European Guidelines for Sclerotherapy in Chronic Venous Disorders

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1 Preamble

This guideline was drafted on behalf of 22 European Phlebological Societies during a Guideline Conference on 7th - 10th June 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.
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. 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 don't 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 Guidelines (Guyatt 2006) (appendix 2).

This guideline focuses on the two sclerosing drugs which are authorized 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 mix and 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 applies also to

the use of sclerosing foam produced by mixing a detergent-type sclerosant with air or another gas, although this is a well-established method in the meantime and authorized in several countries. Therefore it is recommended to use a standardized procedure as described in chapter 11.3.

2 Definition

Sclerotherapy is the targeted chemical ablation of varicose veins by intravenous injection of a liquid or foamed sclerosing agent. 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 further parts of the venous wall. After successful sclerotherapy and in the long term, the veins are transformed into a fibrous cord, a process known as sclerosis (Drake 1996, Rabe 2004, Hamel-Desnos 2007, Chen 2012). The purpose of sclerotherapy is not to achieve thrombosis of the vessel per se, which may recanalise, but definitive transformation into a fibrous cord. The functional result is equivalent to the surgical removal of a varicose vein.

3 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.

4 Indications

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

- ***Incompetent saphenous veins (*Hamel-Desnos 2003 + 2007, Alos 2006, Ouvry 2008, Rabe 2008, Rasmussen 2011, Shadid 2012*) (GRADE 1A)***
- ***Tributary varicose veins (Myers2007) (GRADE 1B)***
- ***Incompetent perforating veins (Guex 2000, van Neer 2006, Myers 2007) (GRADE 1B)***
- ***Reticular varicose veins (*Kahle 2004, Norris 1989, Rabe 2010, Uncu 2010, Alos 2006, Peterson 2012*) (GRADE 1A)***
- ***Telangiectasias (spider veins) (*Kahle 2004, Norris 1989, Rabe 2010, Uncu 2010, Alos 2006, Peterson 2012*) (GRADE 1A)***
- ***Residual and recurrent varicose veins after previous interventions (Kakkos, 2006; McDonagh 2003,Coleridge Smith 2006 + 2009, Myers 2007, Bradbury 2010) (GRADE 1B)***
- ***Varicose veins of pelvic origin (GRADE 1C) (* Sukovatykh 2008, Kakkos 2006, Paraskevas 2011)**

- ***Varicose veins in proximity of leg ulcers (*Stücker 2006, De Waard 2005, Hertzman 2007, Pang 2010*) (GRADE 1B)***
- ***Venous malformations (*Yamaki 2000 + 2008, Blaise 2011*) (GRADE 1B)***

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

Liquid sclerotherapy is considered to be the method of choice for the treatment of C1 (CEAP classification) varicose veins (reticular varicose veins, telangiectasias) (Kern 2004, Rabe 2008, Rabe 2010, Kahle 2004, Peterson 2012).
Foam sclerotherapy is an additional treatment option for C1 varicose veins (Uncu, 2010, Alos 2006, Rao 2005).

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 (Bullens 2004, Schultz-Ehrenburg 1984, Vin 1997, Gohel 2010). This applies in particular to foam sclerotherapy, as has been demonstrated by case control studies and prospective randomized controlled studies conducted in recent years (Wright 2006, Cavezzi 2002, Hamel-Desnos 2003, Hamel Desnos 2007, Rabe 2008, Rasmussen 2011).

5 Contraindications

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

Absolute contraindications (Rabe 2004 + 2008, Breu 2008, Drake 1996, Guex 2005):

- ***Known allergy to the sclerosant***
- ***Acute deep vein thrombosis (DVT) and/or pulmonary embolism***
- ***Local infection in the area of sclerotherapy or severe generalised 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) (Rabe 2008, Breu 2008, Drake 1996, Guex 2005):

- ***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, 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 (Stücker 2006, Hamel-Desnos 2009, Gachet 2002).

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.

6 Complications and risks

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications (Rathbun 2012).

Recommendation 3
We recommend considering the following adverse events after sclerotherapy (Guex 2005, Guex 2010, Munavelli 2007, Weiss 1990, Gillet 2009, Cavezzi 2012, Sarvananthan 2012) (Grade 1B) (Table 1):

Table 1: Adverse events after sclerotherapy modified and updated from **Guex JJ: 2010**

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*

* 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.

