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European guidelines for sclerotherapy in chronic venous disorders

E Rabe¹, FX Breu², A Cavezzi³, P Coleridge Smith⁴, A Frullini⁵, JL Gillet⁶, JJ Guex⁷, C Hamel-Desnos⁸, P Kern⁹, B Partsch¹⁰, AA Ramelet¹¹, L Tessari¹² and F Pannier¹³; for the Guideline Group

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Abstract

Aim: Sclerotherapy is the targeted chemical ablation of varicose veins by intravenous injection of a liquid or foamed sclerosing drug. The treated veins may be intradermal, subcutaneous, and/or transfascial as well as superficial and deep in venous malformations. The aim of this guideline is to give evidence-based recommendations for liquid and foam sclerotherapy.

Methods: This guideline was drafted on behalf of 23 European Phlebological Societies during a Guideline Conference on 7–10 May 2012 in Mainz. The conference was organized by the German Society of Phlebology. These guidelines review the present state of knowledge as reflected in published medical literature. The regulatory situation of sclerosant drugs differs from country to country but this has not been considered in this document. The recommendations of this guideline are graded according to the American College of Chest Physicians Task Force recommendations on Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines.

Results: This guideline focuses on the two sclerosing drugs which are licensed in the majority of the European countries, polidocanol and sodium tetradecyl sulphate. Other sclerosants are not discussed in detail. The guideline gives recommendations concerning indications, contraindications, side-effects, concentrations, volumes, technique and efficacy of liquid and foam sclerotherapy of varicose veins and venous malformations.

Keywords

Chronic venous disease, sclerotherapy, foam sclerotherapy, varicose veins

Preamble

This guideline was drafted on behalf of 23 European Phlebological Societies during a Guideline Conference on 7–10 May 2012 in Mainz (Appendix A). The conference was organized by the German Society of Phlebology.

These guidelines review the present state of knowledge as reflected in published medical literature. The regulatory situation of sclerosant drugs differs from country to country but this has not been considered in this document.

Guidelines are systematically elaborated recommendations designed to support the clinician and practitioner in the decisions about the appropriate care of patients in specific clinical situations.

Guidelines apply to 'standard situations' and take into account the currently available scientific knowledge relating to the subject under consideration.

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Guidelines require ongoing review and possibly modification, in order to adapt to the most recent scientific findings and to practicability in daily routine. Guidelines are not intended to restrict the doctor's freedom to choose the most appropriate method of treatment. Compliance with the recommendations does not always guarantee diagnostic and therapeutic success. Guidelines make no claim to completeness. The decision about the appropriateness of any action to be taken is still the responsibility of the doctor in the light of the individual situation.

The authors of this guideline wrote the text according to their best knowledge based on the available literature. However, they do not take any legal responsibility for the completeness of the recommendations or for the success of the therapist acting according to the guidelines.

The recommendations of this guideline are graded according to the American College of Chest Physicians Task Force recommendations on Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines¹ (Appendix B).

This guideline focuses on the two sclerosing drugs which are licensed in the majority of the European countries, polidocanol (POL) and sodium tetradecyl sulphate (STS). Other sclerosants are not discussed in detail. In general, for liability and safety reasons it is not recommended to use non-approved substances or to change the original composition of medicinal products. This may alter the safety profile and is at the physician's own risk and outside the responsibility of the pharmaceutical manufacturer. In principle, this also applies to the use of sclerosant foam produced by mixing a detergent-type sclerosants with air or another gas. This is a well-established method and licensed in several countries. Therefore, it is recommended to use a standardized procedure as described in chapter 11.3.

Definition

Sclerotherapy is the targeted chemical ablation of varicose veins by intravenous injection of a liquid or foamed sclerosing drug. The treated veins may be intradermal, subcutaneous and/or transfascial (perforating veins) as well as superficial and deep in venous malformations. The sclerosants destroy the venous endothelium and possibly additional regions of the vein wall. After successful sclerotherapy and in the long term, the veins are transformed into a fibrous cord, a process known as sclerosis.²⁻⁵ The purpose of sclerotherapy is not to achieve thrombosis of the vessel per se, which may recanalize, but definitive transformation into a

fibrous cord. The functional result is equivalent to the surgical removal of a varicose vein.

Objectives of sclerotherapy

The objectives of sclerotherapy are

- Ablation of varicose veins;
- Prevention and treatment of complications of chronic venous disorders (CVD);
- Improvement and/or relief of venous symptoms, improvement of quality of life;
- Improvement of venous function;
- Improvement of the aesthetic appearance.

These objectives are in line with other methods of treatment for varicose veins.

Indications

Recommendation 1: We recommend sclerotherapy for all types of veins, in particular:

- Incompetent saphenous veins^{4,6-11} (GRADE 1A);
- Tributary varicose veins^{12,13} (GRADE 1B);
- Incompetent perforating veins^{12,14-16} (GRADE 1B);
- Reticular varicose veins^{7,13,17-21} (GRADE 1A);
- Telangiectasias (spider veins)^{7,17-21} (GRADE 1A);
- Residual and recurrent varicose veins after previous interventions^{12,22-27} (GRADE 1B);
- Varicose veins of pelvic origin (GRADE 1B);^{22,28,29}
- Varicose veins (refluxing veins) in proximity of leg ulcers³⁰⁻³³ (GRADE 1B);
- Venous malformations³⁴⁻³⁶ (GRADE 1B).

