcomes, the management of superficial vein thrombosis (SVT), thrombotic complications of varicose vein treatments, thrombus extension following ablation, management of bleeding varicose veins and the treatment of superficial vein aneurysms. This comprehensive document provides a list of all recommendations (Parts I-II), as well as consensus and best practice statements to aid practitioners with up-to-date, appropriate management of patients with symptomatic lower extremity varicose veins (Clinical stage, Etiology, Anatomy, Pathology [CEAP] Class C2 disease). Updates of other, previously published society guidelines[5,7,42,43] will address the management of venous ulcers, associated with varicose veins (C5-C6 disease), evaluation and treatment of deep vein obstructions and chronic pelvic venous disorders.

METHODS

A multisociety and multispecialty writing group that included 20 members authored both Part I and Part II of these varicose vein guidelines. The methods of writing Part I of the guidelines was described previously.[8] For Part II, the writing committee conducted a survey and held several meetings to compose a list of important clinical topics, not addressed in Part I, that are intended to guide comprehensive, up-to-date prevention and management of varicose veins and associated complications. A final list of 80 questions were divided into five sections, with each assigned to a writing group. The members of the groups performed an extensive search, up to January 31, 2023, of the English-language literature on their relevant topic, using the Ovid MEDLINE, Ovid Embase, PubMed, Scopus, Web of Science, Cochrane Library, and Ovid Cochrane Database of Systematic Reviews databases. Systematic reviews, meta-analyses, randomized controlled trials (RCTs), and prospective and retrospective observational studies that included >10 patients with varicose veins were used. Drafts of the writing groups were discussed on Zoom meetings, and all recommendations and statements were unanimously approved by the writing committee. All clinical practice guidelines in Part II were based on evidence established with one or several systematic reviews, with or without meta-analysis, using the GRADE method,[44-46] as described in detail in Part I of the guidelines.[8] We used the standard nomenclature of "we recommend" and "we suggest" to describe strong and weak recommendations, respectively.

To make these guidelines comprehensive and practical for clinicians, we developed three other types of ungraded statements, in addition to formal graded recommendations. *Good Practice Statements* are recommendations that are supported by indirect evidence that cannot be easily synthesized, yet the topic is usually noncontroversial and agreed upon by most stakeholders.[8] *Implementation Remarks* contain technical information that supports the implementation of specific recommendations.[47] *Ungraded Consensus Statements* refer to evaluation or treatment as a unanimous consensus of the expert panel, based on their own comprehensive review of the literature, even though some of the topics had minimal or low-quality evidence.

RECOMMENDATIONS AND STATEMENTS

1. Evaluation of patients with varicose veins

1.1. Classification and grading of clinical severity of chronic venous disorders.

1.1.1. We recommend the use of the 2020 updated CEAP classification system for chronic venous disorders. The clinical or basic CEAP classification can be used for clinical practice, and the full CEAP classification system should be used for clinical research.

Good Practice Statement

Rationale and evidence. The CEAP classification was designed at a consensus meeting of international experts in 1994,[48] it was updated in 2004,[49] and most recently in 2020.[50] The classification is based on clinical signs, etiology, anatomy and pathology (reflux and obstruction) of chronic venous disorders. The basic or clinical CEAP classification reports the single highest C class, and the advanced CEAP reports all C classes present in the limb. Patients with reticular veins (subdermal veins between 1 and <3 mm in diameter) and telangiectasias (subdermal spider veins, <1 mm in size) belong to Class C1. Varicose veins are dilated subcutaneous tributaries ≥3 mm in diameter and patients with varicose veins belong to CEAP Class C2. CVD is defined as CEAP Class C2 to C6, CVI includes limbs with CEAP Class 3 to 6.[49-52] The term CVI is reserved for advanced CVD with functional abnormalities of the venous system producing edema, skin changes, or venous leg ulcers.[51] Each clinical class has a subscript indicating the presence or absence of symptoms (s or a). Symptoms of varicose veins may include pain, burning, cramping, feeling of limb heaviness or swelling, restless leg or itching. The most important of these have been identified as HASTI symptoms and include heaviness in the legs, achiness, swelling, throbbing, and itching.[53,54] CEAP is

a descriptive instrument designed to categorize the affected limb and not a quantitative severity scale, scoring system, or an outcome measure that reflects changes over time. For a table of the updated CEAP classification please see Part I of the Guidelines.[8]

1.1.2. We recommend the use of the revised Venous Clinical Severity Score (VCSS) for patients with chronic venous disorders for grading of clinical severity and for assessment of post treatment outcome.

Good Practice Statement

Rationale and evidence. The revised VCSS is a physician-derived evaluative instrument that is useful to describe the severity of chronic venous disorders. VCSS is responsive to changes over time and is suitable to document response to treatment. VCSS, together with the CEAP classification, has been widely adopted in North American[5,7] and international[55-59] venous guidelines. The instrument comprises nine categories, each graded on a scale of 0 to 3. The categories include pain, varicose veins, edema, pigmentation, inflammation, induration, presence and size of ulcers, and use of compression therapy (Table I). VCSS has been validated and there is correlation between VCSS, CEAP, the modified Chronic Venous Insufficiency Questionnaire (CIVIQ) patient-reported outcome instrument and venous duplex findings.[60,61] The strongest correlation occurred in pain ($r = 0.55$; $P < .0001$). A good correlation was also found in the ability of VCSS and the Villalta-Prandoni scale to detect mild to moderate post-thrombotic CVD (gamma statistic = 0.71-0.98; $P < .05$).[62]

1.2-1.5. Evaluation with duplex ultrasound scanning.

1.2.1. For patients with CVD of the lower extremities, we recommend duplex ultrasound scanning (DUS) as the diagnostic test of choice to evaluate for venous reflux.

GUIDELINE. Grade of recommendation: 1 (strong), Quality of Evidence: B (Moderate)

For Rationale and Evidence, please see Part I of the varicose vein guidelines.[8]

Implementation remarks.

1.3.1. Reflux is defined as a minimum value of >500 ms of reversed flow in the superficial truncal veins (great saphenous vein [GSV], small saphenous vein [SSV], anterior accessory GSV [AAGSV], posterior accessory GSV [PAGSV]) and in the tibial, deep femoral, and perforating veins. A minimum value of >1 second of reversed flow is diagnostic of reflux in the common femoral, femoral, and popliteal veins. There is no minimum diameter required to have pathologic reflux.

1.3.2. Axial reflux of the GSV is defined as uninterrupted retrograde venous flow from the groin to the upper calf. Axial reflux in the SSV is defined as being from the knee to the ankle. Axial reflux in the AAGSV and PAGSV is retrograde flow between two measurements, ≥5 cm apart. Retrograde flow can occur in the superficial or deep veins, with or without perforating veins. Junctional reflux is limited to the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ). Segmental reflux occurs in only a portion of a superficial or deep truncal vein.

1.3.3. A definition of "pathologic" perforating veins in patients with varicose veins (CEAP clinical class C2 includes those with an outward flow duration of >500 ms and a diameter of >3.5 mm on DUS.

For Rationale and Evidence supporting the Implementation Remarks 1.3.1 to 1.1.3, please see Part I of the varicose vein guidelines.[8]

Good Practice Statements.

1.4.1. We recommend that evaluation of reflux with DUS be performed in an Intersocietal Accreditation Commission or American College of Radiology accredited vascular laboratory by a credentialed ultrasonographer, with the patient standing whenever possible. A sitting or reverse Trendelenburg position can be used if the patient cannot stand.

1.4.2. We recommend that, for evaluation of reflux with DUS, the sonographer use either a Valsalva maneuver or distal augmentation to assess the common femoral vein and SFJ, and distal augmentation should be used with either manual compression or cuff deflation for evaluation of more distal segments. Superficial reflux must be traced to its source, including the saphenous junction, truncal or perforating veins, or pelvic origin varicose veins. The study should be interpreted by a physician trained in venous DUS interpretation.

1.4.3. We recommend that a complete DUS examination for venous reflux in the lower extremities includes transverse grayscale images without and with transducer compression of the common femoral vein, proximal, mid, and distal femoral veins, popliteal veins, the SFJ, and at least two segments along the GSV and SSV.

1.4.4. We recommend that a complete DUS examination for venous reflux in the lower extremities includes measurement of the spectral Doppler waveform using calipers. Reflux at baseline and in response to Valsalva or distal augmentation in the common femoral vein and at the SFJ should be documented. Reflux in response to distal augmentation in the midfemoral and popliteal veins, GSV at the proximal thigh and knee, and in the AAGSV and SSV at the SPJ or proximal calf should also be documented.

1.4.5. We recommend that a complete DUS examination for venous reflux in the lower extremities includes diameter measurements with the patient's leg in the dependent position, from the anterior to posterior wall, at the SFJ, in the GSV 1 cm distal to the SFJ, at the proximal thigh and knee, in the AAGSV, and in the SSV at the SPJ or proximal calf. Images of both normal and abnormal findings should be documented in the patient's records.

For Rationale and Evidence supporting Good Practice Statements 1.4.1 to 1.4.5, please see Part I of the varicose vein guidelines.[8]

Table I. Revised Venous Clinical Severity Score (VCSS)

Characteristics	None: 0	Mild: 1	Moderate: 2	Severe: 3
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin	None: 0	Occasional pain or other discomfort (ie, not restricting regular daily activity)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)
Varicose veins: "Varicose" veins must be ≥3 mm in diameter to qualify	None: 0	Mild: 1 Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Moderate: 2 Confined to calf or thigh	Severe: 3 Involves calf and thigh
Venous edema: Presumes venous origin	None: 0	Mild: 1 Limited to foot and ankle area	Moderate: 2 Extends above ankle but below knee	Severe: 3 Extends to knee and above
Skin pigmentation: Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation owing to other chronic diseases (ie, vasculitis purpura)	None: 0 None or focal	Mild: 1 Limited to perimalleolar area	Moderate: 2 Diffuse over lower one-third of the calf	Severe: 3 Wider distribution above lower third of calf
Inflammation: More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)	None: 0	Mild: 1 Limited to perimalleolar area	Moderate: 2 Diffuse over lower one-third of calf	Severe: 3 Wider distribution above lower one-third of calf
Induration: Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis); includes white atrophy and lipodermatosclerosis	None: 0	Mild: 1 Limited to perimalleolar area	Moderate: 2 Diffuse over lower one-third of calf	Severe: 3 Wider distribution above lower one-third of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 Months	>3 Months but <1 year	Not healed for >1 year
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of compression therapy	0: Not used	1: Intermittent use of stockings	2: Wears stockings most days	3: Full compliance: stockings

From Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, Meissner MH, Rutherford RB; American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg. 2010 Nov; 52(5):1387-96. AVF Document, with permission.

Consensus statements.

1.5.1. In asymptomatic patients with telangiectasias or reticular veins (CEAP Class C1), DUS evaluation of the lower extremity veins should not be performed routinely because testing could result in unnecessary saphenous vein ablation procedures.

Rationale. Asymptomatic CEAP Class C1 venous disorder is usually a cosmetic problem; asymptomatic telangiectasias or reticular veins should not be treated for the purpose of preventing progression to more advanced venous disease. Saphenous vein ablation is not indicated in these patients for medical reasons. The GSV may need to be used in the future

as a conduit for bypass in coronary or leg arteries; therefore, it should be preserved whenever possible. Thus, DUS evaluation of the venous system should not be performed.

Evidence. There is no scientific evidence that complications of venous disorders can be prevented by treatment of asymptomatic telangiectasias or reticular veins. Because the GSV can be used as a conduit for bypass in coronary or leg arteries, it should be preserved whenever possible. The SVS published the "Choosing Wisely" initiative, which suggests that routine venous ultrasound testing in asymptomatic C1 patients should not be performed and that it could result in unnecessary saphenous vein ablation procedures.[63] Ruckley et al[64] found a significant but weak association between advanced telangiectasias, located at the medial thigh and GSV incompetence.

1.5.2. In symptomatic CEAP Class C1 patients with bleeding or with severe symptoms of pain or burning due to moderate to severe telangiectasias or reticular veins, DUS evaluation may be performed to exclude associated venous incompetence; however, saphenous ablation for C1 disease without bleeding is rarely required.

Rationale. DUS examination is only indicated in patients with complicated C1 disorder. The most severe complication is bleeding, but in rare cases, pain and burning due to telangiectasias or reticular veins are also indications for DUS to evaluate and treat associated superficial venous incompetence. Patients with mild symptoms and certainly those with cosmetic telangiectasias with intermittent itching or other mild symptoms do not need Duplex evaluation that could ultimately lead to unnecessary ablation of superficial truncal veins.

Evidence. Studies by Ruckly et al[64] suggest that there are some patients with symptomatic advanced C1 disorder, with telangiectasias and reticular veins located medially along the GSV, who are candidates for saphenous ablation. Evaluation with DUS is recommended by several groups before sclerotherapy in patients with symptomatic telangiectasias and reticular veins.[56,65,66] Engelhorn et al[67] examined 269 limbs of women with telangiectasias (CEAP C1 class). GSV reflux was detected in 44%, but it was segmental in 73% and only 4% had SFJ reflux. The authors propose further research on the management of the GSV in these patients. Interestingly, in this study 78% of the limbs with C1 disease were symptomatic. Somjen et al[65] recommended that incompetent reticular veins, present in 80% to 90% of these cases, should also be treated together with sclerotherapy of the telangiectasias. However, these larger reticular veins (1-3 mm) are always located above the superficial fascia, so they can be well-seen with magnification, or easily detected during the ultrasound guided liquid or FS. This study, therefore, does not support routine preprocedure DUS for patients with C1 disorder.

1.5.3. In symptomatic patients with varicose veins (CEAP Class C2), the deep venous system should be routinely evaluated for infrainguinal obstruction or valvular incompetence.

Rationale. Deep venous pathology, including reflux and obstruction, may affect outcomes and complications following interventions for superficial venous incompetence. Evaluation of the deep system in C2 patients with symptomatic CVD, therefore, is recommended.[8,68]

Evidence. Among 4881 patients who underwent endovenous ablation for superficial truncal vein in the Vascular Quality Initiative database, 2254 patients (46.2%) had combined deep and superficial reflux (Table II). After a median follow-up of 336 days, symptoms improved in both groups and improvement in VCSS score was greater in patients with deep vein reflux. These patients, however, had substantially higher rates of complications (10.4% vs 3.0%; $P < .001$), including paresthesia (2.5% vs 0.7%; $P < .001$), skin pigmentation (1.2% vs 0.4%; $P = .023$), superficial phlebitis (2.0% vs 0.9%; $P = .018$), wound infection (0.8% vs 0.2%; $P = .040$), and proximal thrombus extension (3.1% vs 1.1%; $P < .001$). After controlling for confounding factors, the estimate of effect size for any complication had an odd ratio (OR) of 5.72 ($P < .001$).[74] Gianesini et al[75] retrospectively analyzed long-term results of the CHIVA procedure in 381 patients and found an increased risk of GSV reflux recurrence among those patients who initially had refluxing common femoral veins.[75] Other investigators found that ablation of superficial reflux may restore segmental competence of the deep veins[76] and that clinical outcome is excellent after superficial ablation, despite the presence of deep venous reflux.[60,71] In one study, those with persistent symptoms after superficial vein ablation had femoral or popliteal vein reflux velocities of >10 cm/second.[60]

Data on infrainguinal deep vein obstruction and interventions on superficial veins are sparse because many vascular specialists avoid superficial truncal ablation in patients with extensive post-thrombotic deep vein obstruction. There is a very low level of evidence that saphenous ablation can be performed in patients with femoropopliteal venous occlusion.[77] It is important to remember that, in severely symptomatic patients with infrainguinal obstruction, the GSV may be used for deep vein reconstruction.[78] Occasionally, reconstruction of the femoral vein is needed after superficial truncal ablation in patients, who have congenital absence or severe hypoplasia of the deep veins.[79]

In a systematic review of superficial venous reflux in patients with deep venous obstruction, Benfor and Peden[25] suggested that superficial ablation can be performed in patients with deep vein occlusions, but noted that the evidence to support this recommendation was weak. Most patients in this review had suprainguinal/iliofemoral obstruction and most had advanced CVD. In a series of 29 patients with a history of previous deep vein thrombosis (DVT) Puggioni et al[80] did not find an increased incidence of thrombotic complications after RFA.

1.5.4. In symptomatic patients with varicose veins (CEAP Class C2), evaluation for iliofemoral venous

obstruction with DUS or with other imaging studies should be performed if suprapubic or abdominal wall varicosities are present and in patients with symptoms of proximal obstruction, including thigh and leg fullness, heaviness, swelling and venous claudication. CEAP Classes 3 through 6 warrant DUS or other imaging studies to evaluate for iliofemoral obstruction.

Rationale. Varicose veins can be associated with primary or secondary iliofemoral venous obstruction. Although many C2 patients with simple varicose veins need no evaluation for proximal venous obstruction, those who have more advanced symptoms or signs (C3-C6) due to iliofemoral disease need further investigation and appropriate treatment.

Evidence. In a recent systematic review of 944 limbs with previous DVT or current deep vein obstruction, most patients had iliofemoral venous disease and advanced CEAP class (C4-C6).[25] These patients had better results when vein ablation was combined with treatment of iliac vein obstruction. It should be noted, however, that few C2 patients were included in the review leaving this issue unexplored and unresolved. In the case of iliofemoral venous obstruction, interventions on the superficial venous system should not impair venous return from the limb. For this reason, in patients with symptoms of proximal outflow obstruction, like venous claudication, thigh swelling and pain, or in those with suprapubic or abdominal wall varicosities, or with continuous flow and lack of respiratory variations in the common femoral vein on DUS, investigation of the iliac veins is warranted. During ablation of the incompetent superficial veins, collaterals to the suprapubic and abdominal wall veins should be preserved.

1.5.5. In patients with medial thigh or vulvar varicosities, evaluation of pelvic venous pathology with DUS or other imaging studies is not indicated if they have no symptoms of pelvic venous disease.

Rationale. There is an association between pelvic venous insufficiency and medial thigh and vulvar varicosities, and lower extremity varicosities are often more severe in patients with associated pelvic varicose veins.[81] Although ovarian vein embolization in patients with pelvic venous disorders may be helpful for lower extremity varicosities, embolization in patients with varicose vein without chronic pelvic pain has not been studied. In contrast, direct treatment of pelvic origin lower extremity, vulvar, or perineal varicose veins without ovarian vein embolization can be effective and durable.[82]

Evidence. Nonsaphenous, pelvic origin varicose veins occur in women in the medial and posterior thigh, vulva, and inguinal area.[83] They are the result of reflux from the internal iliac vein through the inguinal, obturator, perineal and gluteal escape points.[42] Vulvar varicosities are estimated to occur in 22% to 34% of women with varicose veins of the pelvis and in 18% to 22% of pregnant women.[82]

Seventy-two symptomatic patients with pelvic source varicose veins, however, only 7% had chronic pelvic pain.[84] In a systematic review of 13 studies on ovarian vein embolization in 866 women, technical success was 99.8%; significant improvement of pelvic pain was reported in nine studies.[85] In one study, lower extremity varicosities recurred only in 13% at 5 years after embolization.[85] Hartung et al[86] reported 51% improvement in lower extremity varicosity following ovarian vein embolization in 119 women, who had both pelvic symptoms and lower extremity varicose veins. In another study of 43 patients, Castenmiller et al[87] showed improvement after ovarian vein embolization in the lower extremity varicose veins in 14%, but the success rate was 88% for treatment of vulvar varicose veins.

Gavrilov reported good clinical results with direct treatment of vulvar varicosities with FS and phlebectomy.[82] In 32 patients with asymptomatic pelvic varicose veins, phlebectomy alone for vulvar varices resulted in no recurrence at 3 to 8 years after the procedure. Sclerotherapy was effective at 1 year in 10 of 12 patients.[82] Current consensus of experts supports the strategy of direct treatment of pelvic origin varicose veins in patients with asymptomatic pelvic reflux using liquid or FS, phlebectomy, or pelvic escape points ligation, without the need for pelvic vein embolization.[56,82,83]

2. Compression therapy

2.1. Compression therapy vs intervention.

2.1.1. For patients with symptomatic varicose veins and axial reflux in the superficial truncal veins, we suggest compression therapy for primary treatment if the patient's ambulatory status or underlying medical conditions warrant a conservative approach or, if the patient prefers conservative treatment, for either a trial period or definitive management.

GUIDELINE. Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

Rationale. In patients with varicose veins, compression therapy has been used for decades to decrease pain and swelling. Graduated elastic compression stockings oppose tissue expansion when muscles contract. It can narrow the superficial veins diameter and therefore decrease the venous reflux and venous hypertension, key elements in the pathophysiology of CVD.

Evidence. The clinical benefit of compression stockings for the initial treatment of varicose veins has been studied in a recent Cochrane review of 13 trials, encompassing >1000 patients[88] (Table III). Compression stockings were compared with no stockings or placebo stockings.[88] Four RCTs showed improvement in symptoms, but they were subject to bias. Three of the four studies reported side effects of discomfort, appearance, and application difficulty. The benefits of stockings were offset by highly variable reports of compliance, presumably due to the most common side effects of itching and irritation.

Table II. Outcome of superficial truncal ablation in patients with deep vein reflux

First author, year	Patients/limbs	Intervention	Comparison	Outcomes	Study design
Sales, 1996[69]	17 patients (C2-C6)	HL&S phlebectomy, perforator vein ligation	None	94% (16/17) resolution of DVR at a mean of 62 days (range, 4-278 days)	Retrospective review
Puggioni, 2003[70]	33/38 (C1-C6)	HL&S or RFA, perforator ligation, sclerotherapy	None	24% (9/38) had complete resolution, 32% (19/59 segments) had segmental resolution of DVR	Retrospective review
Knipp, 2008[71]	364/460 (C1-C6)	EVLA ± phlebectomy ± perforator ligation (311 limbs with DVR)	EVLA ± phlebectomy ± perforator ligation (132 limbs without DVR)	Improvement (VCSS) was independent of DVR. DVR had no effect on EHIT, thrombophlebitis, paresthesias, saphenous occlusion rates or bruising	Retrospective review
Kim, 2017[72]	100/139	RFA ± stab avulsions ± perforator ligation (43 limbs with DVR)	RFA ± stab avulsions ± perforator ligation (96 limbs without DVR)	DVR improved (all) or resolved (30.2%) with superficial venous ablation. DVR did not impact symptom/QOL improvement after superficial venous ablation	Retrospective review
Nishibe, 2020[73]	154/223 (C2 disease)	RFA, 74 limbs (33.2%) with DVR	RFA 80 limbs without DVR	DVR was reduced to 29 limbs (13%, $P <$ .01) by RFA. Deep vein diameters were also reduced.	Retrospective review
Brown, 2021[74]	4881 patients (C2-C6)	RFA or EVLA 2254 patients (46.2%) with DVR	RFA or EVLA 2627 patients (53.8%) without DVR	No difference in symptom improvement between groups. Greater improvement in VCSS score in patients with DVR. These patients also had increased rate of complications, particularly in proximal thrombus extension (3.1% vs 1.1%; $P <$ .001)	Retrospective review of the Vascular Quality Initiative registry

DVR, Deep vein reflux; *EHIT*, endothermal heat induced thrombosis; *EVLA*, endovenous laser ablation; *HL&S*, high ligation and stripping; *QOL*, quality of life; *RFA*, radiofrequency ablation; *VCSS*, Venous Clinical Severity Score.