Anaphylaxis
Anaphylactic shock as well as inadvertent intra-arterial injection are extremely rare complications constituting an emergency situation (Feied 1994, Pradalier 1995).

Recommendation 4:
If anaphylaxis is suspected we recommend to stop 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 (Oesch 1984, Grommes 2010). The risk of intra-arterial injection can be minimised 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 (Cavezzi, 2012).

Recommendation 5:
To prevent inadvertent paravenous or intraarterial injection we recommend to use 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)

Stroke and TIA
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. (Forlee 2006, Bush 2008, Gillet 2009, Sarvananthan 2012, Parsi 2012, Cavezzi 2012). In a few cases air bubbles in brain arteries have been reported (Bush 2008, Leslie 2009, Delaney 2010, Ma 2011).
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 [Harzheim 2000, Caggiati 2010], and strokes related to paradoxical air embolism with an early onset, which is a specific complication of foam sclerotherapy [Parsi 2011, Gillet 2011].
It is essential to notice that all patients with stroke after sclerotherapy related to paradoxical air embolism have had a complete or near complete recovery. No stroke with significant after effects has been reported in these cases to date [Gillet 2011].
Isolated cases of confirmed stroke or TIA with delayed onset have been described both after liquid and foam sclerotherapy representing paradoxical thromboembolism (Deichmann 1995, Kas 2000, Hanisch 2004, Picard 2009, Hahn 2010, Ma 2011, Parsi 2012).

Deep venous thrombosis (DVT) and pulmonary embolism (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 assessment was carried out. DVTs occurring in symptomatic and asymptomatic patients are not often clearly distinguished in studies, while the clinical consequences are probably different (Guex 1996).
Severe thromboembolic events (proximal DVT, pulmonary embolism) occur very rarely after sclerotherapy (Hamel-Desnos 2011, Fabi 2012). The overall frequency of thromboembolic events is < 1 %; in the meta-analysis of Jia the frequency of DVT was 0.6 % (Jia 2007). Most of the DVTs are distal. Most of the cases detected by duplex ultrasound imaging during routine follow-up are asymptomatic (Guex 2005, Gillet 2009). The use of larger volumes of sclerosant, particularly in the form of foam, increases the risk of a thrombosis (Wright 2006, Forlee 2006, Breu 2003, Myers 2008). The same applies to patients with a previous history of thromboembolism or thrombophilia (Hamel-Desnos 2003). In such patients with these risk factors the benefit-risk-ratio must be well established and additional prophylactic measures should be taken (Breu 2008; Hamel-Desnos 2009). Other risk factors, such as overweight or lack of mobility, have to be considered.

Recommendation 7:
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)***

Motor nerve injury
The incidence of nerve injury after sclerotherapy is very rare and lower than after other treatment methods for varicose veins (Zipper 2000).

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 (van der Plas 1994, Kern 2004, Guex 2005, Künzelberger 2006, Gillet 2009). 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 (Morrison 2006, Passariello 2007, Wagdi 2006, Parsi 2011, Parsi 2012).
Visual disturbances occurring after sclerotherapy may correspond to migraine with aura and not to transient ischaemic cerebro-vascular events. *[***Gillet 2010***]*
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. (**Frullini 2012; Frullini 2011).** 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 (Yamaki 2008).

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)***

Superficial venous thrombosis
In literature frequencies between 0 % and 45.8 % with a mean value of 4.7 % are reported (Jia, 2007; Guex 2005, Cavezzi 2012); 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.

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 (Goldman 1995, **Schuller-Petrovic 2011**). 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 (Bergan 2000, Cavezzi 2012). In individual cases, this has been described as embolia cutis medicamentosa or Nicolau phenomenon (Geukens 1999, Ramelet 2010).

Recommendation 9:
To reduce the risk of skin necrosis we recommend to avoid high volume injections. The slerosant should be injected with minimal pressure. (GRADE 1C)

Residual pigmentation
Skin pigmentation has been reported with frequencies ranging from 0.3% to 30 % in the short term (Goldman/Sadick 1995, Reich-Schupke 2010). In general, this phenomenon resolves slowly in weeks or months (Georgiev 1990). The incidence of pigmentation is likely to be higher after foam sclerotherapy (Guex 2005). Intravascular clots should be removed by stab incision and coagulum expression to reduce the incidence of pigmentation (Scultetus 2003). In addition, post-sclerotherapy UV exposition should be avoided for the first period 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 (Goldman 1995). 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 (Cavezzi 2012, Ramelet 2010).