Other indications (e.g. oesophageal varices, haemorrhoids, varicoceles, hygroma, lymph cysts and Baker cysts) are not covered by this guideline.

Liquid sclerotherapy is considered to be the method of choice for the treatment of C1 (clinical, aetiological, anatomical and pathological elements [CEAP] classification) varicose veins (reticular varicose veins and telangiectasias).^{17,19,21,37,38}

Foam sclerotherapy is an additional treatment option for C1 varicose veins.^{7,20,39}

In the treatment of incompetent saphenous veins, thermal ablation or surgery are well established methods. Nevertheless, treatment of saphenous veins by sclerotherapy is also a good and cost-effective treatment option.⁴⁰⁻⁴³ This applies in particular to foam sclerotherapy, as has been demonstrated by case-control studies and prospective randomized controlled studies conducted in recent years.^{4,10,19,44-46}

Contraindications

Recommendation 2: We recommend to consider the following absolute and relative contraindications (GRADE 1C):

Absolute contraindications:^{2,3,38,47,48}

- Known allergy to the sclerosant;
- Acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE);
- Local infection in the area of sclerotherapy or severe generalized infection;
- Long-lasting immobility and confinement to bed.

For foam sclerotherapy in addition:

- Known symptomatic right-to-left shunt (e.g. symptomatic patent foramen ovale).

Relative contraindications (individual benefit–risk assessment mandatory):^{2,38,48}

- Pregnancy;
- Breast feeding (interrupt breast feeding for 2–3 days).
- Severe peripheral arterial occlusive disease;
- Poor general health;
- Strong predisposition to allergies;
- High thromboembolic risk (e.g. history of thromboembolic events, known severe thrombophilia, hypercoagulable state and active cancer);
- Acute superficial venous thrombosis.

For foam sclerotherapy in addition:

- Neurological disturbances, including migraine, following previous foam sclerotherapy.

Anticoagulation treatment *per se* is not a contraindication to sclerotherapy.^{30,49,50}

In addition, consideration should be given to the current Summary of Product Characteristics, the package insert or the Prescribing Information for the sclerosants used in each country.

Complications and risks

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications.⁵¹

Recommendation 3: We recommend considering the following adverse events after sclerotherapy^{52–58} (GRADE 1B) (Table 1).

Table 1. Adverse events after sclerotherapy modified and updated from ref.⁵³

Designation	Incidence	
****Very common	≥ 10%	
***Common	≥ 1% – < 10%	
**Uncommon	≥ 0.1% – < 1%	
*Rare	≥ 0.01% – < 0.1%	
*Very rare and isolated cases	< 0.01%	
Type of adverse event	Frequency	
	With liquid	With foam
Severe complications[†]		
Anaphylaxis	*Isolated cases	*Isolated cases
Large tissue necrosis	*Isolated cases	*Isolated cases
Stroke and TIA	*Isolated cases	*Isolated cases
Distal DVT (mostly muscular)	**Rare	***Uncommon
Proximal DVT	*Very rare	*Very rare
Pulmonary Embolism	*Isolated cases	*Isolated cases
Motor nerve injury	*Isolated cases	*Isolated cases
Benign Complications		
Visual disturbances	*Very rare	***Uncommon
Headaches and migraines	*Very rare	***Uncommon
Sensory nerve injury	*Not reported	**Rare
Chest tightness	*Very rare	*Very rare
Dry cough	*Very rare	*Very rare
Superficial phlebitis	Unclear [‡]	Unclear [‡]
Skin reaction (local allergy)	*Very rare	*Very rare
Matting	****Common	****Common
Residual pigmentation	****Common	****Common
Skin necrosis (minimal)	**Rare	*Very rare
Embolia cutis medicamentosa	*Very rare	*Very rare

TIA, transient ischaemic attack.

[†]Like in all medical treatments it cannot be excluded that some of these severe adverse reactions (e.g. anaphylaxis) might have in a worst case a fatal outcome.

[‡]In literature frequencies between 0% and 45.8% with a mean value of 4.7% are reported (see text below).

Anaphylaxis

Anaphylactic shock as well as inadvertent intra-arterial injection are extremely rare complications constituting an emergency situation.^{59,60}

Recommendation 4: If anaphylaxis is suspected we recommend stopping the injection immediately and to follow with standard emergency procedures including

the administration of epinephrin when appropriate (GRADE 1A).

Large tissue necrosis

Extensive necroses may occur after inadvertent intra-arterial injection.^{61,62} The risk of intra-arterial injection can be minimized by ultrasound guidance with adequate imaging and identification of arteries in close proximity to target veins. If severe pain occurs during injection, the injection should be stopped immediately. If intra-arterial injection is suspected, local catheter-directed anticoagulation and thrombolysis should be performed if possible. This may be completed by systemic anticoagulation. Early administration of systemic steroids may help to reduce inflammation.⁵⁷

Recommendation 5: To prevent inadvertent paravenous or intra-arterial injection, we recommend using ultrasound guidance for both foam and liquid sclerotherapy when the target vein is not visible or palpable (GRADE 1C).

Recommendation 6: We recommend local catheter-directed anticoagulation and thrombolysis if applicable possibly followed by systemic anticoagulation if intra-arterial injection is suspected. Early administration of systemic steroids may help to reduce inflammation (GRADE 1C).