Graduated compression stockings are classified according to the pressure applied at the level of the ankle: Class 1, low-pressure stockings exert an ankle pressure <20 mm Hg; Class 2, moderate compression is between 20 and 30 mm Hg; and Class 3 stocking are high compression stockings with ankle pressures of >30 mm Hg.[89] When comparing against different levels of compression and lengths of stockings, there was no clear difference in this Cochrane review.[88] Patient preference for one stocking over another was largely driven by comfort. None of the studies assessed QOL. Overall, there was insufficient high quality of evidence to determine whether compression stockings are effective as the primary treatment for symptomatic varicose veins and if

Table III. Evidence to support compression stockings for patients with varicose veins

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Knight Nee Shingler, 2021[88]	Adults with varicose veins (CEAP 2)	Compression therapy	No compression therapy	Insufficient high-certainty evidence to determine if compression stockings are effective as the sole treatment of varicose veins, or if any type of stocking is superior to any other type.	Cochrane review, English language RCTs	Age, sex, stocking type, outcomes

CEAP, Clinical stage, etiology, anatomy, pathology; *RCT*, randomized controlled trial.

one stocking is better than the other.[88] Real-world data suggest that compliance with compression stockings can be as low as 37%.[90] For additional evidence, see Part I of the Guidelines.[8]

2.1.2. For patients with symptomatic varicose veins and axial reflux in the GSV or SSV who are candidates for intervention, we recommend superficial venous intervention over long-term compression stockings.

GUIDELINE. Grade of recommendation: 1 (strong), Quality of Evidence: B (moderate)

2.1.3. For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV who are candidates for intervention, we suggest superficial venous intervention over long-term compression stockings.

GUIDELINE. Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

For Rationale and Evidence for Guidelines 2.1.2. to 2.1.3, see Part I of the varicose vein guidelines.[8]

2.1.4. In patients with symptomatic varicose veins who are candidates for endovenous therapy and wish to proceed with treatment, we suggest against a 3-month trial of compression therapy prior intervention.

GUIDELINE. Grade of recommendation: 2 (weak), Quality of Evidence: B (moderate)

Rationale. There is no rationale for a 3-month trial of compression therapy before intervention for patients with CEAP C2 class symptomatic varicose veins who are candidates for endovenous therapy and wish to proceed. Evidence for efficacy of compression therapy in these patients is less than for efficacy of endovenous ablation (Table IV).

Evidence. Insurance companies and the Centers for Medicare and Medicaid Services frequently require a 3-month trial of compression stockings before intervention for patients with C2 disease, despite a lack of evidence for efficacy.[90] In a UK-based cost analysis,[91] accounting for clinical recurrences and need for further treatment, analysis included cost of procedure and subsequent procedures and quality-adjusted life-years. Across all measures, compression therapy was found to be inferior to minimally invasive endovenous therapies (including ultrasound-guided FS [UGFS] and endovenous thermal ablation).[91] Although the cost effectiveness was calculated for the UK, sensitivity analysis suggests that the conclusions are robust to substantial changes in relative cost, and pertinent to other global healthcare markets.

As an example, the REACTIV Trial, in which a subgroup of patients with severe varicosities were randomized to surgical therapy (HL&S, phlebectomy) compared with compression therapy.[92] Consistently, surgical therapy produced better results with regards to anatomical disease extent, patient satisfaction, QOL, and cost effectiveness.[92]

2.2. Compression therapy after intervention.

2.2.1. In patients undergoing thermal ablation for saphenous incompetence, with or without concomitant phlebectomy, we suggest postprocedure compression therapy for a minimum of 1 week for pain reduction.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: B (Moderate)

Rationale. Compression therapy has been used to reduce postoperative bleeding, bruising, edema, and pain after thermal ablation of superficial venous trunks.[93] The type of compression therapy prescribed following treatment of varicose veins is widely variable and driven by institutional-, physician-, and insurer-level preferences. Most commonly, postprocedural compression therapy is delivered with gradient elastic compression stockings or elastic bandages. The presence of a pressure gradient, with the strongest compression at the level of the ankle and lightest at the top provides the most favorable hemodynamic profile for reducing limb edema. Stockings are constructed in various lengths, such as knee high or thigh high, with variable levels of compression. Compression levels range from I to III, with I representing the lowest level of compression and III the highest. Similarly, elastic stockings vary in compressive properties based on the length and type of bandage used.

Evidence. The use of compression therapy after ablation of superficial truncal veins is controversial.[94] In a

Table IV. Benefits of compression therapy for varicose veins before intervention

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Marsden, 2015[91]	Adults with varicose veins (CEAP2)	Compression therapy 3 months before thermal or nonthermal ablation, or surgical stripping	No compression therapy in the months preceding thermal or nonthermal ablation, or surgical stripping.	Interventional treatment is cost-effective, thermal ablation is the most cost-effective.	Economic analysis and meta-analysis of English language RCTs,	Age, sex, concomitant phlebectomy or sclerotherapy
Michael, 2006[92]	Adults with varicose veins (CEAP2)	Surgical treatment (HL&S) and phlebectomy	Compression therapy	Standard surgical treatment is more effective and more cost-effective than compression alone.	English language RCT, observational trial	Age, sex, concomitant phlebectomy or sclerotherapy

CEAP, Clinical stage, etiology, anatomy, pathology; *HL&S*, high ligation and stripping; *RCT*, randomized controlled trial.

meta-analysis including six RCTs with patients Class C2 or higher, those treated with compression had less pain within the first 10 days postoperatively, and earlier return to daily activities.[13] No differences were noted in bruising score, VCSS, QOL, complications, or vein occlusion rate. A subgroup analysis of a meta-analysis, encompassing 1147 patients, suggested that the greatest benefits in pain reduction were in patients undergoing endovenous laser ablation (EVLA), with no benefit seen after RFA.[26] This finding is consistent with other studies demonstrating greater pain with EVLA compared with RFA.[95,96] An RCT by Bootun et al[97] demonstrated a clear benefit of compression leading to significantly better pain scores for the first 5 days after endothermal ablation of saphenous veins. Compression was effective in reducing early pain also in patients who underwent concurrent phlebectomies (Table V).

The duration of therapy has been studied in the context of short-term (24-48 hours), mid-term (1-2 weeks), and long-term (3-6 weeks) therapy. A meta-analysis of 775 patients undergoing endothermal ablation found a difference in postoperative pain at 1 week but not at later time points in patients undergoing 1-2 weeks of compression compared with those with 24 to 48 hours.[99] Long-term therapy has been shown to have equivalent outcomes to midterm therapy.[98] Therefore, application of compression for 1 week after any endothermal treatment, especially those with concurrent phlebectomy may be useful for pain reduction. In the recently published multicenter society guidelines, a compression dressing of >20 mm Hg (corresponding with class II compression stocking pressure) with eccentric pads over the ablation point is recommended for patients undergoing vein ablation for greatest reduction in postoperative pain.[100]

3. Drugs and nutritional supplements

3.1. In symptomatic patients with varicose veins, who are not candidates for intervention, who are waiting for intervention or have symptoms after intervention, we suggest micronized purified flavonoid fraction (MPFF) or Ruscus extracts for treatment of vein related pain, leg heaviness and/or sensation of swelling.*
GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: B (Moderate)

3.2. In symptomatic patients with varicose veins, who are not candidates for intervention, who are waiting for intervention or have symptoms after intervention, we suggest hydroxyethylrutosides or calcium dobesilate or horse chestnut extract or red vine leaf extract or sulodexide for treatment of vein-related pain, leg heaviness, night cramps, and/or sensation of swelling.*
GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (Low to very low)

*These products are not approved drugs by the US Food and Drug Administration. The US Food and Drug Administration does not approve medical food or nutritional supplements (https://www.fda.gov/).

Rationale. Venoactive drugs (VADs), also called phlebotropics or phlebotonics, have shown varying benefits in patients with chronic venous disorders. VADs have been largely prescribed in Europe and other parts of the world,[101] but recently they have gained interest in the United States, where they are available now, mainly as nutritional supplements.[102,103] The most frequently used VADs include MPFF, diosmin, Ruscus extracts, hydroxyethylrutosides, calcium dobesilate, horse chestnut extract/escin, and red vine leaf extract. Sulodexide does not belong to the VAD family, but it has been used for CVD (Table VI). Pentoxifylline is a vasoactive agent that has been beneficial in patients with claudication

Table V. Benefit of compression therapy after endovenous ablation for varicose veins

First author, year	Patient	Intervention/exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Huang, 2013[98]	Adults with varicose veins (C2)	Surgery with compression therapy post procedure	Surgery without compression therapy post procedure	No additional benefit of the long duration (3-6 weeks) over short-duration (3-10 days) compression after surgery	Systematic review and meta-analysis of RCTs	Age, sex, concomitant phlebectomy or sclerotherapy
Ayo, 2017[94]	Adults with varicose veins (C2)	Thermal ablation EVLT or RFA) with compression therapy 7 days post procedure	Thermal ablation (EVLT or RFA) without compression therapy 7 days post procedure	No significant differences between groups in VCSS, reduction in pain (VAS); bruising score; improvement in QOL (CIVIQ); GSV closure	RCT	Age, sex, concomitant phlebectomy or sclerotherapy
Chou, 2019[99]	Adults with varicose veins (C2)	Thermal ablation (EVLT or RFA) with compression therapy post procedure	Thermal ablation (EVLT or RFA) without compression therapy post procedure	Compression therapy following thermal ablations for 1-2 weeks is better than for 24-48 hours in terms of postoperative pain at 1 week and recovery	Systematic review and meta-analysis of RCTs	Age, sex, concomitant phlebectomy or sclerotherapy
Bootun, 2021[97]	Adults with varicose veins (C2)	Thermal ablation (EVLT or RFA) with compression therapy post procedure	Thermal ablation (EVLT or RFA) without compression therapy post procedure	Median pain score in the compression group (7 days) was significantly lower on days 2-5, compared with the no compression group; no difference in clinical score, time to return to normal activities, and ecchymosis	RCT (COMETA Trial)	Age, sex, concomitant phlebectomy or sclerotherapy
Ma, 2022[13]	Adults with varicose veins (C2) undergoing	Thermal ablation (EVLT or RFA) with compression therapy post procedure	Thermal ablation (EVLT or RFA) without compression therapy post procedure	Postoperative compression reduced the mean pain score in the first 10 days and the time to return to normal activities. No difference for other outcomes	Systematic review and meta-analysis of RCTs	Age, sex, concomitant phlebectomy or sclerotherapy
Hu, 2022[26]	Adults with varicose veins (C2)	Thermal ablation (EVLT or RFA) with compression therapy post procedure	Thermal ablation (EVLT or RFA) without compression therapy post procedure	Lower postoperative pain scores with compression. No difference for QOL, vein occlusion rate or time to return to work	A systematic review and meta-analysis of RCTs	Age, sex, concomitant phlebectomy or sclerotherapy

CIVIQ, Chronic Venous Insufficiency Questionnaire; *EVLT,* endovenous laser therapy; *GSV,* great saphenous vein; *QOL,* quality of life; *RFA,* radiofrequency ablation; *VAS,* visual analog scale.

and venous ulcers but it has not been studied in patients with C2 varicose veins.

Evidence. The efficacy and safety of VADs was extensively studied in patients with CVD in double-blind, placebo-controlled, randomized trials and meta-analyses. There have been two Cochrane reviews, the most recent in 2020, that included a systematic review and meta-analysis of 7690 patients, enrolled in 56 studies.[104,105] The VAD used included rutosides, hidrosmine and diosmin, calcium dobesilate, Centella asiatica, aminaftone, French maritime pine bark extract, and grape seed extract. Diosmin is only one component of MPFF, and MPFF studies were analyzed together with non-micronized diosmin trials. Most studies included patients with varicose veins (C2), but also with more advanced CVI, like venous edema (C3), skin changes (C4-C5), venous ulcers (C6). Pooled data analysis of VADs was given, although the document also includes breakdown of the different effect of individual products as well. The number of patients included in many studies was low and the

Table VI. Summary of the pharmacologic properties of venoactive drugs (*VADs*) used for chronic venous disorders[a]

VADs	Pharmacologic properties							
	Venous tone	Vein wall and valve	Capillary leakage	Lymphatic drainage	Hemorheological disorders	Antioxidant properties	Inflammatory reaction	Endothelial function
MPFF	+	+	+	+	+	+	+	+
Ruscus extracts	+	+	+	+	+		+	
Hydroxyethylrutosides	+		+	+	+	+	+	
Calcium dobesilate	+		+	+	+	+		
Horse chestnut extract/escin	+		+			+		+
Red vine leaf extract			+			+		
Sulodexide							+	+

MPFF, Micronized purified flavonoid fraction.
[a]Adapted from Nicolaides A, Kakkos S, Baekgaard N, Comerota A, de Maeseneer M, Eklof B, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol. 2018; 37(3):181-254.[57]

follow-up was short. The review found moderate-certainty evidence that phlebotonics in patients with CVI probably reduced edema in the lower legs, compared with placebo (risk ratio [RR] 0.70; 95% confidence interval [CI] 0.63-0.78; 13 studies; 1245 participants); and probably reduced ankle circumference (MD, −4.27 mm; 95% CI, −5.61 to −2.93 mm; 15 studies; 2010 participants). Moderate-certainty evidence showed that phlebotonics probably make little or no difference in QOL compared with placebo (standard mean difference [SMD], −0.06; 95% CI, −0.22 to 0.10; five studies; 1639 participants); and low-certainty of evidence suggested that they may have little or no effect on ulcer healing (RR, 0.94; 95% CI, 0.79-1.13; six studies; 461 participants). There was low certainty of evidence that phlebotonics may reduce pain, measured as a continuous variable,

Table VII. Clinical benefit of micronized purified flavonoid fraction (*MPFF*)

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Kakkos SK, 2018[14]	Adults with CVD including CEAP C2	MPFF	Placebo	Subjective symptoms, edema assessed by ankle circumference, and/or leg or foot volume. Other objective outcomes: leg redness, skin changes, and clinical improvement assessed by the physician. QOL assessed by CIVIQ-20 MPFF was highly effective in improving leg symptoms, edema and QOL	Systematic review and meta-analysis of 7 double-blind, randomized, placebo-controlled trials	Age, sex, different stages of CVD in patients with varicose veins
Allaert FA, 2012[112]	Adults with lower extremity venous edema	MPFF, hydroxyethylrutosides, ruscus extracts, and diosmin	Placebo or other VAD	Reduction of ankle edema. The meta-analysis supports assigning Grade A evidence to MPFF in the management of symptoms and edema.	Systematic review and meta-analysis of 10 double-blind, randomized, placebo or other VAD-controlled trials	Age, sex, different stages of CVD in patients with varicose veins
Pompilio G, 2021[15]	Adults with chronic venous disease	MPFF, sulodexide, hydroxyethyl rutosides, calcium dobesilate, ruscus extracts, horse chestnut extracts, and pentoxifylline	Placebo in 45 RCTs	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score). MPFF was the most effective treatment in reducing lower leg volume, CIVIQ-20 score and pain VAS scale.	Systematic review and meta-analysis of 45 RCTs and separated analysis of 17 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *CVD*, chronic venous disease; *QOL*, quality of life; *RCT*, randomized controlled trial; *VAD*, venoactive drug; *VAS*, visual analog scale.

compared with placebo (SMD, −0.35; 95% CI, −0.54 to −0.17; 12 studies; 2232 participants). Thirty-seven studies reported on adverse events; the most frequent were gastrointestinal symptoms. Findings for specific groups of VADs were limited due to small study numbers in some studies and the heterogeneous results. The authors downgraded certainty in the evidence from high to moderate because of risk of bias concerns, and further to low because of imprecision. It is clear from this review and multiple other meta-analyses,[14-16,112] however, that some of these drugs or supplements are better than the others.

The clinical benefits of two compounds, MPFF and Ruscus extracts, have been studied more extensively in double-blind, placebo-controlled RCTs and meta-analyses and they are discussed in more detail here. For evidence of clinical efficacy of other VADs, including hydroxyethylrutosides, calcium dobesilate, horse chestnut extract, red vine leaf extract and sulodexide for treatment of CVD, see Appendix I. Most studies with these products have short (3-6 months) follow-ups; therefore, long-term efficacy and possible side effects of long-term treatment have not been formally assessed.

Clinical benefit of MPFF.

Rationale. MPFF is composed of 90% diosmin and 10% hesperidin fraction (hesperidin, diosmetin, linarin, and isorhoifolin). Its beneficial effects in patients with symptomatic varicose veins are related to the effect on venous tone, microcirculation, trophic disorders, edema, inflammation, leukocyte adhesion, and activation.[101] Pharmaceutic formulations that increase intestinal absorption as micronized form, including the MPFF represent an innovation and improvement of the therapeutic efficacy.

Evidence. MPFF has shown several effects beneficial for patients with varicose veins and CVD. Among them are an increase of the venous tone, potentiation of the venous response to norepinephrine,[106] and antioxidant and anti-inflammatory properties.[107,108] Leukocytes adhesion molecules inhibition was confirmed in patients with CEAP Class C2 to C4, in parallel to the improvement of leg heaviness scores.[109] Transient venous reflux was reduced in patients with telangiectasias and reticular veins treated with MPFF.[110]

A meta-analysis by Kakkos and Nicolaides[14] analyzed seven RCTs in 1692 patients with CVD (Table VII). Based on high-quality evidence, the study concluded that MPFF was highly effective in improving leg symptoms, edema, and QOL in patients with CVD. The RELIEF study enrolled 4527 patients with CEAP Class C0 to C4. Approximately 40% of patients belonged to CEAP Class C2. Participants were treated for a period of 6 months and had significant evolving improvement of symptoms, QOL measured by the CIVIQ instrument and edema assessed by leg circumference.[111] More recently, an RCT compared two galenic formulations of MPFF, tablets and sachets, and included 1139 patients with C2s stage representing 44.95% to 49.46%.[113] The authors concluded that both formulations resulted in similar improvement of symptoms and QOL.

A meta-analysis of 10 trials included 1010 patients treated with MPFF, hydroxyethylrutosides, ruscus extracts, and diosmin. MPFF significantly reduced ankle edema ($P < .0001$), while the efficacy of the other two VADS was comparable.[112] Another meta-analysis[15] compared the efficacy of sulodexide, MPFF, hydroxyethyl rutosides, calcium dobesilate, ruscus extracts, horse chestnut extracts, and pentoxifylline. The primary outcome was ulcer healing, but the drug effects on the leg volume, ankle circumference, symptoms, as well as QOL (CIVIQ-20 score) were also assessed. MPFF had superior effectiveness in leg volume reduction, pain, and improved QOL. Although not within the scope of this guideline, it is worth mentioning that in a meta-analysis of five RCTs, MPFF improved ulcer healing.[15,114] The main MPFF component, diosmin, is effective alone, although its efficacy is significantly less than that of MPFF.[112,115]

Five unblinded open-label clinical trials were included in a systematic review investigating the effects of VADs on recovery after surgery, endovenous ablation, or sclerotherapy[20] (Table VIII). All used MPFF; in one study, sulodexide was also given. Three studies reported significantly less postprocedural pain, one observed no significant effect. Two studies reported significant reduction in postprocedural bleeding. Three studies reported greater symptomatic improvement with MPFF treatment. Based on these results, MPFF may help to reduce postprocedural pain, hemorrhage, and CVD-specific symptoms. These benefits appear to be greater when treatment is started 2 weeks before the procedure. When VAD treatment was started only after varicose veins surgery,[117] no benefit was noted.

In a nonrandomized, controlled multicenter prospective study (DEFANCE trial),[118] 245 C2 patients underwent HL&S combined with stab avulsion. Patients in one group ($n = 200$) received 1000 mg of MPFF daily, the control group ($n = 45$) had no drug treatment. Compression (class 2) was prescribed for 4 weeks after surgery for all patients. Hematoma ($P < .05$) and pain (VAS) ($P < .05$) were significantly lower in the MPFF group. The same results were observed for leg heaviness and fatigue. As discussed, however, compression for 1 week after endothermal treatment has also been useful for pain reduction, without MPFF treatment.

Clinical benefit of ruscus extracts.

Rationale. Ruscus extracts increase capillary resistance and reduce capillary filtration.[119]

Evidence. A systematic review and meta-analysis[120] included 20 RCT vs placebo, five vs comparative VAD (hydroxyrutosides and MPFF), and six observational studies, with a total of 10,246 patients (Table IX).

Table VIII. Micronized purified flavonoid fraction (*MPFF*) therapy as adjuvant treatment with intervention

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Mansilha A, 2019[20]	Adults with varicose veins	VAD (MPFF and sulodexide)	Control with no VAD treatment	Postprocedural pain, CVD symptoms and hemorrhage. MPFF reduced postprocedural pain, hemorrhage and CVD specific symptoms.	Systematic review of 5 studies	Age, sex, different stages of CVD in patients with varicose veins
Pokrovsky, AV, 2007[116]	Adults with CEAP C2 undergoing stripping of the GSV combined with stab avulsion	MPFF	Control	Hematoma, pain (VAS), leg heaviness and fatigue MPFF in the preoperative and postoperative period after phlebectomy attenuated pain, decreased postoperative hematomas and accelerated their absorption.	Controlled multicenter prospective trial	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *VAD*, venoactive drug; *VAS*, visual analog scale.

Varicose veins were listed in the inclusion criteria of some of the trials (eg, Capelli[121]), most of them focusing on CVI with CEAP class from C2 to C5. Data quality was heterogeneous, but the study concluded that Ruscus extracts significantly improved symptoms compared with placebo. The best effects were observed on leg heaviness ($P = .001$), pain ($P = .02$), cramps ($P = .025$), and paresthesia ($P = .031$). Venous capacity, assessed by plethysmography, decreased by 0.7 mL/100 mL compared with placebo ($P = .014$). Comparison with hydroxyrutoside and MPFF showed similar effects on the symptoms. A more recent systematic review and meta-analysis[16] included 10 high-quality, double-blind, placebo-controlled RCTs with a total number of 719 patients (CEAP C2-C5). Compared with placebo, the RR for pain was 0.35 ($P < .00,001$), for heaviness 0.26 ($P < .00001$), for sensation of swelling 0.53 ($P < .0001$), for paresthesia 0.27 ($P < .0001$), and for global symptoms 0.54 ($P < .00001$). Ankle circumference and leg volume were significant reduced, and the study concluded that Ruscus extracts were effective in reducing symptoms and edema in patients with CVD.[16] In a meta-analysis,[112] Ruscus extracts significantly reduced ankle circumference vs placebo ($P < .001$), more so than diosmin. Another systematic review and meta-analysis[15] found that Ruscus extracts were the most effective in decreasing foot volume and ankle circumference.