Others
Other general or local transient reactions after sclerotherapy include feeling of tightness in the chest, vaso-vagal reactions, nausea, metallic taste, intravascular coagula, haematomas, ecchymoses at the injection site, pain at the injection site, local swelling, indurations, wheals, blisters and erythema. Additionally, 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 generally improve safety of foam sclerotherapy we recommend:

- ***Injecting a highly viscous foam in varicose veins (C2) (Level 1C)***
- ***Avoiding patient or leg movement for a few minutes after injection, avoiding an 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 (**Morrison 2008 + 2010**). Recently no benefits on neurological disturbances in patients treated with CO2-O2-based foam compared to air-based foam in low volumes have been demonstrated. [Beckitt 2011, Hesse 2012]

7 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 recurrences 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 and may help preventing intra-arterial injections (GRADE 1A), 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)***

8 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 (Rabe 2008).

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

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Duplex ultrasound 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 (Mercer 1998, Blomgren 2005, Cavezzi 2006, Coleridge Smith 2006). Duplex examination should also report the incompetence of terminal and/or pre-terminal saphenous valves. Duplex ultrasound 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 (Rautio 2002).

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

Duplex ultrasound is strongly recommended prior to sclerotherapy in patients with recurrent varicose veins after previous treatment (Franco 1998, Jiang 1999) and in patients with vascular malformations (Lee 2003, Yamaki 2000). Additionally, functional examinations (e.g., photoplethysmography, phlebo-dynamometry, venous occlusion plethysmography) and imaging modalities (e.g. phlebography) may be considered (Schultz-Ehrenburg 1984, Brunken 2009, Darwall 2010).

Recommendation 14:
We recommend duplex ultrasound 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 (Breu 2008).

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.

9 Management of sclerotherapy of varicose veins

9.1 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 mg, 10 mg, 20 mg, 40 mg, 60 mg respectively in a 2 mL-ampoule).

Polidocanol is a non-ionic detergent and a local anaesthetic. The dose of 2 mg polidocanol per kg body weight and per day should not be exceeded (e. g. German Summary of Product Chracteristics / Package Insert for Aethoxysklerol (Kreussler 2012)).
For a patient weighing 70 kg, - independently of the medically indicated amount - a total of up to 140 mg polidocanol (lauromacrogol 400) per kg body weight per day should not be exceeded.

140 mg polidocanol are contained in:

Polidocanol-solution 0.25%	56	mL	injection	solution
Polidocanol-solution 0.5%	28	mL	injection	solution
Polidocanol-solution 1%	14	mL	injection	solution
Polidocanol-solution 2%	7	mL	injection	solution
Polidocanol-solution 3%	4.6 mL injection solution			

Sodium tetradecyl sulphate (STS)

Sodium tetradecyl sulphate is an anionic detergent sclerosant drug. It is supplied in concentrations of 0.2%, 0.5%, 1% and 3% (2 mg/mL, 5 mg/mL, 10/mL 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.

9.2 Sclerotherapy with sclerosant solutions (liquid sclerotherapy)

Recommendation 16:
We recommend the following values for concentration and volume per injection for liquid sclerotherapy. (GRADE 2B). Concentrations and volumes proposed are just indicative and may be changed as to the judgement of the therapist.

Table 2: Suggested volumes per injection for sclerosants (POL and STS) used for liquid sclerotherapy (Kreussler 2012, STD 2012)

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

Table 3: Suggested POL- and STS-concentrations in liquid sclerotherapy Kreussler 2012, STD 2012

Indications	**Concentration % POL**	**Concentration % 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

10 Injection technique and material:

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

10.1 Visual Sclerotherapy

10.1.1 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.***

10.1.2 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***
- ***In 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.***

10.2 Ultrasound-guided sclerotherapy

Ultrasound-guided sclerotherapy 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, groin and popliteal recurrence and venous malformations (Kanter 1996, Grondin 1997, Guex 2000, Schadeck 1997).