Skin necrosis and embolia cutis medicamentosa

Skin necroses have been described after paravenous injection of sclerosants in higher concentrations and rarely after properly performed intravascular injection with sclerosants in low concentrations.⁶³ It has been shown that subcutaneous paravenous injection of liquid or foamed POL was not responsible for skin necrosis after reticular veins or telangiectasias.⁶⁴ In the latter case, a mechanism involving passage of the sclerosant into the arterial circulation via arteriovenous anastomoses or veno-arterial reflex-vasospasm has been suggested.^{57,65,66} In individual cases, this has been described as embolia cutis medicamentosa or Nicolau phenomenon.^{67,68}

Recommendation 7: To reduce the risk of skin necrosis we recommend to avoid high-volume injections. The sclerosant should be injected with minimal pressure (GRADE 1C).

Visual disturbances, headache and migraine

Transient migraine-like symptoms may be observed after any kind of sclerotherapy. They occur more

common after foam sclerotherapy than after liquid sclerotherapy.^{37,52,56,69,70} It has been suggested that a right-to-left shunt (e.g. PFO), which is present in approximately 30% of the general population, might be a factor, allowing foam bubbles to pass into the arterial circulation.⁷¹⁻⁷⁵

Visual disturbances occurring after sclerotherapy may correspond to migraine with aura and not to transient ischaemic cerebro-vascular events.⁷⁶

Visual disturbances can be associated with paraesthesia and dysphasic speech disturbance depending on the extension of the cortical spreading depression which is the pathological correlate of migraine with aura. There is no clear evidence of a relationship between bubbles and visual or neurological disturbances. Recent evidence has shown release of endothelin 1 from the vessel injected with liquid or foamed sclerosants.^{77,78} Up to now, no abnormality has been observed at ophthalmic examination and no durable visual trouble has been reported.

Multiple injections with small single doses may possibly reduce the passage of the sclerosant into the deep veins.⁷⁹

Stroke and transient ischaemic attack

In early-onset neurological disturbances, also reported as 'stroke' in published literature no intra-cerebral clots have been found. This entity seems not to correspond to thromboembolic pathology.^{56-58,71,80,81} In such cases air bubbles in brain arteries have been reported.⁸¹⁻⁸⁴

Among strokes reported after sclerotherapy, we must distinguish strokes related to paradoxical clot venous embolism usually with a delayed onset of symptoms, which have also been reported following various methods of treatment of varicose veins,^{85,86} and strokes related to paradoxical air embolism with an early onset, which is a specific complication of foam sclerotherapy.^{72,87}

It is essential to notice that all patients with stroke after sclerotherapy related to paradoxical air embolism with an early onset have had a complete or near complete recovery. No stroke with significant after effects has been reported in these cases to date.⁸⁷

Isolated cases of confirmed stroke or transient ischaemic attack with delayed onset have been described both after liquid and foam sclerotherapy representing paradoxical thromboembolism.^{71,84,88-92}

Recommendation 8: For patients who have experienced neurological symptoms including migraine after previous sclerotherapy sessions we recommend:

- The patient should remain lying down for a longer period of time (GRADE 2C);

- Avoid injection of large volumes of foam or perform liquid sclerotherapy (GRADE 2C);
- The patient should avoid performing a Valsalva manoeuvre in the early period after the injection (GRADE 2C);
- Decide on a case-by-case basis (perform a benefit–risk assessment based on the particular indication) (GRADE 2C).

DVT and PE

In Table 1, distal DVT is listed as ‘severe complication’ even though it may individually correspond to ‘benign complications’ (e.g. asymptomatic calf vein DVT). Few published data are available to assess the actual frequency of DVT occurring after liquid sclerotherapy. Most of the studies reporting the outcome in patients treated with liquid sclerotherapy are old and no duplex ultrasound (DUS) assessment was carried out. Symptomatic and asymptomatic DVTs are not often clearly distinguished in studies, while the clinical consequences are probably different.⁹³

Severe thromboembolic events (proximal DVT, pulmonary embolism) occur very rarely after sclerotherapy.^{94,95} The overall frequency of thromboembolic events is <1%; in the meta-analysis of Jia *et al.*⁹⁶ the frequency of DVT was 0.6%. Most of the DVTs are distal. Most of the cases detected by DUS imaging during routine follow-up are asymptomatic.^{52,56} The use of larger volumes of sclerosant, particularly in the form of foam, increases the risk of a thrombosis.^{44,47,80,97} The same applies to patients with a previous history of thromboembolism or thrombophilia.⁶ In such patients with these risk factors the benefit–risk ratio must be well established and additional prophylactic measures should be taken.^{47,49} Other risk factors, such as overweight or lack of mobility, have to be considered.

Recommendation 9: In patients with a high risk of thromboembolism such as those with a history of spontaneous DVT or known severe thrombophilia we recommend:

- Use of pharmacological thromboprophylaxis in line with current guidelines/recommendations (GRADE 1C);
- Implement physical prophylaxis (compression, movement) (GRADE 1C);
- Avoid the injection of large volumes of foam (GRADE 1C);
- Decide on a case-by-case basis (perform a benefit–risk assessment based on the particular indication) (GRADE 1C).

Superficial venous thrombosis

In the literature, frequencies between 0% and 45.8% with a mean value of 4.7% are reported;^{52,57,96} however, the definition of phlebitis after sclerotherapy in the literature is controversial. An inflammatory reaction in the injected part of the vein should not be interpreted as phlebitis, whereas superficial vein thrombosis in a non-injected vein would fulfil this definition. Superficial vein thrombosis after sclerotherapy occurs, but the real frequency is unknown.