4. Interventions for superficial truncal reflux

4.1. Endovenous ablation vs high ligation and stripping.

4.1.1. For patients with symptomatic varicose veins and axial reflux in the GSV, who are candidates for intervention, we recommend treatment with endovenous ablation over high ligation and stripping (HL&S) of the GSV.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: B (moderate)

4.1.2. For patients with symptomatic varicose veins and axial reflux in the SSV, who are candidates for intervention, we recommend treatment with endovenous ablation over ligation and stripping of the SSV.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: C (low to very low)

4.1.3. For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, who are candidates for intervention, we suggest treatment with endovenous ablation, with additional phlebectomy, if needed, over ligation and stripping of the accessory vein.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

4.1.4. For patients with symptomatic varicose veins and axial reflux in the GSV or SSV, we recommend treatment with HL&S of the saphenous vein if technology or expertise in endovenous ablation is not available or if the venous anatomy precludes endovenous treatment.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: B (moderate)

4.1.5. For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV, we suggest treatment with ligation and stripping of the accessory saphenous vein, with additional phlebectomy, if needed, if technology or expertise in endovenous ablations is not available or if the venous anatomy precludes endovenous treatment.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

4.1.6. For patients with symptomatic varicose veins and axial reflux in the GSV who place a high priority on the long-term outcomes of treatment (QOL and recurrence), we suggest treatment with EVLA, radiofrequency ablation (RFA), or HL&S over physician-compounded UGFS, because of long-term improvement of QOL and reduced recurrence.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: B (moderate)

4.1.7. For patients with symptomatic varicose veins and axial reflux in the SSV we suggest treatment with EVLA, RFA, or ligation and stripping from the knee to the upper or midcalf over physician-compounded UGFS, because of long-term improvement of QOL and reduced recurrence.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

4.1.8. For patients with symptomatic varicose veins and axial reflux in the AAGSV or PAGSV who place a high priority on the long-term outcomes of treatment (QOL and recurrence), we suggest treatment of the refluxing superficial trunk with EVLA, RFA, or HL&S, with additional phlebectomy, if needed, over physician-compounded UGFS, because of long-term improvement of QOL and reduced recurrence.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

For Rationale and Evidence supporting Guidelines 4.1.1. to 4.1.8, please see Part I. of the varicose vein guidelines.[8]

4.2. Thermal vs nonthermal ablation of superficial truncal veins.

4.2.1. For patients with symptomatic axial reflux of the GSV, we recommend either thermal or nonthermal ablation from the groin to below the knee, depending on the available expertise of the treating physician and the preference of the patient.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: B (moderate)

4.2.2. For patients with symptomatic axial reflux of the SSV, we recommend either thermal or nonthermal ablation from the knee to the upper or midcalf, depending on the available expertise of the treating physician and the preference of the patient.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: C (low to very low)

4.2.3. For patients with symptomatic axial reflux of the AAGSV or PAGSV, we suggest either thermal or nonthermal ablation, with additional phlebectomy, if needed, depending on the available expertise of the treating physician and the preference of the patient.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

For Rationale and Evidence supporting Guidelines 4.2.1. to 4.2.3, please see Part I. of the varicose vein guidelines.[8]

5. Factors affecting choice of superficial truncal ablation and outcomes

5.1.1. In symptomatic patients with C2 disease, we suggest against using truncal vein diameter to determine which patients need venous ablation.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: B (moderate)

Rationale. A commonly accepted diameter threshold for ablation of the GSV or the SSV has been 5 mm. However, data show that ablation of veins <5 mm in diameter also improves symptoms.[122,123]

Evidence. Several studies demonstrated a weak correlation between saphenous vein diameter and increased CEAP clinical class or VCSS; a correlation between QOL and saphenous vein diameter has not been found.[122,124] Most studies segregated veins diameters into >5 mm or <5 mm. Tan et al[124] performed a systematic review of 11 studies and 2732 limbs. Four studies correlated truncal vein diameter with QOL, while seven reported only on clinical severity measures. Four studies found a weak correlation between vein diameter and VCSS, while one demonstrated correlation with VCSS components.[124] The diameters were a poor predictor of HRQOL, with no relationship to patients' perceived impact on CVD. The review concluded that vein diameters should not be used as a single determinant of who needs venous intervention.[124] Perrins et al examined the clinical and anatomical outcomes of RFA of symptomatic small-diameter GSVs.[122] RFA of symptomatic small diameter GSV (<5 mm) provided comparable clinical outcomes (vein closure and improved VCSS at 3 months) and the study suggested that patients with GSV size <5 mm benefit from RFA.[122] Bendix et al[123] reviewed the Vascular Quality Initiative VV Registry and divided patients into those with GSV <5 mm (group 1) vs those with GSV ≥5 mm (group 2). Both groups had improvement in the VCSS and HASTI scores. Group 2 had more complications, more adverse VTE events, required more anticoagulation, developed more recanalization and missed more days of work than group 1. They authors concluded that patients with a smaller vein size should not be denied intervention based on size alone.[123]

5.2.1. In asymptomatic patients with C2 disease, prophylactic intervention does not prevent progression of venous disease. Weight control, compression stockings, and avoiding prolonged standing may be beneficial.

Consensus statement.

Rationale. Studies have noted progression with worsening CEAP class over time.[125-127] This raises the question about the role of prophylactic intervention in asymptomatic patients with varicose veins, to prevent progression to symptomatic disease.

Evidence. As discussed before, the CEAP classification is not a severity scale but a classification scheme for

Table IX. Clinical benefit of Ruscus extracts

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Boyle, 2003[120]	Adults with CVI including CEAP C2	Ruscus extracts	Placebo in 20 RCTs, comparator VAD (MPFF, hydroxyethyl rutosides, dihydroergolamine) in 5 RCTs	4-point symptoms scores (all studies), venous capacity (6 studies) and venous refilling time (5 studies). Calf and ankle circumference (11 and 6 studies). Strong and objective demonstration of the clinical efficacy Ruscus in treating patients with CVI	Systematic review and meta-analysis of 25 RCTs (20 vs placebo and 5 vs other VAD) and 6 single-arm studies	Age, sex, different stages of CVD in patients with varicose veins
Kakkos, 2017[16]	Adults with venous symptoms and edema	Ruscus extracts	Placebo	Symptoms and leg edema Ruscus extract highly effective in reducing symptoms and edema in patients with CVD	Systematic review and meta-analysis of 10 double-blind, randomized, placebo-controlled trials	Age, sex, different stages of CVD in patients with varicose veins
Allaert, 2012[112]	Adults with lower extremity venous edema	Ruscus extracts, MPFF, hydroxyethyl-rutosides, and diosmin	Placebo or other VAD	Reduction of ankle edema. Ruscus extract second best after MPFF in reducing ankle edema.	Systematic review and meta-analysis of 10 double-blind, randomized, placebo or other VAD-controlled trials	Age, sex, different stages of CVD in patients with varicose veins
Pompilio, 2021[15]	Adults with CVD	Ruscus extracts, MPFF, sulodexide, hydroxyethyl rutosides, calcium-dobesilate, , horse chestnut extracts and pentoxifylline	Placebo in 45 RCTs	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score) Ruscus was the most effective in ankle circumference reduction.	Systematic review and meta-analysis of 45 RCTs and separated analysis of 17 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *MPFF*, micronized purified flavonoid fraction; *QOL*, quality of life; *RCT*, randomized controlled trial; *VAD*, venoactive drug; *VAS*, visual analog scale.

patients with chronic venous disorders describing the clinical, etiologic, anatomical, and pathophysiologic features. Conceptually, however, it has often been pondered whether patients with varicose veins (C2) can undergo treatment to prevent progression to CVI later in life. In the Bonn Vein Study,[128] 1978 participants were followed up for a mean of 6.6 years. The prevalence of varicose veins rose from 22.7% to 25.1% (Table X). Participants with C2 disease increased to higher C-classes in 19.8% for nonsaphenous varicose veins and in 31.8% for saphenous varicose veins. The main risk factor for progression was obesity. The Edinburgh Vein Study had a 13-year follow-up; a progression rate of 57.8% (4.3% per year) was reported, of those with C2 disease at baseline, 31.9% progressed to CVI.[126] Risk factors for progression included a family history of varicose veins, previous DVT and obesity. Kostas et al followed 73 mostly asymptomatic contralateral limbs for 5 years in patients who

Table X. Disease progression in patients with varicose veins (C2 disease)

Author, year	Patients/ Limbs	Intervention	Comparison	Outcome	Study design
Palfreyman, 2009[129]	C2 disease 25 studies	Compression therapy	no therapy	Benefit of compression hosiery for varicose veins was equivocal	Systematic review
Kostas, 2010[125]	73 limbs	Treated symptomatic varicose veins	Untreated asymptomatic/min symptomatic contralateral limb	A clinical deterioration of >2 CEAP classes was seen in 23 limbs (32%), only 2 (3%) progressed to C4 disease, none to C6 disease.	Prospective observational cohort
Rabe 2010[130]	1978 patients	6.6 years of follow-up	Patients with preexisting CVD vs patients with no CVD	Prevalence of varicose veins 22.7% to 25.1% CVI 14.5 to 16%. Incidence of new varicose veins 13.7% and new CVI 13.0%	Population-based cohort study
Robertson, 2013[131]	1 study (n = 19) (1620 studies excluded)	Compression stockings in standing workers	no compression	No progression to CVI	Systematic review
Wrona, 2015[128]	3072 patients (6.6 years of follow-up)	none	none	C2 disease patients increased to higher C-classes in 19.8% for nonsaphenous varicose vein and in 31.8% for saphenous varicose vein. The main risk factor for progression was obesity.	Prospective observational
Lee, 2015[126]	880 patients (13.4 years of follow-up)	None	None	Progression rate of 57.8% (4.3% per year). Of those with C2 disease only at baseline, 31.9% progressed to CVI	Prospective observational

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency.

underwent treatment of symptomatic varicose veins of one lower extremity. CVD progression was significantly less in patients who were not obese and did not gain weight during the study.[125] Patients who did not use compression stockings preoperatively and during the follow-up or had stopped using them also had significantly higher incidence of progression compared with those who used compression.[125]

A Cochrane study in 2013 looked at nonpharmacological interventions to prevent CVI in standing workers.[132] This systemic review concluded that due to the limited number of trials and study participants, there was insufficient evidence to draw any conclusions as to whether nonpharmacologic strategies including compression were effective at preventing the development of CVI in standing workers. Another systematic review of compression for uncomplicated C2 disease found no consensus on the class of compression needed for the effective management of varicose veins and no evidence that wearing compression slows the progression or recurrence of varicose veins.[129] Although evidence presented in these guidelines show that interventions on varicose veins are associated with improved QOL and decreased morbidity, no study examined the role of surgical or endovascular therapies on C2 patients to prevent longitudinal progression to CVI. The role of treatment in preventing such progression remains undefined.

5.2.2. Interventions to treat varicose veins can be performed in an office-based setting, surgery center, or hospital operating room, at the discretion of the physician, who is specialized in vein care. Better patient experience and lower cost was reported for procedures performed in an office-based setting.

Consensus statement.

Rationale. In the United States, most venous disease practitioners perform venous procedures, including thermal or nonthermal endovenous ablation, miniphlebectomy and sclerotherapy in an office-based setting. A comparison with the historical method of providing such interventions in the hospital operating room or in surgical centers helps guide providers.

Evidence. Endovenous procedures are safe and effective with high patient satisfaction when performed in an office-based setting (Table XI). Studies have shown high technical success for venous interventions in the office-based setting, which is on par with the operating room setting.[135,137,138] Venous procedures in the office-based setting have a low overall complication rate, comparable with most published series that evaluated similar interventions in the operating room.[135,138,133] Jain et al found that 99% of patients surveyed indicated they would come back to the office for additional procedures.[133] Perkowski et al treated 165 patients in an outpatient office setting with EVLA of either the GSV, SSV, or accessory saphenous veins. No DVT or nerve injury were reported and 97% of patients were mostly or very satisfied with their treatment results.[134] In a retrospective study of 429 office based stand-alone RFA procedures,

Table XI. Outcome of interventions performed in outpatient office-based settings

First author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Jain 2013[133]	785 patients and 1019 venous procedures: 512 EVLT with phlebectomies, 390 phlebectomies, 110 RFA with phlebectomies	EVLT or RFA with or without phlebectomies	None	99% patient satisfaction, 2.2% complication rate	Retrospective review
Perkowski 2004[134]	165 patients 203 limbs	EVLA	none	97% clinical success rate, 97% patient satisfaction, 84% at 1 year had minimal to no symptoms.	Retrospective review
Somasundaram 2019[135]	429 procedures in 394 patients	RFA alone in office-based outpatient setting	none	No major complications, 3 EHIT, reduced cost compared with day surgery, 23% needed further treatment following standalone RFA.	Retrospective review
Jarjous 2015[136]	73 limbs, 63 patients	Office based RFA and UGFS, evaluated at 1 and 6 weeks	Office based RFA and Foam vs success/ complications of staged	100% closure rate of GSV and SSV. 91.7% closure rate of tributaries, No major or minor complications	Controlled nonrandomized observational
Lin 2017[137]	3073 venous procedures, 285 saphenous ablation, 185 phlebectomies, 265 ablations and phlebectomies	Treatment in office-based suite	None	99.2% technical success, complication rate 1%	Retrospective review
Varetto 2018[138]	112 patients	EVLA	Day surgery vs outpatient office-based setting	No difference between groups in technical success, complications, patients' functional and aesthetic satisfaction. In patients >65 years of age better QOL in outpatient setting	Prospective cohort study
Hannon 2022[139]	195 patients with 83% (162) responses	Endovenous ablation w/ phlebectomies in outpatient office	none	98.1% patients satisfied, 99.4% treatment met their expectations, 94.7% would undergo treatment again in outpatient setting.	Prospective cohort study

EHIT, Endovenous heat-induced thrombosis; *EVLT*, endovenous laser therapy; *RFA*, radiofrequency ablation; *UGFS*, ultrasound-guided foam sclerotherapy.

performed under local tumescent anesthesia in 394 patients with varicose veins, Somasundaram et al reported >75% had resolution of symptoms within 1 year, with 3 endothermal heat-induced thrombosis (EHITs) and no major complications. Only 23% needed additional treatments.[135] Cost was significantly lower when compared with RFA procedures performed in a day surgery setting.[135] Combining thermal ablation and other venous treatments such as phlebectomy and sclerotherapy during the same procedure is also safe and effective. Jarjous et al treated 72 extremities in 63 consecutive patients with RFA of the truncal and perforator veins, combined with UGFS procedures of tributary and accessory veins.[136] They reported 100% closure of the treated GSV and SSV and 91.7% closure of tributary veins, 13.9% needed additional treatment and there were no major or minor complications.[136] Lin et al reported on 3073 office-based venous procedures: 285 saphenous vein ablations, 185 miniphlebectomies, and 261 venous ablations with concomitant miniphlebectomy.[137] Overall technical success was 99.2%, with a complication rate of 1%.[137] There are a few studies that looked at patient satisfaction in an office setting compared with an operating room setting. Varetto et al treated 112 patients with GSV insufficiency. Approximately one-half underwent EVLA in day-surgery and one-half in an outpatient office-

based setting. There was no statistical difference in the postoperative success or complications between the two groups.[138] QOL measures did not significantly differ between groups, except for the >65-year-old group, which demonstrated better QOL in office-based setting compared with the day surgery group.[138] Another prospective study sent questionnaires to patients who underwent endovenous ablation with concomitant phlebectomy in the office-based setting and found a high (98.1%) satisfaction level, with 94.7% of the patients stating they would undergo the same procedure again in the same setting, if needed.[139] In summary, varicose vein procedures in the office-based setting have a low complication rate, high patient satisfaction and they are cost effective.

It is important to note, however, that appropriate treatment of patients with venous disease is dependent not just on evidence-based guidelines, but that physicians and qualified health care professionals have the requisite education, training and skills to provide such care. In the context of interventional venous procedures, multispecialty agreement has been reached on the required training and experience needed for physicians to perform specific venous treatments.[140] In addition, the role and degree of involvement by licensed advanced practice providers, physician assistants and nurse practitioners, has also been defined by the Intersocietal Accreditation Commission, along with that of nursing staff and ultrasound technologists. Because these venous interventions are mostly performed in the private office or office-based laboratory setting, the supervising physician has the responsibility to ensure that any procedure, or parts of procedures, not personally performed by them is done by an appropriately qualified and licensed individual under sufficient level of supervision.

5.2.3. In patients with symptomatic C2 disease, isolated SFJ incompetence does not justify ablation of an otherwise competent GSV.

Consensus statement.

Rationale. The impact of junctional reflux on clinical manifestations and treatment outcomes is not clear. Reflux patterns and the presence or absence of SFJ reflux have been evaluated in multiple studies and a significant percentage of symptomatic patients have been shown to have lower extremity reflux without SFJ insufficiency.[141-143] Nevertheless, the presence of junctional reflux often determines insurance coverage for ablation. Assessing the role that junctional reflux plays in patients with symptomatic varicose veins is important to ensure appropriate care.

Evidence. Studies have indicated that the theory of descending saphenous valvular incompetence starting at the SFJ may be inaccurate and therefore there is no rationale for treatment of SFJ incompetence in the setting of a normal GSV.[141-143] Abu-Own et al[141] used DUS to assess 190 limbs with primary varicose veins. Sixty-three limbs (33%) had no SFJ incompetence. Labropoulos et al[144] looked at 255 limbs in 217 patients with superficial venous insufficiency and normal deep veins and perforator veins with DUS. Isolated below-knee reflux was associated with more symptoms and signs than isolated above-knee reflux.[144] Another study by Labropoulos et al[142] looked at the prevalence of reflux in age-matched asymptomatic young patients and found that reflux can occur in any vein segment and the most common site was the below knee GSV. Fassiadis et al studied 611 limbs with primary varicose veins. Of 454 limbs that showed GSV reflux on DUS, 240 limbs exhibited reflux of both the GSV and SFJ and 214 limbs (35%) showed isolated GSV reflux with a competent SFJ. The authors suggested that reflux starts distally and progresses proximally.[143] In light of these studies, treatment of isolated SFJ reflux appears unnecessary.

5.2.4. In patients with symptomatic C2 disease, ablation of the incompetent GSV may be indicated even if the axial reflux is not complete and the SFJ is competent. Ablation of isolated refluxing GSV segments, in the presence of competent segments proximally and distally, is rarely indicated. Shared decision-making with the patient is warranted.

Consensus statement.

Rationale and evidence. Reflux patterns have been evaluated in multiple studies, and as discussed above, a significant percentage of symptomatic patients have been shown to have lower extremity axial reflux without SFJ insufficiency. Engelhorn et al[145] found SFJ incompetence in only 12% of 590 limbs of 326 women with varicose and spider veins (CEAP Class C1-C2). Aurshina et al[146] in their single-center retrospective review of 265 patients including 41 without junctional reflux noted that the location of reflux did not affect patient presentation or outcomes at two years after vein ablation. Others reported more advanced clinical disease in patients with reflux involving the SFJ.[147] The common observation in these studies is that early ablation of the GSV results in good outcome in symptomatic patients, who have competent SFJ but incompetent distal thigh or upper calf GSV.

In contrast, segmental or complete ablation of the GSV is rarely indicated for isolated refluxing segments with competent segments proximally and distally (Table XII). The GSV has an average of 6.7 valves (range, 3-11 valves).[149] Isolated segmental reflux may be identified by ultrasound even in the presence of a competent GSV. Such a phenomenon may occur in a segment between two competent valves when inflow occurs from a competent tributary and outflow from an incompetent tributary or a competent perforator between the two valves.[150] When symptomatic, such incompetent tributaries can be managed with phlebectomy.

5.2.5. In patients with reflux in the below-knee GSV, ablation to the lowest point of reflux resulted in better

Table XII. Outcome of interventions in patients with competent saphenofemoral junction (SFJ)

First author, year	Patients/limbs	Intervention	Comparison	Outcome	Study design
Abu-Own 1994[141]	167 patients with VV	Ultrasound	Patterns of Reflux on US	190 limbs with GSV reflux, 63 had no SFJ reflux	Retrospective review
Engelhorn 2012[145]	326 patients 590 limbs	US in patients with VV but without edema, skin changes or ulcers	Patterns of reflux	Reflux in 80%, junctional reflux only in 12%	Prospective observational study
Chastanet 2013[147]	1882 limbs 1449 patients	Ultrasound	Patterns of reflux	In 1772 limbs with VV 36.1% the GSV and SFJ was competent. In 987 limbs w VV and GSV reflux SFJ was competent in 29.4%	Prospective observational study
Yilmaz 2021[148]	503 patients 787 limbs with GSV insufficiency	DUS examination CEAP, VCSS	Patterns of reflux	14.8% of limbs GSV reflux without SFJ and malleolar reflux and 10.4% with GSV (including malleolar) but no SFJ reflux	Retrospective review

CEAP, Clinical stage, etiology, anatomy, pathology; *GSV*, great saphenous vein; *EHIT*, endovenous heat-induced thrombosis; *SFJ*, saphenofemoral junction; *US*, ultrasound; *VV*, varicose veins; *VCSS*, Venous Clinical Severity Score.

early outcome. Nonthermal techniques are preferred for ablation of refluxing distal calf saphenous veins to avoid thermal nerve injury.

Consensus statement.

Rationale. Studies have shown that thermal ablation of the below-knee GSV is feasible and safe.[151] In addition, nonthermal techniques are available if there are concerns about saphenous nerve injury. Elimination of below-knee GSV reflux has been shown to improve symptoms and reduce the need for additional procedures, compared with ablation of the above-knee GSV only.[152-154]

Evidence. Several studies showed better results of above-knee GSV ablation when there was no residual below-knee GSV reflux.[152,153] In a systematic review, Sussman et al[33] found that above-knee-below-knee EVLA was associated with significantly lower odds of below-knee GSV reflux recurrence compared with above-knee-EVLA only ($P < .0001$). Theivacumar et al[152] randomized 68 limbs of 65 patients with varicosities and both above-knee and below-knee GSV reflux to either EVLA above-knee, EVLA to below-knee midcalf, or above-knee EVLA with concomitant below-knee FS. There was improvement in the Aberdeen Varicose Vein Severity Score at 6 weeks in all groups, although it was greater in the latter two groups; patient satisfaction at twelve weeks was not different between the groups. Compared with above-knee EVLA, concomitant below-knee ablation (laser or sclerotherapy) resulted in fewer varicosities and superior symptom relief at 6 weeks (Table XIII).[152] In another study the same authors treated 69 limbs with above-knee EVLA, 40 with C2 disease.[153] At 6 weeks, residual varicosities, if present, were treated with FS. Reflux in the below-knee GSV was evaluated, and the limbs were allocated into three groups: group A, no reflux; group B, flash reflux <1 second; and group C, significant reflux >1 second. Delayed FS was required in 12% in group A, 14% in group B, and 89% in group C. The improvement in Aberdeen Varicose Vein Severity Score at 6 weeks was 86.2% in group A, 82.1% in group B, and 59.1% in group C ($P < .001$ vs A and B). While EVLA of the above-knee GSV improved all patients, those with persistent reflux in the below-knee GSV had the least improvement. In a different study of 50 patients with complete GSV reflux, 16 patients had EVLA in the above-knee and below-knee GSV in separate sessions, 34 patients had EVLA in the above-knee and below-knee GSV in the same session.[154] Patients with complete GSV reflux complained of ankle pain and swelling. At 11 months, all patients had resolution of their ankle pain, with 44 patients having resolution of swelling. There were four instances of paresthesias.[154] Carradice et al randomized surgical stripping vs EVLA for treatment of varicose veins. Twelve of 23 recurrences of varicosities were due to an incompetent below-knee GSV. GSV ablation in this study could be safely performed in the distal leg.[155] Gifford et al treated 79 limbs with below-knee-GSV EVLT or RFA for reflux at this site, 43 had Class 1 to 3 disease. Only three patients (4%) suffered transient paresthesia.

5.2.6. In patients with an epifascial or superficial saphenous vein, thermal ablation may result in skin burns, hyperpigmentation, or induration, while nonthermal techniques may cause hyperpigmentation or induration. Miniphlebectomy or limited stripping is safe and effective, if the saphenous vein is close to the skin (<0.5 cm).

Consensus statement.

Rationale. Thermal techniques pose the potential for skin burn if the area of ablation is close to the skin. Use of tumescence anesthesia helps overcome this problem

Table XIII. The benefit of treatment of the incompetent below-knee great saphenous vein (GSV)

First author, year	Patients/ Limbs	Intervention	Comparison	Outcome	Study design
Theivacumar 2008[152]	65/68	EVLA	EVLA-above-knee vs ELVA-below-knee vs ELVA above-knee + below-knee foam sclero	Aberdeen Varicose Vein Severity Score improvement in all groups, least in EVLA-above-knee. Concomitant below-knee ablation (laser or sclero) had fewer varicosities and symptoms at 6 weeks	RCT
Theivacumar 2009[153]	64/69	EVLA GSV	Patients with reflux >1 second in below-knee GSV v no reflux or <1 second reflux	Patients with continued reflux in below-knee GSV had less symptom relief and greater need for sclerotherapy to treat residual varicose veins	Retrospective review
Timperman 2007[154]	50/50	EVLA	EVLA-above-knee vs EVLA-below-knee	EVLA-above-knee patients had incomplete relief of ankle pain and swelling	Retrospective review
Carradice 2011[155]	280/280	EVLA or conventional surgery	EVLA vs stripping	ELVA had lower rates of clinical recurrence (4.0% vs 20.4%)	Randomized clinical trial

EVLA, Endovenous laser ablation; *GSV*, great saphenous vein; *RCT*, randomized controlled trial.

in most cases. Nonthermal nontumescent techniques may also be used, although it is not known whether one technique is superior to others for veins close to the skin.