Recommendation 19:
For ultrasound-guided sclerotherapy 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 saphenous veins by direct puncture, it is recommended that venous puncture should be performed in the proximal thigh (GSV and AASV) or calf (SSV) 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 Duplex ultrasound screen before injection***
- ***Injection is performed under ultrasound control***
- ***Foam sclerosants (Polidocanol 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***

10.3 Foam Sclerotherapy

The literature has long contained reports of sclerotherapy with foamed sclerosants (Wollmann 2004). In recent years, as the technology has improved, foam sclerotherapy has become established, especially for the treatment of varicose veins (Bergan 2000, Alos 2006).

Detergent-type sclerosants such as Polidocanol 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 mixing ratio for sclerosant and gas is 1 + 4 (Tessari 2001 Wollmann 2004). The Tessari-DSS (double syringe system) technique involves the turbulent mixing of polidocanol 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 Tessari technique is unstable; with high concentrations it is more stable and viscous. There is no evidence for adverse events with the use of non sterile air in foam production (de Roos 2011)

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 **(Guex 2008. Yamaki 2012***).*

10.3.1 Foam production:

Recommendation 20:
We recommend techniques with 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 gas component for the generation of sclerosing foam for all indications (GRADE 1A) or a mixture of carbon dioxide and oxygen (GRADE 2B).

Recommendation 22:
We recommend a relation of liquid sclerosant and 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 possible, especially with lower concentrations of sclerosing agents.

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.

10.3.2 Foam volumes:

There is no evidence-based limitation for the maximum volume of foam per session. In the European Consensus on Foam Sclerotherapy a maximum of 10 mL of foam was considered as safe as an expert opinion (Breu 2008). The incidence of thromboembolic complications and transient side-effects (e.g. visual disturbances) rises with higher volumes of foam (Myers 2008).

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 benefit-risk-assessment (GRADE 2C).

10.3.3 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 as to the judgement of the therapist.

Table 4: Suggested POL- and STS-concentrations in foam sclerotherapy Kern 2004 Kahle 2004, Norris 1989, Rabe 2010, Peterson 2012, Alos 2006, Uncu 2010, Rasmussen 2011, Stücker 2006, De Waard 2005, Hertzman 2007, Pang 2010, Yamaki 2000 + 2008, Blaise 2010, Blaise 2011, Guex 2000, van Neer 2006, Myers 2007, Kakkos, 2006,Coleridge Smith 2006 + 2009, Myers 2007, Bradbury 2010, Hamel-Desnos 2007, Ceulen 2007, Rathbun 2012, Rao 2005, Breu 2008

Indications	**Concentration % POL**	**Concentration % STS**
Telangiectasias	up to 0.25% (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		
< 4 mm	up to 1% (GRADE 1B)	up to 1% (GRADE 1C)
≥ 4 mm and ≤ 8 mm	1–3% (GRADE 1A)	1–3% (GRADE 1B)
> 8 mm	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)

In incompetent perforating veins, recurrent varicose veins and venous malformations, 1% POL or STS have been used in most of the studies (Van Neer 2006).

11 Post treatment management

Recommendation 26:
For post treatment management we recommend to consider 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)***
- ***Wearing of compression stockings (23-32 mmHg) after sclerotherapy of telangiectasias daily for three weeks enhances results (GRADE 2B).***
- ***Prolonged immobilisation and long distance-travelling in the first period 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 in the weeks following sclerotherapy. (GRADE 1C)***

12 Assessment of the outcome after sclerotherapy:

The evaluation of efficacy of sclerotherapy includes clinical, morphological and hemodynamic 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 standardised 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 duplex ultrasound is required (Coleridge-Smith 2006/1)
Patency, occlusion (total or partial) or vein disappearance should be assessed.
Investigations should include Valsalva and/or compression/release manoeuvres, according to the UIP-guideline (De Maeseneer 2011).
Duplex-investigation includes the following findings (Table 5):

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

Flow and reflux o no flow o antegrade flow without reflux (< 0.5 sec) o reflux < 1 sec o reflux > 1 sec	Morphology and hemodynamics o patency / occlusion: • 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 o vein size: • pre treatment diameter • post treatment inner diameter • length of the occluded segment • length of the patent segment

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 intended vein, but with short patent segments with any blood flow may be considered to be a successful outcome.

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

Where applicable, the improvement of venous function can also be demonstrated by pre- and post-treatment functional measurements (e.g. plethysmography, venous pressure measurements) (Schultz-Ehrenburg 1984, Brunken , Darwall 2010).