Motor nerve injury

The incidence of nerve injury after sclerotherapy is very rare and lower than after other treatment methods for varicose veins.⁹⁸

Residual pigmentation

Skin pigmentation has been reported with frequencies ranging from 0.3 to 30% in the short term.^{63,99} In general, this phenomenon resolves slowly in weeks or months.¹⁰⁰ The incidence of pigmentation is likely to be higher after foam sclerotherapy.⁵² Intravascular clots should be removed by needle aspiration or stab incision and coagulum expression to reduce the incidence of pigmentation.¹⁰¹ In addition, post-sclerotherapy UV exposition should be avoided for the first two weeks after sclerotherapy.

Recommendation 10: To reduce the risk of pigmentation we recommend the removal of superficial clots (GRADE 1C).

Matting

Matting, new occurrence of fine telangiectasias in the area of a sclerosed vein, is an unpredictable individual reaction of the patient and can also occur after surgical or thermal ablation of a varicose vein.⁶³ Inadequate or no treatment of the underlying reflux is the cause in many cases of matting. High initial concentrations or large volumes of sclerosant can also result in inflammation or excessive vein obstruction with subsequent angiogenesis. Treatment of matting should concentrate on the underlying reflux and residual patent veins using low concentrations of sclerosant or phlebectomy.^{57,102}

Others

Other general or local transient reactions after sclerotherapy include feeling of tightness in the chest, vasovagal reactions, nausea, metallic taste, intravascular coagula, haematomas, ecchymoses at the injection site, pain at the injection site, local swelling,

indurations, wheals, blisters and erythema. In addition, complications may arise due to the compression bandage, such as blister formation (e.g. blisters in the area of an adhesive plaster).

Recommendation 11: To improve general safety of foam sclerotherapy we recommend:

- Injecting a highly viscous foam into varicose veins (C2) (Level 1C);
- Avoiding patient or leg movement for a few minutes after injection, avoiding a Valsalva manoeuvre by the patient (Level 1C).

The type of gas (air or physiological gas) used to prepare foam is a controversial topic. If high volumes of foam are injected, the use of low-nitrogen-sclerosing foam seems to reduce early-onset reversible side-effects.^{103,104} Recently no benefits on neurological disturbances in patients treated with CO₂-O₂-based foam compared with air-based foam in low volumes have been demonstrated.^{105,106}

Patient informed consent

Recommendation 12: Before sclerotherapy, we recommend to inform the patients about:

- Alternative treatment methods with their pros and cons (GRADE 1B);
- Details of the sclerotherapy procedure and the post-treatment management (GRADE 1B)
- Serious risks (GRADE 1B);
- Frequently occurring adverse events (GRADE 1B);
- With regard to the sclerotherapy treatment outcome to be expected, patients should be informed (GRADE 1B):
 - about the success rate and rate of recurrence to be expected;
 - that short- and mid-term follow-up may be required;
 - that further sclerotherapy may be necessary in some cases, especially in the treatment of large varicose veins;
 - that foam sclerotherapy is more effective than liquid sclerotherapy (GRADE 1A) and that ultrasound guidance may help prevent intra-arterial injection, but that certain adverse reactions may be more frequent (see section Complications and risks).
- Where applicable, the patient should be informed about the off label-use of medicinal products and foaming of the sclerosing agent (GRADE 1B).

Diagnosis before sclerotherapy and documentation

Successful sclerotherapy requires thorough planning. Sclerotherapy is generally performed in the order of proximal to distal leakage points, and proceeding from the larger to the smaller varicose veins. Therefore, a proper diagnostic evaluation should be performed prior to treatment.³⁸

Standard of diagnostics in patients with chronic venous disorders includes history-taking, clinical examination and DUS investigation by a trained individual. In telangiectasias and reticular varicose veins, cw-Doppler instead of DUS may be sufficient although the general trend is in favour of a complete DUS in these cases.

DUS performed in the standing position is especially suitable for identifying incompetent saphenous trunks and subcutaneous veins, incompetent saphenous junctions, as well as for clarifying post-thrombotic changes in the deep veins and for planning of the treatment.¹⁰⁷⁻¹¹⁰ Duplex examination should also report the incompetence of terminal and/or pre-terminal saphenous valves. DUS offers significant advantages over investigation by hand-held Doppler alone in the pre-treatment assessment of saphenous vein incompetence including measuring the diameter of the vein.¹¹¹

Recommendation 13: We recommend diagnostic evaluation including history-taking, clinical examination and DUS investigation before sclerotherapy. In telangiectasias and reticular varicose veins, cw-Doppler instead of DUS may be sufficient (GRADE 1C).

DUS is strongly recommended prior to sclerotherapy in patients with recurrent varicose veins after previous treatment.^{112,113} In vascular malformations detailed DUS is strongly recommended. In several cases further investigations to explore the anatomic and haemodynamic situation is necessary.^{34,114,115}

In addition, functional examinations (e.g. photoplethysmography, phlebo-dynamometry and venous occlusion plethysmography) and imaging modalities (e.g. phlebography) may be considered.^{41,116,117}

Recommendation 14: We strongly recommend DUS prior to sclerotherapy in patients with recurrent varicose veins after previous treatment and in patients with vascular malformations (GRADE 1B).