Evidence. There is no scientific evidence that supports one type of ablation technique over another, based on depth of vein below the skin. The risk of skin burns appears to be high in limbs with the vein located <0.5 cm from the skin despite using subdermal tumescent anesthesia. Pigmentation has also been observed in these patients. In a systematic review and network analysis that included 51 studies on EVLA, RFA, n-butyl cyanoacrylate ablation or FS, Gasior et al[156] did not report on skin burn as a complication. In the 16 studies that Alozai et al[29] included in their systematic review/meta-analysis of treatment modalities of the AAGSV, there was a 0.7% incidence of paresthesia with no instances of skin burn. The ablation modalities included RFA, EVLA, n-butyl cyanoacrylate and sclerotherapy.[29] The MARADONA trial, a multicenter randomized study that compared MOCA to RFA, did not find a significant difference in the incidence of skin burn or saphenous neuralgia between the two techniques at 30 days.[157]

5.2.7. For patients with large (>10 mm), nonaneurysmal saphenous veins, thermal ablation with EVLA or RFA should be performed over nonthermal techniques.

Consensus statement.

Rationale. While there are many techniques to perform venous ablation and they provide favorable outcomes in the setting of large diameter (>10 mm) veins, thermal ablations have superiority over other treatments.

Evidence. Hamann et al examined the safety and effectiveness of endovenous thermal ablation in 11 limbs with a large GSV, but < 2 cm in size close to the junction (Table XIV).[158] No DVT or EHIT was noted, and truncal obliteration was 80% at 1 year. Atasoy reviewed 44 consecutive patients with large GSVs, with a mean diameter of 16.95 mm (range, 15-26 mm) and found a 100% occlusion rate at 1 year after treatment. All patients had clinical improvement and improved QOL scores.[159] Calcagno et al[160] found no difference in occlusion rates of 246 limbs with saphenous vein diameter ≤12 mm diameter (mean, 8 ± 2 mm) and of 96 with vein >12 mm (mean, 17 ± 4 mm) when treated with RFA. Fernandez et al treated 183 patients with a GSV diameter <12 mm and 74 with a GSV diameter ≥12 mm. There was significant improvement in pain and QOL in both groups, with no difference in occlusion rates or adverse effects at 1, 6, and 12 months.[161] Borsuk and Fokin conducted a prospective study of 261 EVLA procedures of the GSV with a 1470-nm radial tip laser. Mean diameter of GSV at the SFJ was 24 ± 6 mm (range, 21-43 mm).[162] 88% of veins were occluded on day 1; of the 31 nonoccluded veins, 21 of the 31 were occluded by day 7. Ochoa Chaar et al[163] reviewed 732 laser ablations, 88 were performed on veins measuring >10 mm in diameter. Complication and closure rates were similar for larger and smaller veins, unsuccessful closure was more likely in the SSV and anterior accessory saphenous vein (AASV) than in the GSV.[163] In a small case series, Florescu et al[164] performed 20 ablations of veins >10 mm and 4 ablations on veins ≥20 mm in diameter; successful ablation was achieved in 100%. In a retrospective study, 129 patients with a GSV ≥14 mm underwent either stripping or RFA.[165] A composite endpoint of pain, subcutaneous hemorrhage, and paresthesia; the technical outcome at 1 year was evaluated. There were favorable outcomes in

Table XIV. Outcome of interventions with >10 mm superficial truncal veins

First author, year	Patients/ Limbs	Intervention	Comparison	Outcome	Study design
Hamann 2019[158]	13/15	EVLA (4/15 with EVLA+HL	patients with GSV >20 mm or SSV >15 mm close to deep junction	No severe adverse events (no EHIT or DVT). Significant improvement of VCSS at 1 year (6 pre to 2 post procedure)	Single center prospective observational cohort study
Atasoy 2015[159]	44/49	EVLA for Mean GSV diameter 16.95 mm (range, 15-26 mm)	none	Technical success 97.9% at one month and 100% at 6 months	Retrospective review
Calcagno 2009[160]	338 limbs	ClosureFAST RFA	Saphenous vein diameter >12 mm vs <12 mm	Vein diameter >12 mm had no effect on closure rate	Retrospective review
Fernandez 2017[161]	257/257	RFA	GSV diameter >12 mm vs <12 mm	No difference in occlusion rates, pain and QOL improvements or adverse events	Single center prospective study
Borsuk 2020[162]	231/261	EVLA for GSV diameter >20 mm	none	88% occluded on day 1, 96% by day 7. Recanalization of 0.8%	Prospective noncomparative study
Ochoa Chaar 2011[163]	732/732	EVLA GSV, SSV, AASV	Saphenous vein diameter >10 mm vs <10 mm	Complication rates not significantly different for veins >10 mm in diameter vs smaller veins	Retrospective review
Florescu 2014[164]	24 limbs	EVLA	Saphenous vein diameter >10 mm, 4 with diameter >20 mm	Successful ablation in 100%	Retrospective review
Shaidakov 2016[165]	129/129 Saphenous vein diameter >14 mm	RFA	HL&S	Favorable outcome (technical, pain, hemorrhage, paresthesia) was 30.8% after HL&S and 95.3% after RFA	Multicenter retrospective cohort study

AASV, Anterior accessory saphenous vein; *DVT*, Deep vein thrombosis; *EVLA*, endovenous laser ablation; *EHIT*, endovenous heat-induced thrombosis; *HL*, high ligation; *HL&S*, high ligation and stripping; *GSV*, great saphenous vein; *QOL*, quality of life; *RFA*, radiofrequency ablation; *SSV*, small saphenous vein; *VCSS*, Venous Clinical Severity Score.

30.8% of the stripping group vs 95.3% in the RFA group.[165] Postoperative pain was associated with increased BMI and large vein diameter. For large diameter veins, RFA was superior to stripping. These data support that thermal ablation techniques are safe and effective in treating large diameter saphenous veins. There have been no large case series using nonthermal techniques in large veins.

5.2.8. The incidence of superficial thrombophlebitis has been reported to be similar for thermal and nonthermal ablations.

Consensus statement.

Rationale. Different rates of postprocedure thrombophlebitis were reported for different ablation techniques, but most RCTs and meta-analyses found no significant difference in the rates of thrombophlebitis as a minor complication after endovenous ablations.[166]

Evidence. In one of the largest single center retrospective trials of 808 patients, Aurshina et al[167] compared acute thrombotic complications after EVLA with RFA. The incidence of acute superficial thrombosis in varicose veins in the ipsilateral leg was 4.6%, and overall thrombotic complications occurred in 10.5%, more frequent after EVLA than after RFA (11.4% vs 7.7%; $P = .007$). Thrombotic complications in this study, however, also included EHIT. There was no difference in thrombophlebitis following EVLA and RFA in a systematic review of 12 studies that included 1577 patients (RR, 1.03; 95% CI, ; 95% CI,0.56 to 1.92).[166]

When comparing nonthermal and thermal techniques, a systematic review and meta-analysis by Hassanin et al[21] found no significant difference in phlebitis rates between groups (pooled RR, 0.70; 95% CI, 0.32-1.54). Nonthermal ablations in this study included mechanochemical ablation and cyanoacrylate vein ablations. A meta-analysis from Chen et al[22] found similar results, with no difference in phlebitis rates between cyanoacrylate ablations vs RFA (OR, 51.22; 95% CI, 0.70-2.13; $P = .479$). Single center studies published on higher rate of mild phlebitis after cyanoacrylate ablation, likely also due to a periphlebitic

Table XV. Outcome of superficial truncal ablation in patients with deep vein obstruction

Author, year	Patients/limbs	Intervention	Comparison	Outcome	Study design
Benfor and Peden[25]	2428/2476	Concomitant treatment of DVO and SVR in 483 limbs (51.2%)	Treatment of DVO alone in 168 limbs (17.8%) Treatment of SVR alone in 293 limbs (31%)	Ablation of SVR is safe for patients with DVO. Patients with advanced CEAP class (≥4) had better results when ablation of superficial truncal veins was combined with treatment of iliac vein obstruction. Patients with early CEAP class (<4) had a staged approach with initial ablation of SVR and stenting for DVO if no improvement was noted.	Systematic review

CEAP, Clinical stage, etiology, anatomy, pathology; *DVO*, deep vein obstruction; *SVR*, superficial vein reflux.

allergic reaction to cyanoacrylate,[168] while other scoping and systematic reviews and meta-analyses showed lower phlebitis rates after cyanoacrylate treatment of truncal veins vs thermal ablations.[23,24,169] There was a large heterogeneity in these trials and patients represented encompassed the entire spectrum of CVD (CEAP Class 2-6).

There was no difference in phlebitis rates, when mechanochemical ablation was compared with EVLA in the LAMA trial occurring in 7% (5/69) after EVLA compared with 13% (9/69) after MOCA ($P = .262$).[170] In a retrospective trial with 979 limbs, Obi et al[171] found, not surprisingly, more asymptomatic phlebitis in patients who underwent RFA plus transilluminated powered phlebectomy as compared with RFA alone. Combined therapy of endovenous thermal ablation with polidocanol endovenous microfoam (PEM) sclerotherapy also had higher incidence of phlebitis than thermal ablation combined with placebo sclerotherapy (18/79 vs 0/30).[172]

5.2.9. In patients with uncomplicated C2 disease (no venous claudication, thigh swelling, or suprapubic or abdominal wall varicosities) due to concurrent superficial incompetence and iliac or iliofemoral venous obstruction, treatment of superficial incompetence first is indicated.

Consensus statement. For Rationale and Evidence, please see Table XV. and Consensus Statements 1.5.3 and 1.5.4.

6. Interventions to preserve the GSV

6.1.1. For patients with early stages of symptomatic varicose veins we suggest preserving the GSV using the ambulatory selective variceal ablation under local anesthesia (ASVAL) technique, if performed by a physician who is familiar with the strategy.

GUIDELINE. Grade of recommendation 2 (weak), Quality of Evidence B (moderate)

Rationale and evidence. The ASVAL is a GSV-sparing method that involves detailed DUS mapping of all varicose tributaries connecting to the GSV and ambulatory phlebectomy.[173,174] The operation is based on the ascending theory which is that the venous disease process develops in tributaries and distal truncal veins and "ascends" to the junction and the deep venous system.[175] A systematic review of the ASVAL procedure in 2021 included two RCTs, one case-control and three cohort studies, and five case series (Table XVI). Varicose vein recurrence at 1 year ranged from 0.55% to 13.5%, and GSV incompetence resolved in 50% to 85% at 1 year after the intervention.[31] Another study reported absence of GSV reflux at 1 year in 98% of limbs with competent SFJ at presentation and in 42% of those with an incompetent SFJ at presentation.[177] Although the level of evidence was low in the systematic review, ambulatory phlebectomy of varicose tributaries creating a venous reservoir may have a positive effect on truncal reflux and ASVAL may be an effective minimally invasive treatment of CVD. Best results were seen in those patients who had a competent terminal valve at the SFJ.[177] The level of evidence for ASVAL was upgraded to B (moderate) because of the recently published SAPTAP RCT.[176] In this multicenter, noninferiority RCT single ambulatory phlebectomy (SAP) was performed in 227 patients and RFA with phlebectomy was done in 237 patients, all with truncal reflux and varicose veins. At 1 year, VEINES-QOL/Sym scores were noninferior after SAP compared with thermal truncal ablation and SAP was a cost-effective alternative to thermal truncal ablation. Twenty-six percent of the SAP patients underwent additional truncal ablation.[176]

6.1.2. For patients with symptomatic varicose veins, we suggest preserving the GSV using the ambulatory conservative hemodynamic correction of venous

Table XVI. Benefits of the ambulatory selective variceal ablation under local anesthesia (*ASVAL*) procedure

Author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Richards, 2020[51]	Patients with varicose veins and truncal reflux	ASVAL	None	Recurrent varicose veins at 1-year: 0.5-13.5%, GSV reflux resolution at 1 year: 50% to 85%	Systematic review
Scheerders, 2023[176]	Patients with varicose veins and truncal reflux (C2-C6)	ASVAL (SAP) n = 227 patients	TAP: Thermal truncal ablation and concomitant phlebectomy n = 237 patients	At 1 year, SAP patients had noninferior HQL compared with TAP patients. SAP was cost-effective to TAP. 25.6% of SAP patients underwent additional truncal ablation.	Noninferiority RCT (SAPTAP Trial)

GSV, Great saphenous vein; *HQL*, health related quality of life; *RCT*, randomized controlled trial; *SAP*, single ambulatory phlebectomy; *TAP*, thermal truncal ablation.

insufficiency (CHIVA) technique, if performed by a physician who is familiar with the strategy.

GUIDELINE. Grade of recommendation 2 (weak), Quality of Evidence B (moderate)

Rationale. The Ambulatory CHIVA was designed to approach venous hemodynamic insufficiency while preserving the GSV, lower transmural pressure in the superficial venous system and avoid removal of varicose tributaries.[178] The goal of CHIVA is to correct the abnormal hemodynamic pathways that are identified with detailed preoperative mapping using DUS. Three types of "shunts" are identified during DUS. Truncal veins are ligated selectively, at the "escape points," where the reflux starts, and the "reentry points', the perforators, where blood enters from the superficial into the deep system, are preserved. Phlebectomies are not performed and reduction of the venous pressure reduces the size of varicose veins a few months after the operation.[178]

Evidence. Two systematic reviews by Bellmutt-Montoya et al[27,28] studied the CHIVA procedure, comparing them to HL&S and to endovenous procedures (Table XVII). The last review in 2021[28] included six RCTs and 1160 patients, three RCTs compared CHIVA to HL&S, one to compression treatment of venous ulcers, one to HL&S and RFA and another to HL&S and EVLA. Five studies reported recurrence of varicose veins at 18 months to 10 years. The review concluded that CHIVA may make little or no difference to the recurrence of varicose veins compared with stripping (RR, 0.74; 95% CI, 0.46-1.20), and it may make little or no difference in preventing recurrence compared with RFA (RR, 2.02; 95% CI, 0.74-5.53) or to EVLA (RR, 0.20; 95% CI, 0.01-4.06). Side effects were similar, but CHIVA may reduce slightly nerve injury compared with HL&S and may cause more bruising than RFA. Evidence supporting all results in this Cochrane review were of low certainty, based on a small number of trials with high risk of bias, with imprecise results due to the small number of events.

A retrospective study by Maeso et al, reported better clinical results after CHIVA than after HL&S at 3 years.[179] In a subsequent prospective study by the same group, 58 patients underwent the CHIVA procedure, with ligation of the GSV tributary that connected to a re-entry perforator. The ligation eliminated SFJ reflux in all but 5 patients (8%). Saphenous reflux, however, returned in 88% of the limbs by 6 months and 46 patients required a second operation to ligate and divide the proximal GSV. Elimination of the reflux in the GSV after the interruption of the insufficient collaterals was temporary.[181]

A recent RCT by Gonzalez Canas et al[180] analyzed results of RFA, HL& S and CHIVA in 214 limbs. Clinical recurrence rates at 24 months were 4.3%, 7.2%, and 14.7% for HL&S, RFA and CHIVA, respectively. Ultrasound recurrences were 7.1% for HL&S, 13% for RFA, and 46.7% for CHIVA. With an 80% power to assess noninferiority, the study found RFA to be noninferior to CHIVA in terms of clinical recurrence. Considering the steep learning curve of the drained and nondrained strategies, the different types of venous-venous shunts, the need for staged procedures[175,182-184] and that all patients require an individualized strategy, it is clear that CHIVA should only be performed by well qualified surgeons who are dedicated experts in venous hemodynamics and DUS.[185]

7. Treatment of venous tributaries

7.1. Telangiectasias (spider veins) and reticular veins.

7.1.1. For patients with symptomatic telangiectasias and reticular veins we recommend sclerotherapy with liquid or foam.

GUIDELINE. Grade of recommendation 1 (strong), Quality of Evidence B (moderate)

Rationale. Sclerotherapy has been used for decades for treatment of telangiectasias or spider veins (subdermal veins <1 mm in size) and reticular veins (veins <3 mm in size), with good results. FS has been preferred recently for larger reticular veins.

Table XVII. Benefits of the conservative hemodynamic correction of venous insufficiency (*CHIVA*) procedure

Author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Bellmunt-Montoya 2015,[27]	4 RCTs 796 patients	CHIVA	HL&S Compression (C6)	There may be little or no difference in the recurrence of varicosities	Systematic review
Bellmunt-Montoya 2021,[28]	6 RCTs 1160 patients	CHIVA	HL&S, Compression (C6), RFA, EVLA	There may be little or no difference in the recurrence of varicosities	Systematic review
Maeso 2001,[179]	175 patients	CHIVA (90) patients)	HL&S with or without phlebectomy (85)	Less complication in CHIVA group	Retrospective case review
Gonzalez Canas 2020,[180]	225 limbs	RFA,	HL&S, CHIVA	RFA was noninferior in terms of clinical recurrence to CHIVA	RCT, single center,
Alozai, 2021,[29]	16 studies on treatment of AAGSV	CHIVA	Thermal ablation, cyanoacrylate, sclerotherapy,	Lower closure rates with sclerotherapy and CHIVA	Systematic review

AAGSV, Anterior accessory great saphenous vein; *EVLA*, endovenous laser ablation; *HL&S*, high ligation and stripping; *RCT*, randomized controlled trial; *RFA*, radiofrequency ablation.

Evidence. In a recent Cochrane systematic review and meta-analysis 3632 patients from 35 RCTs were studied.[186] Treatments of telangiectasias and reticular veins included sclerosing agents, laser and compression. There was moderate-certainty evidence that sclerotherapy was better than placebo (SMD, 3.08; 95% CI, 2.68-3.48), but it resulted in more hyperpigmentation, matting and pain. Polidocanol had results similar to other sclerosing agents, but it was less painful. Sodium tetradecyl sulphate sclerotherapy resulted in resolution or improvement of telangiectasias similar to other agents but there was more hyperpigmentation, matting and probably more pain. Foam likely caused more matting than liquid sclerosing agents.

Table XVIII. Comparison of using room air and CO_2 for foam sclerotherapy (*FS*)

First author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Jia, 2007[10]	69 studies, >9000 patients	FS	Liquid sclerotherapy, surgery	Serious adverse events were rare; insufficient evidence for meaningful comparison with other minimally invasive therapies	Systematic review
Willenberg, 2013[204]	Over 20,000 patients from 4 RCT, 18 case series and 3 case reports	Sclerotherapy	CO_2-based foam, liquid sclerotherapy	VD following sclerotherapy is an uncommon event with no long-term neurological deficit	Systematic review
Morrison, 2008[203]	177 patients	UGFS with 1% Polidocanol foam mixed with room air	CO_2-based foam	Visual disturbances CO_2: 3.1% (4/128), Room air: 8.2% (4/49) ($P = .15$). Chest tightness (3.1% vs 18%), dry cough (1.6% vs 16%), or dizziness (3.1% vs 12%) were lower in the CO_2 vs air groups ($P < .02$). The proportion of patients with side effects decreased from 39% (19/49) to 11% (14/128) as CO_2 replaced air for foam preparation ($P < .001$).	Prospective observational study
Gillet, 2009[205]	1025 patients	UGFS for GSV or SSV reflux	None	30-day saphenous occlusion: 90.3%. Side effects: n = 27 (2.6%), migraine (n = 8, 4 with VD); VD alone: n = 7. Thromboembolic events: 10 DVTs, 1 PE, 1 ischemic stroke, with complete clinical recovery in 30 minutes, 1 septicemia with satisfactory outcome	Multicenter prospective observational study

DVT, Deep vein thrombosis; *GSV*, great saphenous vein; *PE*, pulmonary embolism; *RCT*, randomized controlled trial; *SSV*, small saphenous vein; *UGFS*, ultrasound-guided foam sclerotherapy; *VD*, visual disturbance.

Table XIX. Outcomes of foam, liquid, and placebo sclerotherapy

First author, year (ref.)	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Todd, 2014[206]	232 patients (C2: 31.9%, C3-C6: 68.1%)	PEM 0.5%, PEM 1% for GSV reflux	Placebo	At 8 weeks PEM 0.5% and 1% was effective and provided clinically meaningful benefit in symptoms (VVSymQ) and appearance of varicose veins vs placebo. Thrombotic complications: thrombus extension 3.9%, DVT 5.6%, isolated gastrocnemius or soleal vein thrombosis 0.9%. No PE.	RCT (VANISH-2)
Todd, 2015[207]	58 patients	1% PEM	None	PEM 1% led to durable, clinically meaningful, and ongoing improvements at 1 year in VV symptoms and appearance	Treatment arm of an RCT followed up to 1 year (VANISH-2)
King, 2015[208]	279 patients (C2: 49.1%, C3-C6: 50.9%)	PEM 0.125%, 0.5%, 1%, 2% for GSV reflux or varicose tributaries	Placebo	At 8 weeks administration of up to 15 mL of PEM was safe and effective. VVSymQ scores for pooled PEM group $P <$ .0001) and individual dose concentrations ($P < .001$) were superior to placebo. IPRV3 and PA-V3 scores were also significantly greater. Most AEs were mild and resolved without sequelae. No PE.	RCT
Gibson, 2017[54]	77 patients (C2: 0, C3-C5: 100%)	PEM, 1% vs placebo for symptomatic, visible varicose veins	Placebo	PEM, 1% had statistically significant improvement vs placebo in symptoms and appearance	RCT
Lal, 2017[209]	221 patients (C2: 41.3%, C3-C6: 48.7%)	PEM 1%	Placebo	20%-30% more patients in PEM 1% group achieved clinically meaningful functional and psychological improvement vs placebo	Pooled data from 2 RCTs
De Avila Oliveira, 2021[196]	4278 patients with varicose veins	sclerotherapy (liquid, foam) for treatment of varicose veins	Placebo, different concentration of same sclerosing liquid, foam, different sclerosing solutions,	Very low-certainty evidence that sclerotherapy is effective and safe compared with placebo. Limited to no evidence for one concentration of foam to another; foam compared with liquid; foam compared with any other substance; or one technique to another.	Systematic review with 28 RCTs
Kim, 2021[210]	60 patients (C2; 32, C3-C6: 28)	PEM for superficial truncal reflux	None	Closure rate 93% at 6 months. VCSS improved from 7.3 to 1.4. ($P < .0001$) Complications: 1 DVT; 8.3 % had thrombophlebitis, 6.6% had skin pigmentation.	Prospective observational study
Jimenez, 2022[211]	49 patients/68 limbs (C2:15, C3-C6:53)	PEM for symptomatic below-knee truncal vein reflux after previous saphenous ablation	None	At a median follow-up of 97 days, PEM ablation resulted in a 96% closure rate, symptomatic relief of 78%, two deep venous thrombus extensions, one requiring anticoagulation.	Retrospective cohort study

Table XIX. Continued.

First author, year (ref.)	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Deak, 2022[212]	1070 patients (C2: 469, C3-C6: 601)	EVLA (n = 550)	PEM (520)	Reflux eliminated in 93.5% (514/550) after PEM and 92.8% (482/520) after EVLA; 3-year follow-up; no neurologic or cardiac adverse events after PEM	Retrospective nonrandomized comparative study

AE, Adverse event; *DVT*, deep vein thrombosis; *EVLA*, endovenous laser ablation; *GSV*, great saphenous vein; *PE*, pulmonary embolism; *PEM*, polidocanol endovenous microfoam; *RCT*, randomized controlled trial; *VCSS*, Venous Clinical Severity Score; *VV*, varicose veins.

7.1.2 For patients with symptomatic telangiectasias or reticular veins we suggest transcutaneous laser treatment if the patient has sclerosant allergy, needle phobia, sclerotherapy failure or small veins (<1 mm) with telangiectatic matting.