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)

13 Efficacy

Sclerotherapy, liquid or foam, is a safe and effective method to treat telangiectasias, reticular varicose veins and subcutaneous varicose veins (Hamel-Desno 2002, Hamel-Desnos 2007, Rabe 2008 , Alos 2006, Ceulen 2007, Kahle 2004, Rao 2005, Yamaki 2004, Ouvry 2008, Coleridge Smith 2009).
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 (Kern 2004, Kern 2007, Kahle 2004, Norris 1989, Rabe 2010, Peterson 2012).
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 (Alos 2006, Uncu 2010).
Foam sclerotherapy of saphenous varicose veins is significantly more effective than liquid sclerotherapy (Hamel-Desnos 2003 + 2007, Alos 2006, Ouvry 2008, Rabe 2008). The occlusion rate depends on the diameter of the vein, on the concentration of the sclerosant and on the injected foam volume (Rabe 2008, Myers 2007). Compared to crossectomy and stripping and to endovenous thermal ablation, foam sclerotherapy shows only a slightly higher mid-term recanalisation/failure rate (Rasmussen 2011, Shadid 2012). Quality of life and discomfort symptoms improve the same way as after surgery or endovenous thermal treatment (Rasmussen 2011). 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 (Ceulen 2010).
Foam sclerotherapy of incompetent saphenous veins with long catheters is also effective (Brodersen 2007, Wildenhues 2005, Hahn 2007, Bidewai 2007, Kölbel 2007, Parsi 2009, Cavezzi 2009).
Re-treatment by sclerosing partially recanalised vein segments during the follow-up is recommended and improves the mid-term result (Blaise 2010, Chapman 2009).
Sclerotherapy of varices in the region of venous ulcers improves the healing rate (Stücker 2006, De Waard 2005, Hertzman 2007, Pang 2010). (GRADE 1B)
Foam sclerotherapy is more effective than liquid sclerotherapy in the treatment of venous malformations (Yamaki 2000 + 2008, Blaise 2011).
Foam sclerotherapy is effective in the treatment of recurrent varices after previous treatment, accessory saphenous varices, non-saphenous varices and incompetent perforating veins (*Guex 2000, van Neer 2006, Kakkos, 2006; McDonagh 2003,Coleridge Smith 2006 + 2009, Myers 2007, Bradbury 2010*).

Compression treatment with medical compression stockings or bandages improves the result of sclerotherapy for spider veins (Goldman 1990, Weiss 1999, Kern 2007, Nootheti 2009) and the incidence of pigmentation may decrease (Weiss 1999, Goldman 1990). Evidence of efficacy for compression after sclerotherapy of saphenous veins is still lacking (**Hamel-Desnos 2010**). Nevertheless compression could have some efficacy, as the need for an additional sclerosing session seems to be inversely proportional to the pressure exerted by 3 different classes of MCS worn for 3 weeks after sclerotherapy (Zarca 2012) and as selective extrinsic compression could reduce recurrence (Ferrara 2009). Local eccentric compression increases significantly the local pressure in the injection area and may improve the efficacy of sclerotherapy (Stanley 1991).

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 recommend against routine elevation of the leg or compression of the junction for safety reasons. (GRADE 2C)

Recommendation 31:
We recommend re-treatment by sclerosing partially recanalised 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 1

Members of the European Guideline Conference

Name	Adress	Country	Society
Antignani, P.L.,	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, F.X.	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.	Amersham	Great Britain	Venous Forum of the Royal Society of Medicine
Fernandez, F.		Spain	Spanish Chapter of Phlebology
Frullini, A.	Florence	Italy	Italian Phlebological Association
Gillet, J.L.	Bourgoin-Jallieu	France	French Society of Phlebology
Goranova, E.	Sofia	Bulgaria	Bulgarian Society of Phlebology
Guex, J.J.	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
Maurins, U.	Riga	Latvia	The Latvian Society of Phlebology
Milic, D.	Nis	Serbia	Serbian Society of Phlebology, Baltic 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
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 2: American College of Chest Physicians Task Force recommendations on Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines (Guyatt 2006)

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 vice versa	RCT‘s without important limitantions 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 vice versa	RCT‘s 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 vice versa	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	RCT‘s without important limitantions 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	RCT‘s 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