Prior to foam sclerotherapy it is not necessary routinely to perform specific investigations for right-to-left-shunt or thrombophilia.⁴⁷

Recommendation 15: We recommend against routine investigation for right-to-left shunts or for the presence

of thrombophilia factors in the coagulation system (GRADE 1C).

The number of treatments (injections and sessions), the injected drug, volumes/concentrations/ratios of foam used as well as the treatment method should be recorded, including pre- and post-treatment mapping.

Management of sclerotherapy of varicose veins

Sclerosing agents

Different sclerosing solutions have been used to treat varicose veins in recent decades, depending on national regulations, national traditions and the size of the veins to be treated.

Polidocanol (lauromacrogol 400). Polidocanol (lauromacrogol 400) is available in different concentrations, for example, 0.25%, 0.5%, 1%, 2% and 3% (this corresponds to 5, 10, 20, 40, 60 mg, respectively, in a 2-mL ampoule).

POL is a non-ionic detergent and a local anaesthetic. The dose of 2 mg POL per kg body weight and per day should not be exceeded (e. g. German Summary of Product Characteristics/Package Insert for Aethoxysklerol (Kreussler 2012)).

For example, in a patient weighing 70 kg – independently of the medically indicated quantity – the total amount of POL injected should not exceed 140 mg.

140 mg of POL are contained in:

- POL solution 0.25% – 56 mL injection solution
- POL solution 0.5% – 28 mL injection solution
- POL solution 1% – 14 mL injection solution
- POL solution 2% – 7 mL injection solution
- POL solution 3% – 4.6 mL injection solution.

Sodium tetradecyl sulphate. Sodium tetradecyl sulphate is an anionic detergent sclerosant drug. It is supplied in concentrations of 0.2%, 0.5%, 1% and 3% (2, 5, 10 and 30 mg/mL, respectively (e. g. Prescribing Information Fibrovein, UK (STD 2012)).

Excessive doses of STS may lead to haemolysis of red blood cells and therefore the manufacturers recommend limiting the dose of STS to not more than 4 mL of 3% solution and not more than 10 mL of all other concentrations per session of treatment.

Sclerotherapy with sclerosant solutions (liquid sclerotherapy)

Recommendation 16: We recommend the following values for concentration and volume per injection for

Table 2. Suggested volumes per injection for sclerosants (POL and STS) used for liquid sclerotherapy^{118,119}

Indications	Volume/injection point (mL)
Telangiectasias (spider veins) (C1)	Up to 0.2
Reticular varicose veins (C1)	Up to 0.5
Varicose veins (C2)	Up to 2.0

Table 3. Suggested POL and STS concentrations in liquid sclerotherapy^{118,119}

Indications	Concentration percentage of POL	Concentration percentage of STS
Telangiectasias (spider veins)	0.25–0.5	0.1–0.2
Reticular varicose veins	0.5–1	Up to 0.5
Small varicose veins	1	1
Medium-sized varicose veins	2–3	1–3
Large varicose veins	3	3

POL, polidocanol; STS, sodium tetradecyl sulphate.

liquid sclerotherapy (GRADE 2B). Concentrations and volumes proposed are just indicative and may be changed as to the judgement of the therapist (Tables 2 and 3).

Injection technique and material

Sclerotherapy can be performed with and without ultrasound guidance and with liquid or foamed sclerosing solutions.

Visual sclerotherapy

Telangiectasias and reticular varicose veins (C1)

Recommendation 17: For liquid sclerotherapy of telangiectasias and reticular varicose veins (C1) we recommend the following (GRADE 1C for the whole procedure):

- Puncture and injection of telangiectasias and reticular varicose veins is performed with the patient's limb in the horizontal position;
- Smooth-moving disposable syringes are recommended;
- Thinner needles (up to 32 G) may be used;
- Air block-technique can be used;
- Repeated sessions may improve the results;
- When treating telangiectasias and reticular varicose veins, emptying of the vein immediately at the beginning of the injections confirms that the injection is performed intravenously;

- In cases of immediate whitening of the skin surrounding the puncture site, injection must be stopped immediately to avoid skin damage;
- In liquid sclerotherapy intravenous injection of the sclerosant is performed slowly, possibly in fractions and checking that the needle is positioned inside the vein;
- Severe pain during injection may be indicative of extravenous or even intra-arterial injection. In such an event injection must be stopped immediately.

Varicose veins (C2)

Recommendation 18: For liquid sclerotherapy of varicose veins (C2) we recommend the following (GRADE 1C for the whole procedure):

- The vein can be punctured using the open-needle- or closed-needle technique;
- Direct injection into perforating veins or saphenous junctions must be avoided;
- Smooth-moving disposable syringes are recommended for sclerotherapy as well as needles with different diameters, depending on the indication;
- Injection devices: the injection can be performed:
 - with the needle mounted on a syringe (e.g. 2.5–5 mL) filled with sclerosant; or
 - with butterfly needles as an option for varicose veins lying close to the skin; or
 - with short catheters as an option for trunks, they allow re-injection; or
 - with long catheters as an option for trunks.
- In foam sclerotherapy for large veins the diameter of the needle should not be smaller than 25 G to avoid degrading the foam quality;
- After the vein has been punctured using the closed-needle technique, the intravenous position is checked by aspiration of blood;
- Several injections along the vein to be treated are possible in one session;
- The injection is usually given with the patient's limb in the horizontal position;
- For liquid sclerotherapy, intravenous injection of the sclerosant is performed slowly; possibly in fractions and checking that the needle or the short catheter is positioned inside the vein;
- Severe pain during injection may be indicative of extravenous or even intra-arterial injection. In such an event injection must be stopped immediately.