GUIDELINE. Grade of recommendation 2 (weak), Quality of Evidence B (moderate)

Rationale and evidence. Surface lasers used to treat telangiectasias have wavelength between 532 nm and 1064 nm.[187] The Nd:YAG 1064 nm laser has shown results close to sclerotherapy but more pain was reported after laser treatment.[188] Parlar et al[188] recommended laser for those who have needle phobia, allergy to sclerosants and for small veins with telangiectatic matting, while sclerotherapy is more effective for larger, feeder veins. A 2021 Cochrane review[186] found no clear difference in resolution or improvement of telangiectasias or matting when laser was compared with sclerotherapy. There was maybe less hyperpigmentation (RR, 0.57; 95% CI, 0.40-0.80) in the laser group. There was more resolution or improvement of telangiectasias in the combined laser and polidocanol group compared with polidocanol alone (low-certainty evidence). Laser treatment may result in less hyperpigmentation (moderate-certainty evidence). Further well-designed studies are required to provide evidence for other available treatments and important outcomes (such as recurrence, time to resolution and delayed adverse events); and to improve our confidence in the identified comparisons.

7.2. Varicose tributaries.

7.2.1. For treatment of symptomatic varicose tributaries, we recommend miniphlebectomy or ultrasound guided sclerotherapy using physician-compounded foam (PCF) or polidocanol endovenous microfoam (PEM).

GUIDELINE. Grade of recommendation 1 (strong), Quality of Evidence B (moderate)

For Rationale and Evidence supporting Guideline 7.2.1., please see Part I of the varicose vein guidelines.[8]

7.2.2. For treatment of symptomatic varicose tributaries, we suggest transilluminated powered phlebectomy as an alternative treatment for patients with large clusters of varicosities by a physician who is trained in the procedure.

GUIDELINE. Grade of recommendation 2 (weak), Quality of Evidence C (low to very low)

Rationale. In patients with large, clustered patterns of varicose veins, transilluminated powered phlebectomy remains an acceptable alternative treatment option which requires fewer incisions and shorter treatment times.

Evidence. Several studies have described the safety and efficacy of ambulatory phlebectomy.[171,189,190] Transilluminated powered phlebectomy is a minimally invasive alternative treatment for varicose veins, it is performed under general or local tumescent anesthesia, combined with irrigated illumination and endoscopic-powered venous resection.[191] Two RCTs concluded that powered phlebectomy procedures are quicker and require fewer incisions than traditional phlebectomy, but a steep learning curve is expected.[192,193] Chetter et al[193] found, however that compared with ambulatory phlebectomy, ecchymosis (39% vs 25%; $P < .001$) and pain were more frequent with powered phlebectomy and reduced the early postoperative QOL. A meta-analysis of Luebke and Brunkwall concluded that powered phlebectomy decreased the number of incisions, improved mean cosmetic score and shortened the duration of the procedure in patients with extensive varicosities. There was less calf hematoma after hook phlebectomy and a worse mean pain score after powered phlebectomy.[11]

7.2.3. For patients with symptomatic varicose tributaries, treatment of the tributaries should be performed even if the superficial trunks are competent.

Consensus statement.

Rationale. In general, treatment for primary or recurrent varicose veins irrespective of axial competence has been shown to be effective and indicated for patients with symptomatic C2 disease.

Evidence. Surgical intervention for symptomatic varicose veins has been widely accepted as being an effective, appropriate therapy with good outcomes for pain reduction and improvement in QOL. A Cochrane review in 2004 compared treatments of varicose veins with surgery vs sclerotherapy and concluded that there was insufficient evidence to preferentially recommend the use of sclerotherapy or surgery.[194] A systematic

Table XX. Treatment of patients with recurrent and residual axial reflux of superficial truncal veins

Author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Theivacumar, 2009[153]	64 patients	EVLA in above-knee GSV	none	Persistent below-knee reflux of the GSV was associated with residual symptomatology	Prospective
Sussman, 2022[33]	15 studies 1368 patients	Ablative/surgical GSV interventions	none	Below-knee reflux recurrence shown to be lower in above-knee+below-knee-EVLA over above-knee-EVLA or above-knee-HL&S	Systematic review
Hwang, 2018[216]	37 limbs	Below-knee-GSV RFA or below-knee-GSV EVLA plus minus stripping	none	94.6 % closure at 12 months	Retrospective
Gifford, 2014[151]	14 limbs	Below-knee-GSV RFA below-knee-GSV EVLA	none	No residual or recurrent disease following repeat ablation	Retrospective
Hernando, 2022[217]	21 patients	Catheter directed sclerotherapy and phlebectomy	none	100% closure up to 6 months, 86% closure at 1 year	Prospective
Bradbury, 2010[218]	Primary disease: 977 (868 C2/3 disease) patients, 1252 limbs Recurrent disease: 372 patients GSV (n = 286) SSV (n = 50) AASV (n = 46)	FS	none	No significant difference in retreatment rates between UGFS for GSV and SSV reflux or between UGFS for primary or recurrent disease	Prospective
Turtulici,[222] 2017	37 patients with recurrent disease	RFA	none	SFJ and perforator treatment failure at 1 year was 17% and 23%	Prospective
Theivacumar, 2008[219]	27 patients with recanalization, 3 patients with repeated EVLA	EVLA	none	Successful EVLA causes GSV shrinkage. remains small with minimal reflux and persisting clinical benefit	Prospective

EVLA, Endovenous laser ablation; *FS*, foam sclerotherapy; *GSV*, great saphenous vein; *RFA*, radiofrequency ablation; *SFJ*, saphenofemoral junction; *SSV*, small saphenous vein; *UGFS*, ultrasound-guided foam sclerotherapy.

review in 2009 by Leopardi et al[195] concluded that sclerotherapy and phlebectomy may be appropriate in patients with minor superficial varicose veins not related to reflux of the saphenous system or as a post- or adjunctive treatment of varicose tributaries, but data were limited. A recent Cochrane review in 2021 addressed the efficacy of sclerotherapy alone for treatment of varicose veins.[196] The study included 28 RCTs involving 4278 participants. None of the RCTs compared sclerotherapy, however, to no intervention or to pharmacological therapy. There was very low to low-certainty evidence that FS alone improved cosmetic appearance, residual varicose veins and symptoms compared with placebo and possible improved QOL and VCSS. The study concluded that there is a need for high-quality trials using standardized sclerosant doses, with well-defined outcome measures and measurement time points to increase the certainty of the evidence. There have been a number of studies that showed benefit of treatment of recurrent varicosities after saphenous ablation using either mini-phlebectomy or sclerotherapy, with good results.[197,198] Currently, UGFS is most commonly used for treatment of recurrent varicose veins,[198] and re-exploration of the groin or phlebectomy in that region is avoided. In the absence of superficial refluxing axial veins or for

Table XXI. Technique and outcome of perforator ablation in recurrent C2 disease

Author, year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
Kianifard, 2007[227]	72 patients	38 patients had standard surgery + SEPS (71% C2 disease)	32 patients with standard surgery (75% C2 disease)	Reduction in IPVs and limbs with IPVs with addition of SEPS. No significant difference in pain (VAS), mobility, cosmetic score or QOL (SF-36, Aberdeen Varicose Vein Questionnaire) between groups.	Randomized control trial
Park, 2012[229]	69 patients (C2, C3) without SFJ reflux but with IPV reflux into GSV	EVLA of IPVs in the thigh followed by ablation of the GSV below the IPV (n = 34)	EVLA of the GSV starting just proximal to the thigh IPV without ablation of the IPV itself (n = 35)	Technical success was significantly lower with IPV ablation (76.5%) compared with GSV ablation alone (100%) [$P = .002$]. No significant difference in closure of treated vein. No significant difference in occurrence and degree of complications between the groups.	Randomized control trial
van Neer, 2006[230]	62 limbs with C2	HL/S of the GSV to knee	none	No difference in 6- month outcome based on preoperative IPV presence.	
Koroglu, 2011[231]	60 limbs in 55 patients	EVLA + FS	EVLA of venous varicosities + FS of IPV	IPV noted in 75% compared with 98.6% for the saphenous veins No significant difference in improvement of VCSS between groups Improvement in VAS score greater after treatment of isolated saphenous vein reflux ($P < .05$)	

EVLA, Endovenous laser ablation; *GSC*, great saphenous vein; *IPV*, incompetent perforator veins; *QOL*, quality of life; *SEPS*, subfascial endoscopic perforator surgery; *SF-36*, Short Form 36; *VAS*, visual analog scale.

patients with prior axial reflux ablation, conservative measures, such as compression or VADs can also be considered for varicose tributaries (see Guidelines 2 and 3).

7.2.4. There is no clinical evidence that FS using room air is less safe and effective than using CO_2 gas mixture.

Consensus statement.

Rationale. Many studies show the benefit of FS for treatment of superficial venous disease, with minimal side effects. While in theory felt to be safer, there is limited data that directly compares the use of CO_2 or CO_2/O_2-based foam to room air when treating with foam sclerosants.

Evidence. UGFS has been shown to be safe and effective for the treatment of superficial venous disease, and it is currently recommended for treatment of reticular and varicose veins, in addition of superficial truncal veins. In a comprehensive review of the literature Cartee et al,[199] discussed factors affecting foam stability and found that the half-life of room air foam was reported to be three times longer than that of CO_2 alone and 1.5 times longer than O_2/CO_2.[200,201]

Morrison et al[202] showed that bubbles were detected in the right heart in all patients after room air FS and high-intensity transient signals were seen in the middle cerebral artery in 4 of 21 patients. Morrison et al[203] looked at side effects using air and CO_2 foam for endovenous chemical ablation and found visual disturbances (VDs) were experienced by 3.1% (4/128) and 8.2% (4/49) patients in the CO_2 and room air groups respectively ($P = .15$). Respiratory difficulties or circumoral paresthesia each occurred in 0.8% (n = 1) of the CO_2 patients. Incidence of chest tightness (3.1% vs 18%), dry cough (1.6% vs 16%), or dizziness (3.1% vs 12%) were significantly lower in the CO_2 vs room air group ($P < .02$). While other

Table XXII. Venous thromboembolism (VTE) after endovenous ablations

First author, year	Patient	Intervention/exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Suarez (2022)[234]	Patients undergoing thermal or nonthermal ablation of the GSV, SSV, or accessory veins	–	–	Pooled incidence of EHIT I-IV, EHIT II-IV, and DVT. Pooled incidence of EHIT II-IV, DVT, and PE together.	Systematic review of observational studies and RCTs with ≥150 patients.	Timing of DUS after ablation
Healy (2108)[235]	Patients undergoing thermal ablation of the GSV	–	–	1. EHIT II-IV + DVT 2. EHIT II-IV, DVT, and PE	Systematic review of observational studies and RCTs with ≥100 patients	Timing of DUS after ablation
Healy, DA (2021)[236]	Patients undergoing thermal ablation of the GSV with DUS within 30 days	–	–	1. EHIT I-IV 2. DVT 3.PE 4. EHIT II-IV + PE	Systematic review of RCTs (17) and case series (58) with ≥100 patients	Timing of DUS after ablation Variable thromboprophylaxis
Turner (2022)[32]	Patients with superficial reflux undergoing endovenous intervention (open surgery excluded)	Mechanical + Pharmacoprophylaxis (single dose, 12 studies; extended, 29 studies; combination, 2 studies)	Mechanical prophylaxis (compression stockings or bandages)	DVT (randomized trials) EHIT III-IV PE Major/minor bleeding	Systematic Review and Meta-analysis	Failure to distinguish EHIT from DVT in some studies. Confounding by indication (observational studies) Poor reporting of mechanical (compression) prophylaxis Differences in anticoagulation regimens (agents, dose, duration)
Alameer (2022)[41]	Patients undergoing varicose vein intervention (open or endovenous)	Pharmacoprophylaxis	Compression	All thrombotic events, DVT, bleeding	Systematic review and meta-analysis	Variable anticoagulation agents and duration Lack of risk stratification

DUS, Duplex ultrasound; *DVT*, deep vein thrombosis; *EHIT*, endovenous heat-induced thrombosis; *GSV*, great saphenous vein; *PE*, pulmonary embolism; *RCT*, randomized controlled trial.

complications were less in the CO_2 group, VDs were not significantly different, but conclusion are limited by the small sample size.

Willenburg et al[204] conducted a systemic review evaluating VD following sclerotherapy of varicose veins, reticular veins and telangiectasias. While the prevalence of VD was difficult to determine, two RCTs reported no VDs (95 and 75 patients treated, respectively). In large case series (>500 patients), the prevalence of VD ranged from 0.09% to 2%. In a meta-analysis that included over 9000 patients, Jia et al[10] found the median rates of VDs and headache were 1.4% and 4.2%, respectively. Chest tightness and coughing occurred in <1%. Room air and CO_2-created foams were included in this metanalysis. Gillet et al[205] evaluated the side-effects and complications of FS in a prospective, multicenter study of room air vs oxygen FS in 1025 patients. The incidence of migraine was 0.78% (with aura 0.59%, 0.19% without aura), VD 0.68%, chest tightness 0.68%, chest tightness with VD 0.49% and transient ischemic attack occurred in 0.1%.

In summary, while theoretically CO_2 foam supposed to improve safety profile compared with room air, the data is limited, and the studies support both methods of FS (Table XVIII). In addition, room air foam is more

Table XXII. IEvidence for treatment of EHIT

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Healy 2021[235]	Patients developing EHIT II-IV after thermal ablation of the GSV ablation	–	–	1. EHIT treatment modality 2. EHIT propagation or embolization	Systematic review (24 studies)	Lack of standardized treatment for EHIT

EHIT, Endovenous heat-induced thrombosis; *GSV*, great saphenous vein.

stable than CO_2 making both the delivery method and provider skill important in achieving the desired outcome.

7.2.5. There is currently no clinical study of sclerotherapy with PCF, prepared using the Tessari method, that shows that it is less safe or effective than PEM.

Consensus statement.

Rationale. PEM, used for treatment of truncal veins and varicose tributaries is a promising product that appears to be more stable and cohesive, with a narrow bubble size distribution compared with physician compounded foam, used for sclerotherapy of varicose tributaries and superficial truncal veins.

Evidence. As articulated in the statement, there is no clinical evidence that sclerotherapy with PCF, prepared using the Tessari method is less safe or effective than PEM. There are no prospective studies comparing the two techniques since the VANISH-2 RCT compared 0.5% and 1% PEM with placebo (Table XIX).[206] In laboratory testing, PEM had a narrow bubble size distribution, better stability, more cohesive properties and lower degradation rate than any PCFs.[213] Prospective randomized studies comparing PEM with PCF in patients with varicose veins are warranted.

8. Treatment of varicose tributaries concomitant or staged with superficial truncal ablation

8.1.1. For patients with symptomatic reflux in the GSV or SSV and associated varicosities, we recommend ablation of the refluxing venous trunk and concomitant phlebectomy or UGFS of the varicosities with PCF or PEM.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: C (low to very low)

8.1.2. For patients with symptomatic reflux in the AAGSV or PAGSV, we suggest ablation of the refluxing venous trunk and concomitant phlebectomy or UGFS of the varicosities with PCF or PEM.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

Table XXIV. Treatment of superficial venous thrombosis

First author, Year	Patients/Limbs	Intervention	Comparison	Outcome	Study design
DiNisio 2018[34]	7296	Fondaparinux, rivaroxaban, LMWH, unfractionated heparin, NSAIDS, compression, topical, IM, IM, surgical	Placebo (few)	SVT extension, VTE, pain, bleeding	RCTs for systematic review
Duffett 2019[35]	6862	NSAIDs, anticoagulant therapies, surgical therapies	Placebo, No therapy (few)	DVT, PE	RCT, cohort for Systematic review
Prandoni, 2022[255]	374	LMWH, fondaparinux, VKA, DOAC (full anticoagulation)	Preventive anticoagulation	SVT extension, VTE, bleeding	Retrospective, registry
Casian, 2022[256]	190/195	Anticoagulation, surgery	None	SVT recurrence, extension, VTE	Prospective observational

DOAC, Direct oral anticoagulant; *LMWH*, low-molecular-weight heparin; *NSAID*, nonsteroidal anti-inflammatory drug; *PE*, pulmonary embolism; *RCT*, randomized controlled trial; *SVT*, superficial vein thrombosis; *VKA*, vitamin K agonist; *VTE*, venous thromboembolism.

8.1.3. For patients with symptomatic reflux in the GSV or SSV, we suggest ablation of the refluxing venous trunk and staged phlebectomy or UGFS of the varicosities only if anatomical or medical reasons are present. We suggest shared decision-making with the patient regarding timing of the procedure.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

8.1.4. For patients with symptomatic reflux in the AAGSV or PAGSV, we suggest ablation of the refluxing venous trunk and staged phlebectomy or UGFS of the varicosities only if anatomical or medical reasons present. We suggest shared decision-making with the patient regarding timing of the procedure.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

8.2. For patients with symptomatic reflux in the major superficial venous trunks and associated varicosities undergoing initial ablation alone, we recommend follow-up for ≥3 months to assess the need for staged phlebectomy or ultrasound-guided sclerotherapy for persistent or recurrent symptoms. Longer follow-up is recommended for those with recurrence or more advanced CEAP class.

Good clinical practice statement. For Rationale and Evidence supporting Guidelines 8.1.1. to 8.1.4. and Good Clinical Practice statement 6.2, please see Part I of the varicose vein guidelines.[8] The panel strongly recommended concomitant procedures to treat truncal incompetence and varicose veins at the same settings, since most patients would like to have a single operation, but the evidence supporting the efficacy of a concomitant procedure had to be downgraded to C (low to very low), because the meta-analysis by Aherne et al[214] included 12 nonrandomized studies with the intrinsic associated bias. A subanalysis of three RCTs showed no difference in reinterventions between the groups. In addition, 63.9% of the patients with planned staged intervention never had a second procedure. The study counted the second operation of a staged procedure "reinterventions" and the percent of reinterventions after the staged procedures was not investigated. In one of the RCTs,[152] the need for staged treatment of varicose tributaries was only 17% in those patients who underwent extended EVLA for axial, below-knee saphenous incompetence.

Table XXV. Top 20 topics for future research on varicose veins

N.	Topic of research
1.	Comparative studies of polidocanol endovenous microfoam vs physician compounded foam for treatment of varicose tributaries.
2.	Comparative studies of polidocanol endovenous microfoam vs other techniques of thermal and nonthermal ablations of incompetent superficial truncal veins.
3.	Best metric of axial reflux to determine ablation of superficial truncal veins: vein diameter, reflux time, reflux volume or combination of these metrics.
4.	Longitudinal studies to identify risk factors for progression of C2 to C4 disease.
5.	Comparative studies of thermal vs nonthermal ablations.
6.	Studies to identify patients who need periprocedural thrombosis prophylaxis and define optimal drugs (LMWH, DOACs), dose, and duration of prophylaxis.
7.	Cost and QOL comparisons between staged vs concomitant phlebectomy after saphenous ablation.
8.	Clinical trial to evaluate efficacy and cost effectiveness of 20-30 mm Hg compression stockings vs venous ablation as initial treatment of patients with C2 disease.
9.	Outcome of thermal vs nonthermal ablation of saphenous veins >10 mm in diameter.
10.	DOAC for treatment SVT of the GSV ≤3 cm from the saphenofemoral junction (SFJ).
11.	Comparative studies of varicose vein treatment in patients with and without proximal deep vein occlusion.
12.	Best treatment option for lower extremity and vulvar varicose vein tributaries: miniphlebectomies vs FS
13.	Best treatment options for telangiectasia and reticular veins: foam vs liquid sclerotherapy vs surface laser.
14.	Comparative study of cyanoacrylate vs thermal closure of perforating veins.
15.	Appropriate training for treatment of varicose veins.
16.	Treatment of superficial thrombophlebitis affecting varicose veins.
17.	Adjuvant medical treatment of patients with C2 varicose veins.
18.	Long-term outcome after SSV and AAGSV ablations.
19.	Treatment of saphenous aneurysms <3 cm in size <3 cm from the SFJ with thermal ablation vs open surgery.
20.	Management of intravenous line related thrombophlebitis: role of NSAIDs and warm compresses.

AAGSV, Anterior accessory great saphenous vein; *DOAC*, direct oral anticoagulant; *FS*, foam sclerotherapy; *LMWH*, low-molecular-wight heparin; *NSAID*, nonsteroidal anti-inflammatory drug; *QOL*, quality of life; *SFJ*, saphenofemoral junction; *SSV*, small saphenous vein; *SVT*, superficial vein thrombosis.

9. Management of recurrent varicosities

9.1.1. For patients with symptomatic recurrent varicosities, clinical evaluation and DUS should be performed before treatment to determine the potential source of recurrence.

Consensus statement.

Rationale. Mandatory follow-up for C2 patients for several years post intervention is costly and not indicated. Patients who present with recurrent symptoms are common, however, and require thorough evaluation to determine the source of recurrence.

Evidence. Evaluation of symptomatic recurrent varicose veins should be performed after a careful clinical examination of the patient in the standing position and

Table XXVI. Clinical benefit of hydroxyethylrutosides

First author, year	Patient	Intervention/exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Aziz Z, 2015[17]	Adults with CVI including CEAP C2	Hydroxyethylrutosides with or without compression bandaging	Placebo with or without compression bandaging, compression bandaging alone in one RCT	Pain, heavy legs, and cramps. Safety analysis. **Modest improvement in several symptoms of CVI (pain, heaviness, cramps)**	Systematic review and meta-analysis of 15 RCT.	Age, sex, different stages of CVD in patients with varicose veins
Allaert FA, 2012[112]	Adults with lower extremity venous edema	Hydroxyethyl-rutosides, Ruscus extracts, MPFF, and diosmin	Placebo or other VAD	Reduction of ankle edema **Third best VAD for reduction of ankle circumference**	Systematic review and meta-analysis of 10 double-blind, randomized, placebo or other VAD-controlled trials	Age, sex, different stages of CVD in patients with varicose veins
Pompilio G, 2021[15]	Adults with Chronic Venous Disease	Hydroxyethyl rutosides, Ruscus extracts, MPFF, sulodexide, calcium-dobesilate, horse chestnut extracts and pentoxifylline	Placebo in 45 RCT	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score) **First top rank to be the better treatment for pain, cramps, swelling sensation and heaviness score measured by Likert scale**	Systematic review and meta-analysis of 45 RCTs and separated analysis of 17 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *MPFF*, micronized purified flavonoid fraction; *RCT*, randomized controlled trial.

with DUS to assess the etiology, source, type, and extent of recurrent varicose veins. The entire ablated vein, sites of reflux at the SFJ or SPJ and at sites of potential incompetent perforating veins should be investigated. DUS can identify refluxing, recanalized axial veins, and residual saphenous stumps but it only has a sensitivity of 62% and a positive predictive value of only 26% to correctly identify neovascularization.[215]

Recurrent varicose veins after surgery have been reported to occur between 6.6% to 37.0% at 2 years and upwards of 50% at 5 years.[7] We recommend that all patients who have undergone a venous intervention for varicose veins have at least one follow-up visit when symptoms related to the procedure are likely to have resolved and interval healing has occurred. Any residual symptoms or problematic residual varicose veins should be reassessed and documented. Reevaluation after 3 months may be patient initiated based on recurrent symptoms.

9.1.2 For patients with symptomatic recurrent varicosities due to persistent or recurrent reflux of the GSV or AAGSV, treatment either with open surgical or endovascular techniques may be performed, with good outcomes expected.

Consensus statement.

Rationale and evidence. Theivacumar et al treated 64 patients with EVLA of the above knee (above-knee) GSV. Above-knee-GSV EVLA improved symptoms regardless of persisting below-knee reflux; the latter, however, was responsible for residual symptoms and a greater need for sclerotherapy for residual varicosities.[153] A systematic review in 2021 investigated the incidence of below-knee residual reflux in patients who underwent ablation of the GSV.[33] HL&S in the above-knee GSV (6 studies, 525 limbs), as well as EVLA, above-knee only (7 studies, 696 limbs) and above-knee+below-knee ablation (2 studies, 147 limbs), were included. The authors found that above-knee+below-knee EVLA was

Table XXVII. Clinical benefit of calcium dobesilate

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Ciapponi A, 2004[18]	Adults with CVI including CEAP C2	Calcium dobesilate	Placebo	Pain, heaviness, night cramps, discomfort, paresthesia, malleolar swelling **Calcium dobesilate suggested as more effective than placebo in improving symptoms. Higher efficacy in more severe disease.**	Systematic review and meta-analysis of 10 RCTs	Age, sex, different stages of CVD in patients with varicose veins
Pompilio G, 2021[15]	Adults with Chronic Venous Disease	Calcium dobesilate, Hydroxyethyl rutosides, Ruscus extracts, MPFF, sulodexide, horse chestnut extracts and pentoxifylline	Placebo in 45 RCTs	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score) **Calcium dobesilate the most effective treatment in reducing leg volume**	Systematic review and meta-analysis of 45 RCTs and separated analysis of 17 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins
Allain H, 2004[298]	Adults with CVD, diabetic retinopathy, and hemorrhoids	Calcium dobesilate	NA	Adverse events **The risk of an adverse event with calcium dobesilate is low. 13 known cases of agranulocytosis, less than incidence in general population**	Review of the adverse events and safety profile	Age, sex, different stages of CVD and different diseases

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *NA*, not applicable; *QOL*, quality of life; *RCT*, randomized controlled trial.

associated with significantly lower odds of below-knee reflux recurrence compared with above-knee-EVLA alone (OR, 0.1857; 95% CI, 0.076-0.4734; $P < .0001$). No statistically significant difference was observed in below-knee-GSV reflux recurrence between patients receiving above-knee-EVLA and those receiving above-knee-HL&S.

Endovenous treatment of below-knee refluxing segments of GSV was investigated in a 2018 retrospective study of 37 limbs using RFA and EVLA.[216] Complete closures were found in 35/37 limbs and VCSS was reduced in both groups. Ecchymosis scores were significantly lower after RFA vs EVLA with a 980 nm system, but no difference was reported when compared with a group where a 1470 nm fiber was used. Gifford et al also reported good outcomes with few complications in a retrospective series of below-knee-GSV ablation mainly with EVLA (77 limbs) with only about half of the cohort including patients with C1 to C3 classification and concomitant ambulatory phlebectomies being performed in 75% of cases.[151]

Catheter-directed FS has also been investigated as a treatment modality for recurrent GSV reflux in a small prospective analysis of 21 patients in Brazil with mostly C2 disease.[216] FS was performed as a pull-back procedure developed by Parsi with either 3% sodium tetradecyl sulfate or polidocanol 3%, using ultrasound guided tumescent anesthesia. Closure rate was 100% up to six months and 86% at one year. There were no complications.

Table XXVIII. Clinical benefit of horse chestnut extract

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Pittler MH, 2012[300]	Adults with CVI including CEAP C2	Horse chestnut extract	Placebo	CVI related signs and symptoms: pain, leg volume. **Overall improvement of pain, edema and pruritus. Mild and infrequent adverse events**	Cochrane Database Systematic review	Age, sex, different stages of CVD in patients with varicose veins
Pompilio G, 2021[15]	Adults with CVD	Horse chestnut extracts, calcium-dobesilate, Hydroxy-ethyl rutosides, Ruscus extracts, MPFF, sulodexide, and pentoxifylline	Placebo in 45 RCTs	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score) **Only one study could be used for VAD comparisons.**	Systematic review and meta-analysis of 45 RCTs and separated analysis of 17 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *RCT*, randomized controlled trial; *VAD*, venoactive drugs; randomized controlled trial.

Bradbury et al studied 1252 legs with C2 to C6 disease.[218] They were treated with UGFS. There were 868 C2 and C3 patients. The authors found that out of 1031 patients initially treated for GSV reflux, only 11.8% required a second UGFS for recurrent reflux. Of the 139 patients with AAGSV reflux, 10.1% required a second UGFS for recurrent reflux. Of the 239 patients with SSV reflux, 10.5% required retreatment for axial vein reflux. New reflux rates found in follow-up included 3.4% GSV, 6.5% AASV, and 3.4% SSV.

Hernando et al[217] treated 21 patients 16 with C2 disease, for recurrent symptomatic varicose veins. Previous interventions included CHIVA, mechanochemical ablation, thermal ablation, and cyanoacrylate closure. The patients were treated with catheter directed foam for the refluxing axial veins, and phlebectomy for the varicose tributaries. Catheter-directed sclerotherapy was performed in 18 GSVs. Closure at 1 week and at 6 months was 100%, and at1 year it was 86%.

Turtulici et al[222] studied 37 patients with recurrent varicose veins. Ten patients had reflux in the SFJ, 21 had single or multiple recanalized and refluxing perforator veins, and 6 had a combination of SFJ reflux and perforator vein reflux. All patients were treated with RFA. Recanalized axial veins were found in 4%, but no retreatment was required. The vein diameters were small and the Aberdeen Varicose Vein Severity scores of the limbs decreased.

9.1.3. For patients with symptomatic recurrent varicosities due to persistent or recurrent reflux at the groin, either EVLA or RFA can be used if there is a straight GSV stump, long enough for thermal ablation. Sclerotherapy or phlebectomy should be performed for recurrence due to neovascularization.

Consensus statement.

Rationale. Groin recurrence can be due to recanalized or enlarged remnants of the GSV or tributaries due to neovascularization or disease progression from other vein segments.

Evidence. The Edinburgh group[220] has classified recurrence into the following subtypes: residual GSV (type 1A), residual tributaries that have enlarged (1B), or neovascularization (1C). The disease from new segments, type 2 is subdivided into cross-groin connections (2A) and thigh perforators (2B). Recurrent veins are often difficult to classify[221] and difficult to treat and there is no preferred mode of treatment. Options include surgical removal, sclerotherapy, and thermal ablation. All modalities have their challenges, including easy tearing and bleeding in the presence of scarring from previous open procedures. UGFS is used with increasing frequency instead of open surgery. EVLA can be performed if there is a straight stump but it can also be challenging in patients with tortuous or short GSV stumps.

9.1.4. For patients with symptomatic recurrent varicosity due to persistent or recurrent reflux of the SSV, UGFS should be performed.

Consensus statement.

Rationale and evidence. SSV recurrence is rare but can occur following incomplete obliteration distal to the SPJ and in patients with persisting reflux in tributaries associated with the saphenous stump. Recurrence can also occur if there is neovascularization that reconnects the

Table XXIX. Clinical benefit of Red vine leaf extract

First author, year	Patient	Intervention/ exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Azdhari M, 2020[307]	Adults with CVI	Red vine leaf extract	Placebo?	Leg volume, calf circumference, tired and heavy legs, sensation of tension, tingling and pain. In some trials significant improvement of leg volume, calf circumference, tired and heavy legs, sensation of tension, tingling and pain, cutaneous microcirculation and O_2 pressure.	Systematic review. 5 trials	Age, sex, different stages of CVD in patients with varicose veins
Stucker M, 2019[303]	Adults with CEAP C1s to C4	Red vine leaf extract	Placebo	Leg edema reduction assessed by volumetry, and venous symptoms (heaviness, tingling and pain). Significant and relevant clinical efficacy over placebo in patients CEAP C1s to C4, on edema, tension, heaviness, tingling and pain	Review	Age, sex, different stages of CVD in patients with varicose veins
Kalus U, 2004[304]	Adults with CVI grade I or II of Widmer classification n = 71	Red vine leaf extract	Placebo	Cutaneous microvascular blood flow, transcutaneous oxygen pressure, leg edema Improvement of microvascular blood flow, oxygen pressure and leg circumference ($P <$ .0001)	Crossover RCT vs placebo	Age, sex, different stages of CVD in patients with varicose veins
Rabe E, 2011[306]	Adults with varicose veins and CEAP C3-C4a n = 248	Red vine leaf extract	Placebo	Leg volume by water plethysmography Symptoms (10-cm VAS). Global efficacy evaluations. Significantly reduced limb volume ($P =$ .0268) and improved pain ($P =$ .047)	RCT	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *RCT*, randomized controlled trial; *VAD*, venoactive drugs; randomized controlled trial; *VAS*, visual analog scale.

Table XXX. Clinical benefit of sulodexide

First author, year	Patient	Intervention/exposure	Comparison	Outcomes	Study design	Possible explanations of heterogeneity (factors to be used to stratify analysis)
Bignamini AA, 2020[19]	Adults with CVD any stage n = 1901	Sulodexide	None or heparan sulphate	Leg edema reduction assessed by volumetry, and venous symptoms (heaviness, tingling and pain). Decrease of pain, cramps, heaviness, edema and total symptoms score. Reduced inflammatory mediators. Low risk of adverse events (3%)	Systematic review and meta-analysis of 13 studies	Age, sex, different stages of CVD in patients with varicose veins
Pompilio G, 2021[15]	Adults with Chronic Venous Disease	Sulodexide, Horse chestnut extracts, calcium -dobesilate, Hydroxy-ethyl rutosides, Ruscus extracts, MPFF, and pentoxifylline	Placebo in 45 RCTs	Ulcer healing, leg volume, ankle circumference, symptoms such as pain assessed by VAS, feeling of swelling, heaviness, as well as QOL (CIVIQ-20 score). Sulodexide at least as effective as pentoxifylline for ulcer healing. Based on observational studies it is effective in improving venous symptoms and signs.	Systematic review and meta-analysis; 45 RCTs; 18 observational studies with sulodexide	Age, sex, different stages of CVD in patients with varicose veins

CEAP, Clinical stage, etiology, anatomy, pathology; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *CVD*, chronic venous disease; *CVI*, chronic venous insufficiency; *MPFF*, micronized purified flavonoid fraction; *QOL*, quality of life; *RCT*, randomized controlled trial; *VAD*, venoactive drugs; randomized controlled trial.

popliteal vein to the superficial network or if there are other sources of proximal reflux connecting to the SSV, not treated initially (Table XX). Currently UGFS appears to be the preferred treatment.[221]

9.1.5. For patients with residual or recurrent varicosity due to incompetent perforator veins (IPVs), treatment with both open and endovascular techniques may be used depending on the physician's experience, patient wishes, and availability of technology.

Consensus statement.

Rationale. There are no high-level data to compare outcome of different techniques to treat IPVs responsible for recurrent/persistent varicose veins. One should rely on experience, patient wishes, and the availability of the various techniques reviewed above.

Evidence. A 2016 prospective trial with 296 IPV closures on 112 patients compared three methods of IPV closure (RFA, EVLA, and FS) in mostly C5 and C6 patients.[223] Closure success was significantly better with RFA (73%; $P = .05$) vs FS (57%) but failed to reach significance vs EVLA (61%; $P = .09$). Interestingly, when patients failed FS and were subsequently treated with thermal ablation, RFA success improved to 89% ($P = .003$) and EVLA success improved to 85% ($P = .03$). The authors concluded that RFA was found to be the most reliable means of IPV closure. After failed FS attempts, IPV closure was enhanced when thermal ablation was used as a secondary technique. A common factor leading to increased failure in all groups was morbid obesity. Although C2 to C6 patients were enrolled in this study, only three with C2 disease were included and all three were treated with foam initially, thereby significantly limiting the applicability of the findings to C2 disease. More recently, a technique for cyanoacrylate closure of perforating veins has been described in a retrospective series of 83 patients with C2-6 disease (27% C2 patients) showing a success rate of 86.5% at 72 days with complications of mainly superficial phlebitis in about 16% of treated veins recorded within 4 weeks.[224] For further evidence on efficacy of IPV ablation, see Guideline 10.

10. Ablation of incompetent perforating veins

10.1.1. For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the GSV or SSV, we recommend against treatment of

Table XXXI. Evidence to decision framework: Compression therapy vs intervention

Domain	Evidence/panel input	Judgment
How substantial are desirable effects of the strategy?	Overall, there was insufficient high Quality of Evidence to determine whether compression stockings are effective as the primary treatment for symptomatic varicose veins and if one stocking is better than the other. However, some studies reported improvement in symptoms.	Probably yes
How substantial are the undesirable anticipated effects?	Reported side effects of discomfort, appearance, and application difficulty. The benefits of stockings were offset by highly variable reports of compliance, presumably due to the most common side effects of itching and irritation.	Probably yes
Do the desirable effects outweigh the undesirable effects?	Probably	Probably yes
What is the overall certainty of the evidence of effects?	Low with significant heterogeneity of data	Low
How large are the resource requirements associated with the intervention?	No available data	Unknown
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

incompetent perforating veins concomitant with initial ablation of the saphenous veins.

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: C (low to very low)

10.1.2. For patients with varicose veins (CEAP class C2) who have significant, symptomatic axial reflux of the AAGSV or PAGSV, we suggest against treatment of incompetent perforating veins concomitant with initial ablation of the superficial truncal veins.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

For Rationale and Evidence supporting Guidelines 10.1.1 and 10.1.2, please see Part I of the varicose vein guidelines.[8]

10.2. For patients with incompetent pathologic perforators associated with symptomatic residual, recurrent, and rarely primary varicosities, without associated saphenous incompetence, either open or endovascular techniques can be used to treat the perforator veins.

Consensus statement.

Rationale. Since IPVs are potential sources of recurrence, occlusion of relevant IPVs is indicated in C2 patients who have symptomatic recurrent or residual varicose veins after previous superficial truncal ablation and tributary treatment. Perforating veins may also rarely be source of primary varicose veins in the absence of saphenous incompetence.

Evidence. Various techniques have been used to treatment of IPV, from the Linton procedure to subfascial endoscopic perforator surgery (SEPS) and to less invasive techniques of ligation through mini phlebectomy and endovenous procedures.[225] The Linton and the SEPS procedures today are of historic interest only, but SEPS was useful to gain insight into the efficacy of occlusion of IPVs.[226] In an RCT by Kianifard et al,[227] 72 patients with C2 disease were treated with HL&S ± phlebectomy, 38 also underwent the SEPS procedure. At 1 year, no additional clinical benefit could be observed, when SEPS was added to HL&S. It should therefore be emphasized that SEPS or any other technique for perforator treatment concomitant with initial superficial axial reflux treatment in C2 disease is not recommended.[8]

Despite these general findings, perforating veins may occasionally be the source of primary varicose veins in the absence of saphenous reflux. In a review of 835 limbs referred to the vascular laboratory for CVD, isolated non-saphenous origin reflux was found in 84 (10%).[228] Ninety percent of these limbs were CEAP class 1 t 3. Thigh perforators were found in 36 limbs (43%, although only 53% of these demonstrated reflux) while 8% of limbs had reflux arising from the vein of the popliteal fossa, and 4% from knee or posterior tibial perforators.

Table XXXII. Evidence to decision framework: Intervention vs compression therapy

Domain	Evidence/panel input	Judgment
How substantial are desirable effects of the strategy?	Recommendations for superficial venous intervention over compression for patients with symptomatic varicose veins and axial reflux in the GSV or SSV are based on the Cochrane Review for compression effectiveness and two comparative randomized trials with consistent results.	Yes
How substantial are the undesirable anticipated effects?	Possible side effects are related to the surgical interventions. However, these interventions are considered as safe with low rate of complications.	Probably yes
Do the desirable effects outweigh the undesirable effects?	Probably	Probably yes
What is the overall certainty of the evidence of effects?	Moderate	Moderate
How large are the resource requirements associated with the intervention?	No available data	Unknown
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

GSV, Great saphenous vein; *SSV*, small saphenous vein.

For treatment of recurrent or residual veins due to IPVs, several techniques of IPV occlusion were reported (Table XXI). Park et al used EVLA to occlude the saphenous vein that had retrograde flow from an IPV of the thigh in 69 patients.[229] This RCT concluded that direct IPV treatment was not justified since the technical success of the perforator ablation was significantly lower than just closure of the GSV (76.5% vs 100%). The outcomes were not different for either clinical success or complications between the two groups (one with direct IPV treatment, one without). FS for IPVs has also been analyzed in conjunction with GSV ablation in a prospective trial[231]; at 6 months it showed a closure rate of 75% for IPVs vs a 98% closure of GSV. A prospective trial on 296 IPV closures in 112 patients compared three methods (RFA, EVLA, and FS); most patients had C5 or C6 disease.[223] Closure success was significantly better with RFA (73% $P = .05$) vs FS (57%), but failed to reach significance vs EVLA (61% $P = .09$). More recently, a technique for cyanoacrylate closure of perforating veins was described in a retrospective series of 83 patients with C2 to C6 disease (27% C2 patients). IPV closure rates were excellent, 96 % at 16 days and 86% at 72 days. There were no DVTs, but one patient needed antibiotic treatment for septic thrombophlebitis.[224]

In summary, there is little to no randomized data for the perforator treatment of choice for patients with recurrent/persistent C2 disease, with an associated IPV. When treatment of an IPV in a C2 patient is desired, one should rely on experience, patient wishes, and the availability of the various techniques reviewed above.

11. Management of ablation-related thrombus extension (ARTE) and DVT after endovenous ablations

11.1. Postprocedure DUS

11.1.1. In an average-risk patient who is asymptomatic following thermal ablation of the saphenous vein, we recommend against routine early postprocedural DUS to detect ARTE (formerly known as endovenous heat induced thrombosis [EHIT]) or DVT.

GUIDELINE. Grade of recommendation 1 (strong), Quality of Evidence B (moderate)

11.1.2. In an average-risk patients who is asymptomatic following nonthermal ablation of the saphenous vein, routine early postprocedural DUS may be performed to detect ARTE or DVT.

Consensus statement

11.1.3. In a high-risk patient who is asymptomatic following thermal or nonthermal saphenous ablation early DUS to exclude ARTE or DVT should be performed.

Table XXXIII. Evidence to decision framework: Immediate intervention vs 3-months trial of compression

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	There is no data proving the value of a 3-month trial of compression stockings before intervention for patients with C2 disease, required by some Insurance companies. Compression therapy was found to be inferior to minimally invasive endovenous therapies (including UGFS and endovenous thermal ablation) that produce better results with regards to anatomical disease extent, patient satisfaction and QOL.	Probably no
How substantial are the undesirable anticipated effects?	Reported side effects of discomfort, appearance, and application difficulty. The benefits of stockings were offset by highly variable reports of compliance, presumably due to the most common side effects of itching and irritation.	Probably yes
Do the desirable effects outweigh the undesirable effects?	Probably	Probably yes
What is the overall certainty of the evidence of effects?	Low with practically no data	Low
How large are the resource requirements associated with the intervention?	No available data	Unknown
How large is the incremental cost relative to the net benefit?	Compression therapy was found to be inferior to minimally invasive endovenous therapies (including UGFS and endovenous thermal ablation) that produce better results with regards to cost effectiveness.	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

UGFS, Ultrasound-guided foam sclerotherapy; *QOL*, quality of life.

Consensus statement

11.1.4. In patients who are symptomatic following thermal or nonthermal ablation, we recommend early DUS to exclude ARTE or DVT.

GUIDELINE. Grade of recommendation 1 (strong), Quality of Evidence A (high)

Rationale. Based on early reports of a high incidence of thrombus extension at the SFJ[232] (endothermal heat induced thrombosis [EHIT]) following thermal ablation of the GSV as well as ready access to ultrasound in most venous clinics, screening for EHIT and DVT with early DUS has become a common practice. EHIT is commonly classified as thrombus extension to the AFJ ort SPJ (I), involvement of <50% of the deep venous lumen (II), involvement of >50% of the deep venous lumen (III), or occlusive DVT (IV).[233] As technology has evolved over the last two decades, it has become clear that junctional thrombus extension can occur after nonthermal as well as thermal ablation. Accordingly, we suggest that the term EHIT" be replaced by "ARTE." ARTE is an all-encompassing term that includes junctional extension associated with any ablation modality including thermal, foam, mechanicochemical, and cyanoacrylate ablation. This includes events previously described as EHIT, postablation superficial thrombus extension, endovenous glue induced thrombosis, and endovenous foam-induced thrombosis. To ensure consistency with previous reports, ARTE should be classified similar to EHIT (I-IV), although it must be acknowledged that the clinical relevance of ARTE I and likely even ARTE II is minimal. In the following discussion, the preferred terminology "ARTE" will be used whenever possible, although the term "EHIT" will still be used for studies specifically reporting this as an outcome.

Previous guidelines from the AVF and SVS have suggested that venous duplex examination be performed withing 1 week of the index procedure as an ungraded best practice recommendation.[233] The European Society for Vascular Surgery has similarly considered ultrasound surveillance after treatment of a saphenous trunk as a consensus recommendation.[56] However, despite this guidance, most evidence suggests that the incidence of thromboembolic complications after saphenous

Table XXXIV. Evidence to decision framework: Postprocedure compression therapy

Domain	Evidence/panel input	Judgment
How substantial are desirable effects of the strategy?	Application of compression for one week after any endothermal ablation with and without concomitant phlebectomies appeared to be effective in reducing pain within the first 5-10 days after endothermal ablation and phlebectomies with the greatest benefits in patients undergoing EVLA. Earlier return to daily activities was also observed.	Probably yes
How substantial are the undesirable anticipated effects?	Reported side effects of discomfort, appearance, and application difficulty. The benefits of stockings can be offset by highly variable reports of compliance, presumably due to the most common side effects of itching and irritation.	Probably yes
Do the desirable effects outweigh the undesirable effects?	Probably not	Probably not
What is the overall certainty of the evidence of effects?	Moderate	Moderate
How large are the resource requirements associated with the intervention?	No available data	Unknown
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

EVLA, Endovenous laser ablation.

ablation is low, with the combined incidence of ARTE, DVT, and pulmonary embolism (PE) being 1.3% to 1.7%.[234-236] Given this low incidence, the potential magnitude of effect of any intervention such as routine ultrasound surveillance after venous ablation would be classified as "trivial" to "small" (<5 events per 1000

Table XXXV. Evidence to decision framework: Micronized purified flavonoid fraction (*MPFF*) and Ruscus

Domain	Evidence/panel input	Judgment
How substantial are desirable effects of the strategy?	Overall, there was a moderate Quality of Evidence to determine whether MPFF or Ruscus are effective in symptomatic patients with varicose veins for treatment of vein related pain, leg heaviness and/or sensation of swelling.	Yes
How substantial are the undesirable anticipated effects?	Main side effects are mild gastro-intestinal disturbances potentially alleviated by administration with a meal.	Probably no
Do the desirable effects outweigh the undesirable effects?	Probably	Yes
What is the overall certainty of the evidence of effects?	Moderate, as most of the studies address the cohort of patients with Chronic Venous Disease and varicose veins patients are only part of them	Moderate
How large are the resource requirements associated with the intervention?	MPFF or Ruscus nutritional supplements are not expensive and available in the US	Low
How large is the incremental cost relative to the net benefit?	No available data for the varicose veins	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

Table XXXVI. Evidence to decision framework: Drugs and nutritional supplements

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	Overall, there was a moderate Quality of Evidence for calcium dobesilate and low Quality of Evidence for hydroxyethylrutosides or horse chestnut extract or red vine leaf extract or sulodexide to determine whether these compounds are effective in symptomatic patients with varicose veins for treatment of vein related pain, leg heaviness and/or sensation of swelling.	Probably yes
How substantial are the undesirable anticipated effects?	Main side effects for hydroxyethylrutosides or horse chestnut extract or red vine leaf extract or sulodexide are mild gastrointestinal disturbances potentially alleviated by administration with a meal. Calcium dobesilate adverse events included fever, gastrointestinal disorders, skin reactions, arthralgia, and agranulocytosis.	Monitor agranulocytosis with calcium dobesilate
Do the desirable effects outweigh the undesirable effects?	Probably yes	Monitor agranulocytosis with calcium dobesilate
What is the overall certainty of the evidence of effects?	Moderate for calcium dobesilate, low for hydroxyethylrutosides or horse chestnut extract or red vine leaf extract or sulodexide. Most of the studies address the cohort of patients with CVD and varicose veins patients are only part of them	Moderate to low
How large are the resource requirements associated with the intervention?	Only horse chestnut extract or red vine leaf extract are available in the United States as inexpensive nutritional supplements	Low
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

CVD, Chronic venous disease.

subjects to 5-20 events per 1000 people) according to criteria developed by a Chest expert panel.[237] No trials randomizing patients to early ultrasound screening vs observation have been performed, and are unlikely to be done, given the large number of patients such a trial would require achieving adequate power in the setting of this low event rate. Assuming a pooled incidence of all venous thromboembolic (VTE) events of 1.5%, a randomized clinical trial evaluating the ability of screening DUS to reduce the incidence to 1% would require approximately 15,500 patients.[238] Furthermore, routine ultrasound screening is not recommended even in populations at higher risk for VTE, including critically ill patients with coronavirus 2019 (ungraded consensus recommendation)[239]; those undergoing orthopedic surgery (Grade 1B against),[240] nonorthopedic surgery (Grade 2C against)[241]; and major trauma patients (Grade 2C against).[241] Based on the low incidence of thromboembolic complications in asymptomatic patients, the high cost of routine DUS, the futility of performing randomized trials evaluating the utility of routine DUS, and recommendations against screening in other higher-risk populations, we recommend against routine ultrasound surveillance following saphenous vein ablation in low or average risk patients for thrombotic complications Although evidence in randomized trials of routine ultrasound screening is lacking, the strength of our recommendation is 1 (strong) against screening in this patient population, given the futility of performing such studies.