Ultrasound-guided sclerotherapy

Ultrasound-guided sclerotherapy (UGS) with liquid and foamed sclerosants has proved to be a useful

addition to the range of methods for treating venous insufficiency. It is in particular beneficial when treating saphenous veins, tributaries, perforating veins, popliteal recurrence and venous malformations.^{14,120–122}

Recommendation 19: For UGS we recommend the following (GRADE 1C for the whole procedure):

- The vein segment to be injected and the neighbouring arteries are identified by ultrasound before puncturing;
- When treating incompetent saphenous junctions and saphenous stems by direct puncture, it is recommended that one venous puncture should be performed in the proximal thigh (great saphenous vein and anterior accessory saphenous vein) or calf (small saphenous vein) area;
- In all other cases the vein should be punctured at the safest and the most easily accessible location;
- The vein is localized by ultrasound imaging in longitudinal and/or transverse section;
- The vein is punctured under ultrasound control and the tip of the needle is placed in the centre of the lumen;
- Venous blood backflow into the needle or catheter is checked and a few drops of sclerosant or a few bubbles are pushed into the vein and checked on the DUS screen before injection;
- Injection is performed under ultrasound control;
- Foam sclerosants (POL and STS) are more suitable for UGS than liquid since bubbles are an excellent contrast medium, providing visibility of the sclerosing agent;
- In the post-injection ultrasound control, the distribution of the sclerosant and the reaction of the vein, including venous spasm, are checked.

Foam sclerotherapy

The literature has long contained reports of sclerotherapy with foamed sclerosants.¹²³ In recent years, as the technology has improved, foam sclerotherapy has become established, especially for the treatment of varicose veins.^{7,95,124}

Detergent-type sclerosants such as POL or STS can be transformed into fine-bubbled foam by special techniques. It is produced by the turbulent mixture of liquid and gas in two syringes connected via a three-way stopcock (Tessari method). In the original Tessari method, the ratio of sclerosant to gas is 1 + 4.^{124,125} The Tessari-DSS (double-syringe system) technique involves the turbulent mixing of POL with gas in a ratio of 1 + 4 in two syringes linked via a two-way connector. With low concentrations of sclerosant, foam produced by the

Table 4. Suggested POL and STS concentrations in foam sclerotherapy^{4,7,10,12,14,16–22,24–26,30–37,39,47,51,129,130}

Indications	Concentration percentage of POL	Concentration percentage of STS
Telangiectasias	Up to 0.5 (GRADE 1B)	Up to 0.25 (GRADE 2C)
Reticular varicose veins	Up to 0.5 (GRADE 2C)	Up to 0.5 (GRADE 2C)
Tributary varicose veins	Up to 2 (GRADE 1B)	Up to 1 (GRADE 1C)
Saphenous veins (mm)		
<4	Up to 1 (GRADE 1B)	Up to 1 (GRADE 1C)
≥4 and ≤8	1–3 (GRADE 1A)	1–3 (GRADE 1B)
>8	3 (GRADE 1A)	3 (GRADE 1B)
Incompetent perforating veins	1–3 (GRADE 2B)	1–3 (GRADE 2B)
Recurrent varicose veins	1–3 (GRADE 2B)	1–3 (GRADE 2B)
Venous malformation	1–3 (GRADE 2B)	1–3 (GRADE 2B)

POL, polidocanol; STS, sodium tetradecyl sulphate.

Tessari technique is unstable; with high concentrations it is more stable and viscous. There is no evidence of adverse events attributable to the use of non-sterile air in foam production.¹²⁶

Foam sclerotherapy may be performed with (USG) or without (nUSG) ultrasound guidance. It is possible and appropriate to treat visible or easily palpable varicose veins without ultrasound guidance.^{127,128}

Foam production

Recommendation 20: We recommend the use of a three-way stopcock (Tessari method) or two-way connector (Tessari-DSS method) for the generation of sclerosant foam for all indications (GRADE 1A).

Recommendation 21: We recommend air as the gas component for generation of sclerosing foam for all indications (GRADE 1A) or a mixture of carbon dioxide and oxygen (GRADE 2B).

Recommendation 22: We recommend a ratio of liquid sclerosant to gas for the production of a sclerosing foam of 1+4 (1 part liquid+4 parts air) to 1+5 (GRADE 1A). When treating varicose veins (C2), viscous, fine-bubbled and homogenous foam is recommended (GRADE 1C).

Increasing the proportion of the sclerosant is acceptable, especially with lower concentrations of sclerosant drugs.

Recommendation 23: We recommend that the time between foam production and injection is as short as possible (GRADE 1C).

Changing the physical properties (e.g. freezing or heating) may change the safety profile of the used sclerosants.

Foam volumes. There is no evidence-based limit for the maximum volume of foam per session. In the previous European Consensus on Foam Sclerotherapy a maximum of 10 mL of foam was considered as safe as an expert opinion (47). The incidence of thromboembolic complications and transient side-effects (e.g. visual disturbances) rises with higher volumes of foam (82).