Evidence. A systematic review of 39 RCTs and 33 observational studies (31,663 patients in total) undergoing routine DUS within 4 weeks of thermal or nonthermal ablation of the GSV, SSV, or accessory veins, found a very low incidence of EHIT (2.9%), DVT (0.26%), and PE (0.03%).[234] Most EHITs were types I and II, with the incidence of EHIT III to IV being only 0.5%. The pooled incidence of any VTE event (EHIT II-IV, DVT, and PE) was 1.32% (95% CI, 0.75%-2.02%) with significant heterogeneity. The cost of routine ultrasound screening was estimated to be $61,292 per EHIT III or IV or DVT prevented.

A second, large systematic review (52 studies, 16,398 patients) evaluated only observational studies or

Table XXXVII. Evidence to decision framework: Routine ultrasound screening in asymptomatic average-risk patients

Domain	Evidence/panel input	Judgment
How substantial are desirable effects of the strategy?	Routine screening associated with substantial cost, resource utilization, and cost. Risk of bleeding events associated with anticoagulation for asymptomatic ultrasound identified events.	Large
How substantial are the undesirable anticipated effects?	Risk of asymptomatic thrombus progression/embolization if not identified. Incidence of these events is very low (approximately 1.5%). However, risk of progression/ embolization in these patients is unclear.	Probably low
Do the desirable effects outweigh the undesirable effects?	Yes	Yes
What is the overall certainty of the evidence of effects?	High certainty regarding low incidence of thrombotic events after ablation. Low certainty regarding the natural history of rare asymptomatic events identified by ultrasound.	
How large are the resource requirements associated with the intervention?	Very high	Very high
How large is the incremental cost relative to the net benefit?	Very high	Very high
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes (resource saving)	Yes

randomized trials including patients undergoing thermal ablation of the GSV and having ultrasound surveillance within 1 month of the procedure.[235] The pooled incidence of EHIT II to IV or DVT was 1.7% (95% CI, 0.9%-2.7%), for EHIT II to– IV 1.4 % (0.8%-2.3%), for DVT 0.3% (0.2%-0.5%), and for PE 0.1% (0.1%-0.02%). Significant heterogeneity was noted for EHIT II to IV + PE and EHIT II to IV, but not for DVT or PE.

A third systematic review including 75 studies (23,265 patients) included both RCTs and case series and found very similar incidences of EHIT II to IV (1.27%; 95% CI, 0.74-1.93%), DVT (0.28%; 95% CI, 0.18-0.4%), and PE (0.11%; 95% CI, 0.06-0.18%).[236] Other systematic reviews have found the majority of DVTs to be confined to the calf veins, with the incidence of proximal DVT varying between 0% and 0.4%.[41]

Table XXXVIII. Evidence to decision framework: Pharmacoprophylaxis after endovenous ablation

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	Routine thromboprophylaxis appears to reduce the risk of postprocedural thrombotic events, but the data is heterogenous and the magnitude of effect is low.	Low
How substantial are the undesirable anticipated effects?	Low risk of increased bleeding with pharmacoprophylaxis. No data regarding the cost and inconvenience of pharmacoprophylaxis.	Probably low
Do the desirable effects outweigh the undesirable effects?	Probably, but with very low magnitude of effect.	Probably yes
What is the overall certainty of the evidence of effects?	Low with significant heterogeneity and low magnitude of effect	Low
How large are the resource requirements associated with the intervention?	No available data	Unknown
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Probably yes
Is the opinion feasible to implement?	Yes	Yes

Table XXXIX. Evidence to decision framework: Treatment of symptomatic ablation-related thrombus extension (*ARTE*) according to established guidelines for acute deep vein thrombosis (*DVT*)

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	The value of routine treatment of symptomatic DVT is well established although it is less certain that the natural history of ARTE is identical to DVT.	Probably beneficial
How substantial are the undesirable anticipated effects?	Low risk of major bleeding (approximately 1%) with direct oral anticoagulants. Inconvenience and cost of anticoagulation. High cost and inconvenience of routine ultrasound follow-up.	Low
Do the desirable effects outweigh the undesirable effects?	Probably favors anticoagulation in symptomatic patients	Probably yes
What is the overall certainty of the evidence of effects?	Low with uncertain natural history of ARTE High certainty regarding low risk of anticoagulation	Low
How large are the resource requirements associated with the intervention?	Low: Fewer resources required for anticoagulation in comparison with ultrasound follow-up	Low
How large is the incremental cost relative to the net benefit?	No available data	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	No data available	Unknown
Is the opinion feasible to implement?	Yes	Yes

Although randomized trials evaluating screening DUS vs no ultrasound in asymptomatic patients after saphenous ablation have not been done, two such trials have been performed in orthopedic patients.[240] These trials failed to demonstrate a benefit to routine postoperative screening, although major bleeding rates were higher in the screening arms.

In one of the systematic reviews,[234] nonthermal techniques were associated with a higher incidence of DVT than thermal techniques (0.43 vs 0.23%; $P = .02$), although this difference was due to a higher incidence of DVT in patients undergoing sclerotherapy (Table XXII). Although total VTE events were higher among patients undergoing RFA in comparison with EVLA (3.1% vs 2.2%; $P < .001$), EHIT was higher in patients undergoing EVLA (4.4% vs 3.0%; $P < .001$). However, a second large metanalysis found the incidence of thrombotic events to be similar for RFA and EVLA.[235]

Although some data suggests that the incidence of thromboembolic complications has decreased since 2009,[242] older meta-analyses[243] have demonstrated a similarly low incidence of thromboembolic complication

Table XL. Evidence to decision framework: Treatment of superficial vein thrombosis (*SVT*) (main saphenous trunks and tributaries above the knee >3 cm from the saphenofemoral junction [SFJ] and ≥5 cm in length)

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	Prevention of key outcomes: SVT extension, recurrent SVT, VTE clinically and statistically significant	Large
How substantial are the undesirable anticipated effects?	Risk of clinically relative bleeding low	Low
Do the desirable effects outweigh the undesirable effects?	Yes	Yes
What is the overall certainty of the evidence of effects?	High certainty regarding low incidence of thrombotic events after treatment	
How large are the resource requirements associated with the intervention?	Low	Very high
How large is the incremental cost relative to the net benefit?	Low	Very high
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	Similar to other guidelines	Yes
Is the opinion feasible to implement?	Yes	Yes

VTE, Venous thromboembolism.

Table XLI. Evidence to decision framework: Superficial vein thrombosis (*SVT*) of the main saphenous trunks and treatment with low-molecular-weight heparin (LWMH) and nonsteroidal anti-inflammatory drugs (*NSAIDs*)

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	NSAIDS reduce SVT pain and extension	Large
How substantial are the undesirable anticipated effects?	Low risk of increased bleeding, gastrointestinal intolerance with NSAIDs Risk of VTE	Large
Do the desirable effects outweigh the undesirable effects?	Probably, especially for distal DVT	Yes
What is the overall certainty of the evidence of effects?	Moderate certainty	Yes
How large are the resource requirements associated with the intervention?	Low	Unknown
How large is the incremental cost relative to the net benefit?	Low	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	Yes	Yes
Is the opinion feasible to implement?	Yes	Yes

DVT, Deep vein thrombosis.

after thermal ablation or FS of the GSV. Among studies evaluating the incidence of thromboembolic complications after thermal ablation (12 RCTs, 19 case series) or FS (12 RCTs, 6 case series), the individual incidence of EHIT, DVT, and PE was <1% for all treatment modalities (RFA, laser ablation, FS). Differences between treatment modalities were judged not to be clinically meaningful.

While thrombotic complications after isolated endovenous ablation are uncommon, the incidence in patients undergoing open procedures such as HL&S and/or phlebectomy may be as high as 6.25%.[39,244] Concomitant phlebectomy of tributaries has been identified as an independent risk factor for VTE development.[242] These patients may not identify VTE symptoms due to pain and swelling associated with phlebectomy and many VTE are asymptomatic.[244] Thus, the role, or lack thereof, of surveillance duplex in this patient population remains to be defined.

While we recommend against routine ultrasound screening in asymptomatic, average-risk patients, clinicians should have a low threshold for obtaining such studies in patients with postoperative symptoms suggestive of DVT and should consider such studies in selected high-risk patients. The recommendation for DUS in patients with postprocedure symptoms suggestive of DVT (1A) is based on a meta-analysis performed by the American Society of Hematology in support of their guidelines for evaluation of patients with a high pretest probability of DVT.[245] As discussed below (guideline 11.2.1.), consistently defining the risk factors constituting a "high-risk" patient is more difficult and requires clinical judgment. With respect to ablation technique, some randomized trials[206,246] and meta-analyses[234] have suggested a higher thrombotic risk with FS, although such reports are not consistent across studies.[243] The clinical relevance of these ultrasound-

Table XLII. Evidence to decision framework: Treatment of isolated thrombosis of varicose tributaries or limited involvement of the great saphenous vein (GSV)

Domain	Evidence/Panel input	Judgment
How substantial are desirable effects of the strategy?	Surgical stripping reduces pain and discomfort	Probably beneficial
How substantial are the undesirable anticipated effects?	No reduction in VTE	Low
Do the desirable effects outweigh the undesirable effects?	Probably in select circumstances	Probably yes
What is the overall certainty of the evidence of effects?	Low with no RCTs	Low
How large are the resource requirements associated with the intervention?	Moderate	Low
How large is the incremental cost relative to the net benefit?	Moderate	Unknown
What would be the effect on health inequalities?	None	None
Is the opinion acceptable to key stakeholders?	Yes	Unknown
Is the opinion feasible to implement?	Yes	Yes

RCT, Randomized controlled trial; *VTE*, venous thromboembolism.

detected events in asymptomatic patients is unclear and requires further study. Data from at least one RCT of PEM demonstrated no difference in outcome among patients with ultrasound-detected postprocedural thrombotic events regardless of whether they were treated with anticoagulants or not.[206]

11.2. Pharmacological thromboprophylaxis

11.2.1. For high-risk patients undergoing endovenous ablation, we suggest pharmacological thrombo prophylaxis.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

Rationale. This guideline is consistent with that previously suggested by the AVF/SVS.[233] Other guidelines include those from the UK Royal Society of Medicine which suggest preoperative assessment of all patients for both VTE and bleeding risk with pharmacological prophylaxis for 7 to 14 days in intermediate-risk patients and for 4 to 6 weeks in high-risk patients.[247] The European Society for Vascular Surgery recommends VTE risk assessment in all patients with consideration of individualized thromboprophylaxis (Class IIa, Level B).[56]

Although the weight of the evidence does suggest some benefit to pharmacological thromboprophylaxis, the evidence is difficult to generalize due to the limited magnitude of effect among those systematic reviews reporting a benefit of routine thromboprophylaxis (number needed to treat 25.4-172.4 for the prevention of DVT), lack of risk stratification in most studies, and significant heterogeneity in the results. In addition to the uncertain value of routine thromboprophylaxis, there is little data regarding optimal agents, dose, or duration of thromboprophylaxis if used. We therefore suggest pharmacoprophylaxis in high-risk patients, but with a low certainty of evidence.

Evidence. Despite the very low incidence of thromboembolic events among patients undergoing endovenous ablation, one large systematic review did find a significantly lower incidence of EHIT among those receiving pharmacological prophylaxis (1.63% vs 3.04%; $P < .001$).[234] However, this was not a uniform finding across individual studies and there was heterogeneity in the prophylactic regimes used. Another systematic review included 8 studies (3 RCTs, 5 cohort studies, 6479 patients) comparing pharmacoprophylaxis to no prophylaxis following a variety of varicose vein procedures.[41] Five studies evaluated prophylaxis after open surgery and three after EVLA. The risk of DVT was lower for endovenous procedures than for open surgery. Prophylaxis was associated with a nonsignificant reduction in the composite risk of DVT, PE, and superficial venous thrombosis (pooled RR, 0.63; 95% CI, 0.04-10.43; $P = .74$) and of DVT alone (pooled RR, 0.59, 0.08-4.60; $P = .61$). There was significant heterogeneity in both results. Notably, confining the analysis to randomized trials did show a significant reduction in the risk of DVT (0.22 vs 4.15%: RR, 0.05; 95% CI, 0.02-0.13, $P < .00,001$). Among the two studies reporting bleeding risk, there was no difference among those receiving or not receiving prophylaxis. Although a few included studies evaluated the efficacy of fondaparinux and rivaroxaban as well as short vs extended courses of prophylaxis, conclusions based on the available data are difficult.

A second broader meta-analysis included 47 randomized trials, 105 prospective cohort studies, 67 retrospective cohort studies, and 2 case control studies including a total of 476, 266 patients undergoing a variety of superficial endovenous interventions with exclusion of open venous surgery.[32] Notably, most studies excluded patients with a history of DVT. Although significant heterogeneity precluded analysis of all study arms, among prospective studies additional pharmacological prophylaxis reduced the incidence of DVT to 0.73% (95% CI, 0.52%-1.02%) from 1.31% (1.15%-1.48%) for mechanical prophylaxis alone (compression stockings/bandages). No significant difference was noted between single-dose and extended pharmacoprophylaxis. There were no significant differences in PE (0.14%, 0.07%-0.28% vs 0.16%, 0.15%-0.18%) or EHIT III to IV (0.35%, 0.09%-1.40% vs 0.88%, 0.28%-2.70%) in comparing pharmacoprophylaxis to mechanical prophylaxis alone. Major bleeding was quite rare (1 case) while minor bleeding was observed in 0% to 10% of patients. Risk of bias was estimated to be high, and the Quality of Evidence was moderate among randomized trials and very low among nonrandomized trials.

A systematic review included in the AVF/SVS EHIT guidelines, which included only retrospective observational studies, failed to show a lower incidence of EHIT with pharmacological thromboprophylaxis.[233]

11.2.2. For patients undergoing endovenous ablation routine risk stratification should be performed to assess the need for periprocedural thromboprophylaxis.

Consensus statement.

Rationale and evidence. The literature reflects great uncertainty regarding the value of risk assessment in determining the need for thromboprophylaxis in patients undergoing superficial venous interventions.[32] Defining the risk factors for DVT/EHIT after saphenous ablation is unfortunately difficult due to the very low number of events and limited statistical power. Although inconsistent across studies, suggested risk factors for EHIT/DVT have included age, male gender, CEAP class, personal or family history of VTE, known thrombophilia, reduced mobility, obesity, hormone therapy, active cancer, concomitant procedures including sclerotherapy and microphlebectomy, large GSV diameter, and a history of SVT.[41,233,242,247,248] Given such uncertainty, deciding who constitutes a high-risk patient requires some degree of clinical judgment at present. Although one single-center study has shown the Caprini risk

assessment score to be associated with the development of EHIT (OR, 1.58; 95% CI, 1.24-2.0; $P = .0002$), only ultrasound identified EHIT I to II were found in this study and it remains unclear whether the Caprini score is predictive of clinically relevant thrombotic events after superficial venous intervention.[248]

Currently, no specific guidelines address the role of VTE risk stratification in the ambulatory surgery setting. Data from patients undergoing both inpatient and outpatient procedures suggests that identification of patient and procedural related risk factors allows for identification of 15- to 20-fold variation in VTE risk. Individualized risk stratification allows for the identification of low-risk patients in whom the risk-benefit ratio is unfavorable, and potentially for the identification of patients at high VTE risk in whom the benefit of receiving chemical chemoprophylaxis outweighs the attendant bleeding risk. A widely accepted risk threshold is a calculated VTE risk of 3%, assuming a two-fold reduction in VTE events compared with expected bleeding events from administration of an anticoagulant.[241] Currently, no VTE risk assessment model (RAM) has been validated in patients undergoing varicose vein procedures.

Indirect evidence suggests that risk stratifying patients undergoing varicose vein procedures may have potential benefits. Namely, among patients undergoing a variety of ambulatory surgical procedures, those undergoing procedures for varicose vein procedures are at the highest risk for development of VTE.[249] Second, variations in VTE rate among patients undergoing venous procedures have been identified according to patient and procedure related characteristics. For instance, patients undergoing open surgery or longer operations are at greater risk at developing VTE.[250] Third, limited evidence suggests that those with a higher composite VTE RAM score, such as that used in the Caprini RAM, have an increased VTE and ARTE risk.[251] Finally, a recent meta-analysis suggested that in patients undergoing inpatient and outpatient surgical procedures (including those undergoing venous procedures) with a Caprini score of ≥7 benefited from chemoprophylaxis in terms of VTE risk reduction without an increase in bleeding.[252] This data highlights the critical need to determine from a specific VTE RAM the threshold at which chemical thromboprophylaxis is favorable for the patient undergoing outpatient axial and/or tributary bed treatment. Future studies should likely focus on clinically relevant venous thromboembolic events (DVT, PE) and should include some measure of risk.

11.3. Treatment of varicose vein procedure related DVT and ARTE

In patients with DVT after endovenous ablation, we endorsed the recommendations of Stevens et al, Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021; 160(6): e545-e608.[253] The evidence base for these guidelines was adopted without review.

11.3.1. For patients with acute isolated distal DVT after varicose vein procedure, without severe symptoms or risk factors for extension we suggest serial imaging of the deep veins for 2 weeks.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: B (moderate)

11.3.2. For patients with isolated distal DVT after varicose vein procedure and severe symptoms or risk factors for extension we suggest anticoagulation.

GUIDELINE: Grade of recommendation: 2 (weak), Quality of Evidence: C (low to very low)

11.3.3. For patients with acute proximal DVT after varicose vein procedure, we recommend anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist).

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: B (moderate)

11.3.4. For patients with symptomatic ARTE after endovenous ablation, we recommend anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist).

GUIDELINE: Grade of recommendation: 1 (strong), Quality of Evidence: C (low to very low)

11.4.1. For patients with asymptomatic ARTE III and IV after endovenous ablation, anticoagulation with a direct oral anticoagulant (over a vitamin K antagonist) should be performed.

Consensus statement

11.4.2. For patients who receive anticoagulation for ARTE following endovenous ablation, treatment should be continued until the thrombus retracts.

Consensus statement.

Rationale. As discussed, routine screening of asymptomatic, average-risk patients for ARTE/DVT is not recommended and asymptomatic ARTE/DVT in these patients should rarely be diagnosed. The majority of ARTEs are ARTE I and II,[234] which is of minimal clinical relevance. Although previous guidelines[233] have recommended either no treatment (EHIT I), weekly surveillance (EHIT II), or consideration of antiplatelet vs anticoagulant therapy (high-risk patients with EHIT II), these should be rarely encountered in the absence of routine ultrasound surveillance. ARTE III and IV are presumably more likely to be symptomatic and to be suspected based on accepted clinical indications. Although it is not entirely clear that the natural history of ARTE III to IV is the same as DVT,[233] a conservative approach would suggest treatment similar to established guidelines for DVT treatment.[253] However, as the natural history of ARTE is not well-documented, the value of alternative approaches such as anticoagulation until thrombus resolution as observed by ultrasound cannot be entirely excluded. Given the uncertain benefit, treatment of symptomatic ARTE according to established guidelines for acute DVT

is a weak suggestion. Furthermore, as this evidence is extrapolated from current guidelines for the management of DVT and is therefore indirect, for the management of ARTE the level of evidence has been downgraded to C.

Further research is needed regarding the natural history of ARTE. More data is particularly needed regarding the value of anticoagulation vs serial follow-up and the duration of anticoagulation in treated patients. Given the uncertainty of the evidence, at present, duration of anticoagulation should be at the judgment of the clinician.

Evidence. The management of symptomatic DVT is generally guided by the Chest guidelines for *Antithrombotic Therapy for VTE Disease*[253] and the reader is referred to that manuscript for the supporting evidence.

Unfortunately, the data regarding the management of ARTE are substantially less robust. The evidence regarding the treatment of ultrasound detected (most presumably asymptomatic) ARTE is derived from small case series and retrospective studies and is accordingly quite variable. One systematic review evaluated the management of ARTE detected by routine ultrasound screening in 24 studies for which the treatment was described.[236] Among the 25 included studies, anticoagulation was the most common treatment for EHIT, with two studies reporting selective use of antiplatelet therapy and seven studies reporting observation only. Irrespective of treatment, there were no reports of propagation or embolization of EHIT II to IV once identified. The authors concluded that the natural history of EHIT is generally benign (Table XXIII).

12. Management of SVT in patients with varicose and nonvaricose veins

Guideline 12. Address the management of SVT in patients who have not recently undergone superficial venous interventions. The management of EHIT and other thrombotic complications of superficial venous interventions were presented in Guidelines 11.

12.1.1. For patients with SVT of the main saphenous trunks and tributaries above the knee >3 cm from the SFJ and ≥5 cm in length, whether or not associated with varicose veins, we recommend fondaparinux 2.5 mg subcutaneously daily for 45 days; alternatively, rivaroxaban 10 mg/d for 45 days may be appropriate for patients unwilling or unable to perform subcutaneous injections.

GUIDELINE. Grade of recommendation: 1 (strong), Quality of Evidence: A (high)

12.1.2. For patients with SVT of the main saphenous trunks ≤3 cm from the SFJ, treatment with full anticoagulation for a minimum of 6 weeks should be continued.

Consensus statement.

12.1.3 For patients with SVT of the main saphenous trunks we suggest against using prophylactic or therapeutic dose low-molecular weight heparin (LMWH) and nonsteroid anti-inflammatory drugs (NSAIDs). While both have been found to reduce SVT pain and extension, they have failed to prevent VTE. If NSAIDs are used for treatment of short segment distal SVT, surveillance with DUS for VTE extension is recommended due to the high prevalence of concomitant DVT.

GUIDELINE. Grade of recommendation: 1 (strong), Quality of Evidence: A (high)

12.1.4. For selected patients with isolated thrombosis of varicose tributaries or limited involvement of the GSV, we suggest phlebectomy as a safe alternative.

GUIDELINE. Grade of recommendation: 2 (weak), Quality of Evidence: B (moderate)

12.1.5. In patients with saphenous thrombophlebitis, ablation should be performed once the inflammation has resolved if there is evidence of pathologic reflux on DUS.

Consensus statement.

Rationale. Despite recognition that superficial thrombophlebitis, also known as SVT, is more common than DVT, there is less awareness of its associated morbidity and little consensus on its management.[254] While traditionally thought of as benign, recent studies have highlighted its association with DVT and PE if left untreated. Studies show that SVT may progress to DVT in 6% to 44% of patients; 20% to 33% may have asymptomatic PE; and 2% to 13% may have symptomatic PE. Superficial venous thrombosis involving the saphenous trunk has the greatest association with VTE.[34] Although the majority of SVT occurs in varicose veins, SVT in nonvaricose veins confers greater morbidity and few studies have stratified treatment based on this distinction.[34] Several therapies including surgery, compression stockings, and nonsteroidal anti-inflammatory drugs (NSAIDs) aim to reduce pain and inflammation, however, given the associated progression to VTE, anticoagulation is recommended. Of note, the application of warm compresses to the site of SVT has never been evaluated in any study.