Recommendation 24: We recommend a maximum of 10 mL of foam per session in routine cases (GRADE 2B). Higher foam volumes are applicable according to the individual risk–benefit assessment (GRADE 2C).

Concentration of the sclerosant in foam sclerotherapy.

Recommendation 25: We recommend choosing the following concentration in relation to the diameter of the venous segment to be treated. Concentrations and volumes proposed are just indicative and may be changed according to the judgement of the therapist (Table 4).

In incompetent perforating veins, recurrent varicose veins and venous malformations, 1% POL or STS have been used in most of the studies (11).

Post-treatment management

Recommendation 26: For post-treatment management we recommend consideration of the following:

- A careful watch must be kept for any signs of adverse reactions (GRADE 1B);
- After sclerotherapy, medical compression may be applied to the treated extremity. Compression can be performed using either a medical compression stockings or compression bandages (GRADE 2C);

Table 5. Findings included in the duplex-ultrasound investigations after treatment

Flow and reflux	Morphology and haemodynamics
<ul style="list-style-type: none"> • No flow • Aantegrade flow without reflux (<0.5 seconds) • Reflux <1 second • Reflux >1 second 	<ul style="list-style-type: none"> • Patency/occlusion: <ul style="list-style-type: none"> ○ Complete disappearance of treated vein ○ Complete occlusion (total non-compressibility) of the treated venous segment ○ Partial occlusion of the treated venous segment ○ Complete patency of the treated venous segment • Vein size: <ul style="list-style-type: none"> ○ Pre-treatment diameter ○ Post-treatment inner diameter ○ Length of the occluded segment ○ Length of the patent segment

- Wearing of compression stockings (23–32 mmHg) after sclerotherapy of telangiectasias daily for three weeks improves results (GRADE 2B);
- Prolonged immobilization and long-distance travel in the first week after sclerotherapy may increase the risk of thromboembolic events (GRADE 1C);
- Residual blood coagulum removal (with or without sonographic guidance) should be performed when feasible at the follow-up visit (GRADE 1C).

Assessment of the outcome after sclerotherapy

The evaluation of efficacy of sclerotherapy includes clinical, morphological and haemodynamic issues.

In telangiectasias and reticular varicose veins, clinical outcome assessment is sufficient.

Clinical outcome:

- Clinical assessment in everyday practice: varicose vein presence/absence/improvement in the treated area by means of doctor's and/or patient's assessment;
- Clinical outcome also includes evolution of venous ulcers, oedema, haemorrhages, inflammation etc;
- Symptom assessment: where appropriate (e.g. during scientific investigations), more sophisticated and standardized symptom-score systems such as the VCSS (Venous Clinical Severity Score) and patient-reported outcome scores may be used.

Morphological and hemodynamic outcome:

Morphology of the treated veins can be investigated through compressibility by means of duplex investigation in standing position; appropriate setting of DUS is required.¹⁰⁹

Patency, occlusion (total or partial) or vein disappearance should be assessed.

Investigations should include dynamic manoeuvres, according to the UIP guideline.¹¹⁰

Duplex investigation includes the following findings (Table 5):

These parameters of investigation are applicable for all endovenous treatment methods (laser, radiofrequency, sclerotherapy) and could facilitate comparability, especially in scientific studies.

From the clinical point of view a good outcome is the disappearance of the varicose veins/venous symptoms.

From the duplex investigation point of view the optimal outcome is the disappearance or total occlusion of the intended vein segments.

Clinical improvement of the patient with the occlusion of the treated vein, but with short patent segments with any blood flow may be considered to be a successful outcome, at least in the short (or mid) term.

A wide spectrum of clinical and duplex outcomes is possible after sclerotherapy and these do not necessarily correspond to clinical outcome.

Where applicable, the improvement of venous function can also be demonstrated by pre- and post-treatment functional measurements (e.g. plethysmography and venous pressure measurements).^{41,115,117}

Recommendation 27: To assess the outcome after sclerotherapy we recommend clinical outcome evaluation in telangiectasias and reticular varicose veins (C1) and clinical and ultrasound outcome assessment in varicose veins (C2) and venous malformations (GRADE 1C).

Efficacy

Sclerotherapy, liquid or foam, is a safe and effective method to treat telangiectasias, reticular

varicose veins and subcutaneous varicose veins.^{4,7,8,13,17,25,38,39,46,128,131}

Liquid sclerotherapy is the method of choice for ablation of telangiectasias and reticular varicose veins, allowing improvement of more than 90% to be achieved at the end of the treatment.^{13,17–19,37,132} Foam sclerotherapy is an alternative method for ablation of telangiectasias and reticular varicose veins with comparable occlusion rates and side-effects if a low concentration of more liquid foam is used.^{7,21}

Foam sclerotherapy of saphenous varicose veins is significantly more effective than liquid sclerotherapy.^{4,6–8,19} The occlusion rate depends on the diameter of the vein, on the concentration of the sclerosant and on the injected foam volume.^{12,19} Compared with cross-section and stripping and to endovenous thermal ablation, foam sclerotherapy shows only a slightly higher mid-term recanalization/failure rate.^{10,11} Quality of life and discomfort symptoms improve the same way as after surgery or endovenous thermal treatment.¹⁰ There is no evidence for an improvement of the occlusion rate or reduction of side-effects by leg elevation or compression of the junction with the duplex probe.¹³³

Foam sclerotherapy of incompetent saphenous veins with long catheters is also effective.^{130,134–139}

Re-treatment by sclerosing partially recanalized vein segments during the follow-up is recommended and improves the mid-term result.^{140,141}

Sclerotherapy of varices in the region of venous ulcers improves the healing rate^{30–33} (GRADE 1B).