Evidence. These recommendations are supported by two recent systematic reviews[34,35] (Table XXIV). The 2018 Cochrane review included 33 studies involving 7296 patients with SVT of the legs.[34] Treatments evaluated included fondaparinux, rivaroxaban, LMWH, unfractionated heparin, NSAIDS, compression stockings, and topical, intramuscular, or intravenous treatment as well as surgical thrombectomy or ligation. A minority of studies compared treatment to placebo and most studies were small and of poor quality. Further, most studies excluded patients with SVT that was within 3 cm of the SFJ. The recommendations are primarily based on one large placebo controlled RCT of 3002 participants who received fondaparinux and demonstrated a significant reduction in symptomatic VTE, SVT extension, and SVT recurrence in comparison with placebo. Major

bleeding was infrequent in both groups. A second systematic review and meta-analysis included seventeen studies and 6862 patients with SVT and confirmed that fondaparinux achieved the lowest rate of progression to DVT and PE without conclusions about other treatment due to low quality evidence.[35] In the Surprise study, patients with SVT and one or more risk factors for VTE were randomized to 45 days of fondaparinux or rivaroxaban 10 mg.[257] The results suggested that rivaroxaban was as effective as fondaparinux, however, the study was not powered to prove noninferiority. A call for further studies was prompted by the nonsignificant increase in the primary composite outcome as well as by an increase in clinically relevant nonmajor bleeding in the rivaroxaban group. These recommendations are similar to those, published recently on management of SVT in the CHEST guidelines.[253]

Low-quality evidence in one study found that prophylactic LMWH reduced extension of SVT (statistically significant), but did not reduce incidence of VTE, while therapeutic LMWH evaluated in one study reduced both SVT extension (statistically significant) and progression to VTE, but improvement was less significant at 3 month follow-up due to a catch-up phenomenon.[34] NSAIDS were also found in one study to reduce SVT extension (statistically significant).[258] However, there were no differences in the resolution of local symptoms and signs of SVT and in the incidence of VTE. While there were no major bleeding episodes recorded in either the NSAID or placebo groups, indomethacin increased the rate of adverse effects.[259] NSAIDs have also been found to increase the risk of gastric pain three-fold compared with placebo.[258,259]

Compared with elastic stockings alone, one study showed that HL&S plus elastic stockings reduced the risk of SVT extension and recurrence (RR, 0.09; 95% CI, 0.01-0.64) and was associated with a lower, statistically not significant, incidence of VTE (RR, 0.37; 95% CI, 0.08-1.78).[260] However, most studies evaluating surgery and topical treatments did not report SVT progression, VTE, or adverse events.[34]

A recent analysis from the RIETE registry of patients with thrombosis involving main trunk of the GSV within 3 cm of the SFJ compared those treated with full dose fondaparinux or LMWH followed by VKA (227 patients) to those (147 patients) who received prophylactic doses of fondaparinux or intermediate dose LMWH.[255] Those receiving full-dose anticoagulation received a longer course of treatment and all patients were followed for 3 months. There was no difference in the incidence of VTE or recurrent SVT between the groups or in the safety outcomes of major bleeding or clinically nonmajor bleeding. The authors concluded that these findings are hypothesis generating and support a trial evaluating the efficacy of preventative dose anticoagulation in comparison with therapeutic anticoagulation for treatment of SVT approaching the SFJ.

There is a paucity of studies specifically evaluating the management of SVT in patients with varicose veins. In a prospective observational study of 195 limbs with SVT and varicose veins treated with surgery or anticoagulation, there was no difference in the primary composite outcome of SVT extension/recurrence, incidence of DVT or symptomatic PE.[256] The authors concluded that urgent surgery is not associated with reduction in the incidence of VTE compared with anticoagulation alone but could be safely performed in selected patients with isolated thrombosis of varicose tributaries or limited involvement of the saphenous trunk.

A single-center randomized trial of 73 patients compared the use of thigh-high 23 to 32 mm Hg compression stockings to no compression stockings for 3 weeks in patients with isolated SVT of the legs who all received prophylactic dose LMWH with or without NSAIDS.[261] The addition of compression stockings resulted in no significant difference in reduction of pain, consumption of analgesics, thrombus length, skin erythema, D-dimer, or QOL. However, patients wearing compression had significantly faster thrombus regression at 7 days.

The recurrence rate of SVT is between 10 and 20%. One large case series of SVT patients described a recurrence rate of 15% among 221 patients.[262] In modern times with widespread application of anticoagulant therapies, the risk of recurrence or VTE is ~6%, with the highest risk occurring among patients with previous episodes of SVT and long segment thrombosis.[263] Although not addressed by a randomized control trial, best practice would include informing patient of the risk of recurrent SVT and offering surgical or endovascular therapy for the treatment of symptomatic recanalized varices and axial reflux (if present in the recanalized saphenous vein after completion of evidence based antithrombotic therapy).

13. Management of bleeding varicose veins.

13.1. For patients presenting with acute bleeding from varicose veins, leg elevation, direct compression, and sclerotherapy should be attempted before suture ligation to control bleeding.

Consensus statement.

13.2. For patients with bleeding due to varicose veins, prompt referral to a venous specialist should be done.

Consensus statement.

13.3. For patients who presented with bleeding from varicose veins, and bleeding has been controlled, evaluation for superficial venous incompetence and appropriate intervention should be done to control venous hypertension and reduce the risk of recurrent hemorrhage.

Consensus statement.

13.4. Patients with varicose veins or venous ulcerations should be counseled on the possibility of venous bleeding and their families, caregivers, or friends educated regarding leg elevation and simple compression techniques to control severe bleeding.

Consensus statement.

Rationale. The true incidence of bleeding from varicose veins is unknown due to under-reporting but appears to occur in approximately 4% of patients presenting with varicose veins.[264,265] Bleeding often arises from small veins at the ankle with surrounding skin pigmentation and induration or following exacerbation of a venous ulcer leading to erosion of veins underlying the ulcer bed.[266] Patients may report bleeding when the varicosities are exposed to warm water (in the shower or bathing), causing the veins to vasodilate, or bleeding can occur because of minor trauma. Patients with right heart failure or cardiomyopathy may also experience intermittent, often heavy, bleeding from dilated veins. Regardless of the cause, when a varicose vein ruptures, profuse bleeding can occur due to associated venous hypertension.

Although most bleeding associated with varicose veins is not associated with hypotension and does not require transfusion,[267] fatal hemorrhage is an uncommon, but not entirely rare event.[266] Most cases of fatal variceal hemorrhage have come from autopsy reports. A 2011 report documented <100 fatalities over several decades.[268] Twenty-three fatalities were reported in England and Wales in 2001.[266] A systematic review including 17 articles found that deaths secondary to bleeding varicose veins accounted for 0.01% of autopsy cases.[269] The victims were patients aged 60 to ≥90 years of age with no gender discrimination. Deaths due to hemorrhage occurred in older persons who lived alone, were mobility impaired, had skin fragility or an ulcer located near the malleolus, were on anticoagulation or antiplatelet medication, or had a comorbidity such as dementia or liver failure. These rare case reports describe pulsatile bleeding both from the thin-wall veins themselves and from exposed veins in a venous ulcer bed leading to hypovolemic shock and death, especially in the presence of ischemic heart disease.[270] Another single-center study found that patients with bleeding episodes had decreased access to basic first aid or hemorrhage control techniques.[264]

As many of the fatal hemorrhagic events can be prevented, it is critical that patients be asked about prior bleeding episodes, be warned about the possibility, and be instructed in first aid and hemorrhage control techniques, such as leg elevation and direct compression on the bleeding varicose veins. The danger of applying venous tourniquets and increasing venous pressure has often been emphasized in the literature.[266]

Evidence. Both because of the infrequency of bleeding events and the difficulty in leaving such patients untreated, no studies comparing intervention to conservative management have been performed. However, very limited evidence does suggest that fatal hemorrhage usually occurs after a previous untreated episode of bleeding[266] and there is general consensus that patients should be treated after the first episode of hemorrhage.[267,271] Furthermore, there is evidence from single-center series that superficial venous intervention reduces recurrent hemorrhage. Selection of an appropriate treatment modality is somewhat dependent of the patient's venous anatomy and size of the bleeding vein. Among 5 patients reported in one series, acute control of venous hemorrhage was successfully achieved with direct injection of 1% polidocanol foam into the bleeding varicosity with or without FS (3% polidocanol) of the associated saphenous trunk. No recurrent bleeding was noted after a mean follow-up of 17.4 months.[272] A larger series reported successful acute control of bleeding in 72 patients treated with FS.[271] In comparison with 52 patients treated with simple suture ligation, FS was associated with faster wound healing (7 vs 14 days; $P < .001$) and a lower risk of recurrent bleeding at 12 months (0% vs 23%, $P < .001$). Others have similarly reported excellent control of bleeding from smaller veins (<1 mm) with sclerotherapy, while bleeding from larger veins was successfully controlled with high ligation, stripping, and phlebectomy. Recurrent bleeding was noted in only 1 of 14 patients (7%) after a mean follow-up of 21.3 months.[267] Venous ablation has been used more recently in patients with varicosities, with small series (n = 13) demonstrating 85% of patients to be free from recurrent bleeding at a mean follow-up of 2.26 years.[265]

Although the supportive evidence is quite limited, the literature does suggest that acute bleeding is optimally managed with sclerotherapy, while prevention of recurrence may warrant ablation of any truncal venous incompetence.

14. Management of superficial vein aneurysms

14.1. For patients with superficial truncal vein aneurysm, located within 3 cm of the SFJ or SPJ, open surgical excision, with high proximal and distal ligations should be performed. If symptomatic saphenous reflux is present, endovenous or open surgical ablation (phlebectomy or limited stripping) of the distal saphenous vein should be performed.

Consensus statement.

14.2. For patients with an asymptomatic superficial truncal vein aneurysm, located >3 cm distal to the SFJ, endovenous ablation alone should be performed. Thromboprophylaxis in these patients reduces the risk of VTE.

Consensus statement. 14.3. Patients with symptomatic, thrombosed or large (>3 cm) aneurysms in the superficial veins are best treated with surgical excision.

Rationale. Focal dilation of the saphenous veins (GSV, SSV, AAGSV, or PAGSV) that measures ≥20 mm for GSV and 15 mm for SSV, or has a diameter that is three times the upper limit of the average saphenous diameter is considered an aneurysm.[273] Most patients are asymptomatic or have a palpable lump at the groin or in the popliteal fossa.[274] Many patients present only with symptoms of varicosity or CVI.[158,275,276] Patients occasionally complain of a tender lump,[277] that can be firm, if the aneurysm is thrombosed.[278] Evaluation with duplex scanning is usually satisfactory, but congenital superficial truncal vein aneurysms may occur in patients with venous malformations (Klippel-Trenaunay syndrome)[279] and saphenous aneurysms may occasionally mimic femoral hernia,[274] synovial,[280,281] or Baker cyst[282] or venous leiomyosarcoma.[283] In these patients further evaluation with computed tomography or magnetic resonance imaging is warranted. When the saphenous aneurysm is near the femoral or popliteal vein, open surgical excision is indicated, with ligation or oversewing of a dilated proximal saphenous stump. In patients with symptomatic saphenous reflux, endovenous ablation, tumescent anesthesia aided phlebectomy or limited stripping of the distal segment is performed. If the aneurysm is located >3 cm distal to the SFJ or SPJ, permitting safe proximal occlusion with endovenous techniques, endovenous ablation alone is frequently possible and safe, although most large (>3 cm) or symptomatic, thrombosed aneurysms are better treated with surgical excision at any location. There is also significant risk of sural nerve injury, when thermal ablation is used to treat proximal SSV aneurysm. Ablation of saphenous aneurysms within 3 cm. of the SFJ and SPJ should not be treated with UGFS due to the increased risk of propagation of larger amount of foam into the deep venous system.

Evidence. Similar to deep vein aneurysms,[284-286] there is evidence that saphenous vein aneurysms carry a risk of VTE.[287-289] Treatment is recommended whether or not there is thrombus in the aneurysm sac. Conservative therapy with elastic compression for small aneurysms and in those who are not candidates for intervention decreases the risk of thrombotic complications. Most reports describe open surgical excision of saphenous aneurysms, with proximal and distal ligation or distal saphenous ablation.[274,277,278,287-290] In two smaller series of mostly small GSV aneurysms (<3 cm in size), located close to the SFJ, endovenous ablation alone was used, without proximal high ligation.[158,276]

Pavlović, et al[276] treated 11 limbs of 8 patients with RFA alone, without high ligation. All GSV aneurysms were located near the SFJ, distal to the preterminal valve. Median aneurysm diameter was 21 mm (interquartile range, 17.2-23.4 mm), all patients had incompetent GSV and CVD. The catheter tip was placed at 1 to 2 cm from the SFJ, within the aneurysmal segment. Extra tumescent anesthetic and compression was used, and the first segment was treated with three cycles using RFA. Thromboprophylaxis was given for 7 days. At a median follow-up of 8 years median saphenous diameter was reduced to 5.8 mm, the aneurysmal segment was either completely or partly obliterated, and, if partly patent, always had an antegrade flow. One patient (9.1%) had EHIT III despite thrombosis prophylaxis.

In a prospective study, Hamann et al[158] treated 15 limbs of 13 patients with GSV aneurysm, located within 2 cm of the SFJ. Four aneurysms were surgically excised, with proximal ligation, because they were located near the SFJ and had a diameter >3 cm. The other 11 were treated with endovenous ablation alone. A generous amount of tumescent anesthesia was used to diminish the aneurysm as much as possible. Additional energy was applied in the aneurysmal segment, either 100 Joules/cm for EVLA or 3 energy cycles for RFA. No patient had DVT or thrombus extension into the femoral vein. At 1 year, none of the aneurysms were visible on duplex. Three patients needed retreatment for partial or segmental recanalization, with good result. Thromboprophylaxis was given to patients with a history of VTE or SVT.

Further experience with larger number of patients is needed to recommend endovenous ablation alone for treatment of large aneurysms or for those located <3 cm to the SFJ or SPJ. One of the main reasons for this study is that current North American guidelines suggest placement of the tip of thermal ablation catheters ≥2 cm distal to the SFJ.

15. Future research

The writing committee of the Varicose Veins Guidelines identified several gaps in our knowledge on the natural history, evaluation, prevention and treatment of patients with varicose veins. Table XXV **includes the top 20 recommended topics on future research on varicose veins, in order of importance.**

DISCLOSURES

J.F. is a paid speaker for Janssen Pharmaceuticals. M.L.G. has been paid a consulting fee by VitasupportMD and is on their advisory board. R.K. is a paid consultant for Abbott, Auxetics, Boston Scientific, Diachii Sankyo, Koya Medical, Medtronic, Penumbra, Philips, Surmodics, USA Therm, and VB Devices; is on DSMB/CEC for NAMSA and Prairie Education and Research Cooperative; and is on the Board of Trustees of The VIVA Foundation, the Society for Vascular Medicine, the American Vein and Lymphatic Society, and the Intersocietal Accreditation

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APPENDIX (online only).

1. VADs for CVD

This section reviews briefly the scientific evidence supporting the clinical benefit of Hydroxyethylrutosides, calcium dobesilate, Horse chestnut extract, Red vine leaf extract and Sulodexide for patients with varicose veins and CVD. None of these products are approved by the US Food and Drug Administration for use in patients with venous disease.

Clinical benefit of hydroxyethylrutosides.

Rationale. Hydroxyethylrutosides are composed by one or several bioflavonoids obtained from hydroxyethylation of rutoside (a combination of flavonol quercetin and disaccharide rutinose). Hydroxyrutoside is a potent inhibitor of inflammation-related gene expression, and production of inflammatory cytokines (nitric oxide, tumor necrosis factor-alpha, IL-1, IL-6) in macrophages and neutrophils.[101]

Evidence. A systematic review and meta-analysis of 15 trials with 1643 patients[17] evaluated the effect of hydroxyrutoside, with or without compression bandaging vs placebo, with or without compression bandaging, and hydroxyrutoside vs compression bandaging alone. Compared with placebo, a significant but modest reduction of pain, leg heaviness and cramps were reported. The trials were of limited quality.

Clinical benefit of calcium dobesilate.

Rationale. Calcium dobesilate (calcium 2,5-dihydroxybenzene-sulphonate) is a synthetic drug used for CVI, hemorrhoids, and diabetic retinopathy. Experimental studies claimed a protective action against oxidative stress in varicose veins[291] and other beneficial effects such as regulation of apotosis,[292] increased nitric oxide synthase activity, inhibition of prostaglandin synthesis, diminished capillary fragility and hyperpermeability, reduction of platelet aggregation and blood viscosity.[101]

Evidence. An RCT[293] demonstrated improvement of plethysmographic measurements after 6-month treatment. However, comparison vs placebo in another 3-month trial[294] failed to show a significant difference for edema, symptoms of CVD, and QOL, with exception of QOL at 12-month follow-up, better in calcium dobesilate group. A more recent trial with calcium dobesilate vs MPFF[295] reported similar and significant pain reduction in both groups. In an RCT vs placebo in patients with CEAP C3-4,[296] calcium dobesilate significantly decreased leg volume ($P = .0002$) and improved symptoms (discomfort, heavy legs, tired legs, tingling, itching and cramps ($P < .05$).[297]

A meta-analysis performed in 2004[18] found 10 RCTs (778 patients) comparing calcium dobesilate with placebo for CVI. The methodological quality was good in 3 RCTs (608 patients). Calcium dobesilate decreased night cramps and discomfort more than placebo with number of patients needed to be treated of 4 (95% CI, 3-7) vs 8 (95% CI, 4-50). Greater improvement was reported in severe CVD as compared with the mild disease, for leg volume decrease, pain, heaviness, malleolar swelling, and paresthesia. Interestingly, no dose effect was noticed: 1000 mg was as effective as 1500 mg/d. A meta-analysis[15] found calcium dobesilate effectiveness comparable to Ruscus extracts in reducing foot volume and ankle circumferences. Data from a postmarketing surveillance report 1974 to 1998, the international literature (1970-2003) and periodic safety update report 1995 to 2003 from the French Regulatory authorities, was reviewed to assess the safety profile of calcium dobesilate.[298] Adverse events included fever (26%), gastrointestinal disorders (12.5%), skin reactions (8.2%), arthralgia (4.3%), and agranulocytosis (4.3%). No death was related to calcium dobesilate administration. The authors concluded that the adverse events' risk with calcium dobesilate is low despite 13 known cases of agranulocytosis in patients treated by calcium dobesilate.

Clinical benefit of horse chestnut extract.

Rationale. Horse chestnut extract contains escin, a mixture of triterpene saponins, and some benzopyrones. Escin has a veno-contractile properties and a protective effect on endothelium, through the increased production of nitric oxide.[299]

Evidence. A Cochrane review[300] covered electronic data bases search and material collected from manufacturers of horse chestnut extract products with published and unpublished studies and non-English articles. The included RCTs in patients with CVI compared efficacy and safety of oral horse chestnut extract monopreparations with placebo, or reference therapy. Assessment of symptoms shown significantly better than placebo efficacy in improvement of leg pain (7 RCT). Evaluation of the leg volume change in 6 placebo-controlled trials reported a 32.1 mL weighted mean difference (95% CI, 13.49-50.72) in favor of horse chestnut extract. This efficacy was found comparable to compression stockings in another trial.[301] The treatment safety was excellent. The authors concluded that "horse chestnut extract is an efficacious and safe short-term treatment for CVI." The most recent systematic review and meta-analysis on VAD effectiveness[15] confirmed value of horse chestnut extract therapy, although the other VAD were found more effective, MPFF in reducing leg volume and pain, and improving QOL; calcium dobesilate and Ruscus extracts in reducing foot volume and ankle circumference.

Clinical benefit of red vine leaf extract.

Rationale. Red vine leaf extract was found to improve cutaneous microcirculation in patients with CVI, thanks to the increased nitric oxide synthase and decreased oxidative stress.[302]

Evidence. A review paper estimated a statistically significant and clinically relevant efficacy of red vine leaf extract.[303] on leg edema reduction assessed by

volumetry, and on symptoms (heaviness, tingling and pain). Three double-blind vs placebo RCTs support these findings. One[304] crossover trial vs placebo, in 71 patients with CVI Widmer grade I to II, reported a significantly decreased leg circumference ($P < .0001$) and an increased cutaneous microvascular blood flow ($P < .0001$) as well as transcutaneous oxygen pressure ($P < .0001$). Another RCT, in 260 patients CEAP C2 to C4,[305] evaluated leg volume by water displacement volumetry and noted marked dose-dependent difference favoring AS 195 group ($P < .001$), parallel to the ankle/calf circumference pattern ($P < .001$). The third trial confirmed previous results in 248 patients with varicose veins and CEAP C3 to C4a.[306] Pain improvement and decrease of the leg volume assessed by water displacement volumetry vs placebo were significant; $P = .047$ and $P = .0268$ respectively. Safety of AS 195 treatment was excellent. In a recent systematic review[307] significant improvement of symptoms and edema was observed in some studies. The safety of Red vine leaf extract treatment was excellent.

Clinical benefit of sulodexide.

Rationale. Sulodexide contain a purified glycosaminoglycan mixture of low molecular weight heparin (80%) and dermatan sulfate (20%), components of glycocalyx glycoproteins.[101] Protection of glycocalyx integrity is essential in the preservation of the vascular endothelial function and mitigation of the inflammatory reaction.

Evidence. A systematic review and meta-analysis of 13 studies with sulodexide[19] included 1901 participants with CVD at any stage of the disease, classified or nonclassified, was considered. Sulodexide decreased the intensity of pain, cramps, heaviness, edema, total symptom score and reduced inflammatory mediators in patients with CVD.

In a meta-analysis comparing efficacy of different VADs[15] sulodexide was included only in a single network meta-analysis for the proportion of patients with complete ulcer healing and it showed to have the highest probability of being the best treatment (48%) compared with pentoxifylline (37%) and MPFF (16%). The assessment of the sulodexide efficacy on venous symptoms was done in the meta-analysis of 18 observational studies showing a significant improvement of pain, feeling of swelling, heaviness and paresthesia measured by Likert scales.

In one randomized trial endovenous laser treatment of the GSV and phlebectomy were followed by sulodexide twice daily for 1 month and compared with the control group with no adjunctive pharmacotherapy. compared with the control group, in the main group there was a statistically significant decrease in VCSS and improvement in the QOL assessed by CIVIQ-20. The microcirculation of the skin was assessed by laser Doppler flowmetry. Laboratory examinations measured markers of endothelial dysfunction (homocysteine, von Willebrand factor, PAI1, soluble (s)E-selectin, sP-selectin, sICAM-1, and sVCAM-1). An increase in tissue perfusion, and an improvement in the microcirculation was found in the sulodexide group.[308]

A prospective, multicenter, RCT assessed sulodexide as adjunctive treatment to the sclerotherapy. Group A ($n = 354$ patients) received sulodexide twice a day for 7 days before sclerotherapy and group B ($n = 366$ patients) received standard sclerotherapy alone. Polidocanol and 20 to 30 mm Hg compression stockings were used in both groups for 7 days. After 1 month, the incidence of hyperpigmentation was 8.7% in group A and 14.8% in group B ($P = .01$). Group A developed an average area of hyperpigmentation of 10.7% compared with 18.2% in group B ($P = .01$), and the skin tone of the hyperpigmented area was lower in group A than in group B ($P = .02$). However, the latter difference was not significant after 3 months. The overall vein disappearance rate was similar in both groups.[309]