Foam sclerotherapy is more effective than liquid sclerotherapy in the treatment of venous malformations.^{34–36}

Foam sclerotherapy is effective in the treatment of recurrent varices after previous treatment, accessory saphenous varices, non-saphenous varices and incompetent perforating veins.^{12,14,16,22–26}

Compression treatment with medical compression stockings or bandages improves the result of sclerotherapy for spider veins^{132,142–144} and the incidence of pigmentation may decrease.^{142,144} Evidence of efficacy for compression after sclerotherapy of saphenous veins is still lacking.¹⁴⁵ Nevertheless, compression may have some influence on efficacy, as the need for an additional sclerosing session seems to be inversely proportional to the pressure exerted by three different classes of MCS worn for three weeks after sclerotherapy¹⁴⁶ and as selective extrinsic compression may reduce recurrence.¹⁴⁷ Local eccentric compression significantly increases the local pressure in the injection area and may improve the efficacy of sclerotherapy.¹⁴⁸

Recommendation 28: We recommend liquid sclerotherapy as the method of choice for ablation of telangiectasias and reticular varicose veins (C1) (GRADE 1A).

Foam sclerotherapy of C1 varicose veins is an alternative method (GRADE 2B).

Recommendation 29: We recommend foam sclerotherapy over liquid sclerotherapy for the treatment of saphenous veins (GRADE 1A), venous malformations (GRADE 2B) and recurrent varices after previous treatment, accessory saphenous varices, non-saphenous varices and incompetent perforating veins (GRADE 1C).

Recommendation 30: We do not recommend for mandatory elevation of the leg or compression of the junction for safety reasons during or after treatment (GRADE 2C).

Recommendation 31: We recommend re-treatment by sclerosing partially recanalized vein segments during the follow-up (GRADE 1B).

Recommendation 32: We recommend sclerotherapy of varices in the region of venous ulcers to improve the healing rate (GRADE 1B).

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Appendix A

Members of the European Guideline Conference

Name	Adress	Country	Society
Antignani PL	Roma	Italy	Italian Society of Angiology and Vascular Medicine
Bihari I	Budapest	Hungary	Hungarian Venous Forum
Böhler K	Vienna	Austria	Austrian Society of Phlebology and Dermatologic Angiology
Breu FX	Rottach-Egern	Germany	German Society of Phlebology
Cavezzi A	San Benedetto del Tronto	Italy	Italian College of Phlebology
Ceulen R	Dordrecht	Netherlands	Benelux Society of Phlebology
Coleridge Smith P	London	Great Britain	Venous Forum of the Royal Society of Medicine, British Association of Sclerotherapists
Fernandez F		Spain	Spanish Chapter of Phlebology
Frullini A	Florence	Italy	Italian Phlebological Association
Gillet JL	Bourgoin-Jallieu	France	French Society of Phlebology
Goranova E	Sofia	Bulgaria	Bulgarian Society of Phlebology
Guex JJ	Nice	France	French Society of Phlebology
Guggenbichler S	München	Germany	German Society of Phlebology
Hamel-Desnos C	Caen	France	French Society of Phlebology
Kern P	Vevey and Lausanne	Switzerland	Swiss Society of Phlebology
Islamogu F	Izmir	Turkey	Turkish Society of Phlebology
Kuzman G	Sofia	Bulgaria	Bulgarian Society of Phlebology
Larin S	Wolgograd	Russia	Russian Phlebological Association
Mansilha A	Porto	Portugal	Portuguese Society of Angiology and Vascular Surgery
Maurins U	Riga	Latvia	Baltic Society of Phlebology
Milic D	Nis	Serbia	Serbian Society of Phlebology, Balkan Venous Forum
Pannier F	Cologne	Germany	German Society of Phlebology
Partsch B	Vienna	Austria	Austrian Society of Phlebology and Dermatologic Angiology
Rabe E	Bonn	Germany	German Society of Phlebology
Radu D	Timisoara	Romania	Romanian Society of Phlebology
Ramelet A-A	Bern and Lausanne	Switzerland	Swiss Society of Phlebology

(continued)

Continued

Name	Adress	Country	Society
Rasmussen L	Copenhagen	Denmark	Scandinavian Venous Forum
Schuller-Petrovic S	Vienna	Austria	Austrian Society of Phlebology and Dermatologic Angiology
Sommer A	Maastricht	Netherlands	Benelux Society of Phlebology
Strejcek J	Prague	Czech Republic	Czech Society of Phlebology
Stücker M	Bochum	Germany	German Society of Phlebology
Tessari L	Trieste	Italy	Italian College of Phlebology
Tüzün H	Istanbul	Turkey	Turkish Society of Phlebology
Urbanek T	Katowice	Poland	Polish Society of Phlebology

Appendix B

American College of Chest Physicians Task Force recommendations on Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines¹

Grade of recommendation/description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A – strong recommendation high-quality evidence	Benefits clearly outweigh risk and burdens or <i>vice versa</i>	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B – strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens or <i>vice versa</i>	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C – strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or <i>vice versa</i>	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A – weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient's or societal values
2B – weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient's or societal values
2C – weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimation of benefits, risks and burden; benefits, risks and burdens may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable