NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ultrasound-guided foam sclerotherapy for varicose veins

Treating varicose veins with foam injections using ultrasound guidance

Small valves inside the veins help blood flow properly through them. Varicose veins develop when these valves do not work properly, allowing blood to collect in the veins. This enlarges them and causes the valves to deteriorate further. Varicose veins commonly occur in the legs. Many people have no symptoms, but if they do, these can include heaviness, aching, throbbing, itching, cramps or tiredness in the legs. In severe cases, patients may have skin discolouration or inflammation, or skin ulcers. Foam sclerotherapy involves mixing a chemical with air or another gas to produce a foam, which is injected into the affected vein using ultrasound imaging to monitor its progress. This causes scarring of the inside of the vein so that it becomes blocked. Sometimes patients may need more than 1 injection to block the vein.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2012 and updated in November 2012.

Procedure name

- Ultrasound-guided foam sclerotherapy for varicose veins

Specialist societies

- The Vascular Society
- British Society of Interventional Radiologists

Description

Indications and current treatment

Varicose veins are enlarged tortuous veins with deficient valves. Venous insufficiency occurs when blood collects in them rather than being pumped back to the heart. Most people with varicose veins have no symptoms, but venous insufficiency may cause fatigue, heaviness, aching, throbbing, itching and cramps in the legs. Chronic venous insufficiency can lead to skin discolouration, inflammatory dermatitis and ulceration. Great saphenous vein insufficiency is the most common form of venous insufficiency in people presenting with symptoms.

Conservative methods such as compression hosiery (support stockings or tights) may help people with symptomatic varicose veins. If symptoms are severe the main treatment options include surgery (ligation and stripping of the great saphenous veins or ligation with or without stripping of thesmall saphenous veins, and phlebectomy), endovenous laser treatment and radiofrequency ablation.

What the procedure involves

The aim of ultrasound-guided foam sclerotherapy for varicose veins is to damage the endothelial surface of the vein causing scarring and leading to blockage of the treated varicose veins. Sclerosant, in the form of a foam, is intended to have good surface area contact with the vein walls

The procedure may be carried out with local anaesthesia. Sclerosant foam is injected into the affected veins using ultrasound guidance. The foam causes an inflammatory reaction in the vein wall blocking the vein. Compression bandages are applied after the procedure and are typically worn for between a week and a month.

More than 1 vein may be treated during the same session. If any vein is incompletely treated, further injections may be given in the same or subsequent sessions.

Outcome measures

CEAP classification

The CEAP (clinical, etiological, anatomic and pathophysiologic) classification from the American Venous Forum is often used to classify venous disease of the lower limb. Clinical signs are classified as: C0 – no signs of venous disease; C1 – telangiectases or reticular veins; C2 – varicose veins; C3 – oedema; C4a – pigmentation or eczema; C4b – lipodermatosclerosis or atrophie blanche; C5 – healed venous ulcer; C6 – active venous ulcer.

Aberdeen Varicose Vein Questionnaire (AVVQ)

AVVQ is a 13-point questionnaire covering multiple elements of varicose vein disease (including pain, patient satisfaction and limitations on daily activity) on a scale of 0–100, with higher score indicating severe effect.

Venous Clinical Severity Score (VCSS)
VCSS includes 9 clinical characteristics of chronic venous disease scores graded from 0 (absent) to 3 (severe), with a maximum score of 30 (indicating severe).

Venous Segmental Disease Score (VSDS)
VSDS (range 0–10), weights 11 venous segments for their relative importance when involved with reflux and/or obstruction. This is a modification of the CEAP classification.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ultrasound-guided foam sclerotherapy for varicose veins. Searches were conducted of the following databases, covering the period from their commencement to 2 November 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with varicose veins.
Intervention/test	Ultrasound-guided foam sclerotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 11,480 patients from 1 systematic review[1], 2 randomised controlled trials[2–3], 9 case series [4–6;12–14;16–18] ,9 case reports [7–11;15;19–21]and 1 registry report[22] (there may be some overlap of patients included in the systematic review). Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

The previous guidance 'Ultrasound-guided foam sclerotherapy for varicose veins' (NICE interventional procedure guidance 314) was based on approximately 842 patients from 2 randomised controlled trials, 4 case series, 4 case reports, and UK clinical audit data provided by a Specialist Adviser on approximately 7027 patients.

Table 2 Summary of key efficacy and safety findings on ultrasound-guided foam sclerotherapy for varicose veins

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details

Jia X (2006)[1]

Systematic Review

UK

Search period: 1966–May 2006

Study population: adults undergoing foam sclerotherapy

Nine RCTs, 1 registry report, 8 non-randomised comparative studies, 43 case series and 6 case reports.

n=**6856**

Age: 62% ≥ 16 years

Sex: 44% female

Study selection criteria: includes both English and non-English language full text and conference abstracts

Technique: studies reported using STS or POL as sclerosing agents. Techniques for producing foam varied between studies.

Follow-up: **ranged from 3 months to 10 years**

Conflict of interest/source of funding: review was commissioned by NICE

Key efficacy findings

Complete occlusion of treated veins (classed as successful treatment)

Median rate (%) (range): 84.4% (range 67–94%) (n=640; 5 RCTs; follow-up ranged from 3 months to 10 years)

Meta-analysis of 2 RCTs (n=340) comparing foam (n=174) with liquid sclerotherapy(n=166): RR 1.5 (95% CI 0.6 to 3.6); I^2=95.2% (follow-up 1 to10 years)

Meta-analysis of 2 RCTs (n=324) comparing foam (n=117) with surgery involving stripping (n=207): RR 0.9 (95% CI 0.7 to 1.1); I^2= 61.9% (follow-up 3 months to 1 year).

Healing of venous ulcers

3 case series (n=216): The rate of longer-term (>30 days) ulcer healing rate ranged from 76% (55/72) to 100%(28/28) (follow-up between 60 days to 6 years).

Recurrence rates: ranging from 0.5% to 5.9% of patients at follow-up ranging from 2 to 3.4 years.

In 1 RCT of 129 patients, 51% (66/129) of patients had recurrence of varicose veins after foam sclerotherapy, and varicose veins recurred at a higher rate in patients treated with foam compared with both surgery (ligation) (RR 1.4 95% CI 1.0 to 1.8) and surgery combined with liquid sclerotherapy (RR 1.4, 95% CI 1.1 to 1.9) (duration of follow-up 10 years).

Quality of life

Study type; n; follow up;	Outcome	Foam	Comparator*
1 RCT; n=75; 1 year	Patient satisfaction median (range)	7.4 (1.2)	7.2 (1.5)
1 RCT; n=30; 3 months	Return to normal activity (days)	2	8

Key safety findings

Adverse events [number of studies]	Median rate (%) (range); n
Arterial events [2][a]	2.1 (1.4, 2.8); n=6/253
DVT [26]	0.02 to 0.7 (0, 5.7); n=1/6395 to 16/2076 <30 days: 0 to 4.2
PE [5]	0 (0, 0.3); n=1/1316
Cutaneous: necrosis [9]	0 (0,0.2) to 1.3(0.3, 2.6); n=1/766 to 8/781
Cutaneous: ulceration [1]	0 to 3.6;<30 days: 2.6 n=1/38
Visual disturbance[15][b]	0.3 to 5.9
Transient confusion [3]	0.5 (0, 1.2)
Headache [4]	0 to 14.2 (5.4, 23.0)
Systemic symptoms [6] (coughing, chest tightness/heaviness, panic attack, malaise and vasovagal attack)	0.2 to 0.5 (0, 2.8)
Local effects: 'minor' vein thrombosis[8]	0.1 to 8.8 (0, 17.6)
Thrombophlebitis [21]	0.05 to 9.2 (0, 45.8)
Neurological injury [8]	0 (0, 0.7)
Matting/skin staining/pigmentation [15]	2.3 (0, 19.8) to 31.6 (7.8,55.1)
Pain at site of injection [8]	0.3 (0, 0.5) to 4.2 (0, 11.2)

No cases of anaphylaxis or intra-arterial injection reported

[a]Arterial events: 1 case of stroke and 5 cases of transient embolic events.

[b]Visual disturbance included blurred vision, migraine with

Comments

This is a systematic review that was commissioned by NICE for previous guidance (IPG 217) (carried out by the Review Body for Interventional Procedures [ReBIP]).

Study design issues:

- Quality assessment of studies undertaken using adapted checklists or those developed by ReBIP.
- Reporting of efficacy outcomes varied between studies and terminology for safety outcomes was not consistent across the included studies.
- Patient satisfaction assessed using

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
	1 RCT; n=30; 3 months — AVVQ score (median) — Baseline: 15.4 Follow up: 9.3 — Baseline: 26.1 Follow up: 14.1 1 RCT; n=30; 3 months — CEAP score (median) — Baseline: 4 Follow-up:1 — Baseline:4 Follow-up:1 *No significant difference' between foam and liquid sclerotherapy for patient satisfaction (RCT; n=75) or between foam and surgery for change in disease severity (RCT; n=30).	aura or scotoma. Visual disturbance did not last longer than 2 hours and no long-term or permanent visual impairment was reported. Unpublished case report: 1 myocardial infarction 30 minutes after injection; 1 grand mal epileptic fit 40 minutes after injection. No septal defects in either patient.	a scale ranging from 0–10 (no details) **Other issues**: • Results for safety outcomes include data extracted from conference abstracts.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details

Shadid N (2012)
RCT
Netherlands
Recruitment period: 2005–07
Study population: patients with GSV incompetence
n=**460 (233 UGFS vs 227 surgery)**
Age: mean 55 years
Sex: 73% female
Patient selection criteria: included patients with primary GSV incompetence in combination with SFJ, with presence of 1 or more venous symptoms, reflux time >0.5s, and normal deep venous system. Patients with signs of previous DVT, active ulcer were excluded.
Technique: Under US guidance, sclerosing foam (1:4 ratio of sclerosant:air) of 3% POL was injected. Compression was applied over the treated area and antiembolism stockings worn for 1 week. Majority of the patients received an injection of 5 ml or more.

83% received only 1 treatment session.

Key efficacy findings

Number of patients analysed: **390 (213 UGFS vs 177 surgery)**

Reflux at 2 years (%)

	UGFS	Surgery	Difference; p value
Reflux (irrespective of venous symptoms)	35	21	14.0 (4.4 to 22.5) p=0.003
Reflux (in combination with symptoms)	11[a]	9[a]	p=0.41
Reflux (in distal GSV below knee)	41.3	42.9	p=0.75

[a]estimated from graph

Recurrent reflux defined as reflux for more than 2 cm in length in the treated vein segment (assessed using Doppler).

Symptom scores

	UGFS	Surgery	p
VCSS (mean change in baseline)	-1.49	-1.75	0.23
VAS (mean change	-0.36	-1.8	0.56
EQ-5D (mean change in utility score; minus score at baseline)	0.064	0.061	0.89

Key safety findings

Early complications (within 1 week)

Complications	UGFS (n=230)	Surgery (n=200)	p value
Thrombophlebitis	7.4 (17)	0	<0.001
Pulmonary embolism[a]	0.4 (1)	0	0.35
DVT[a]	0.4(1)	0	0.35
Headache/migraine	1.3 (3)	0	0.11
Pain at injection site	2.6(6)	0	0.02
Paraesthesia	0	3(6)	0.008
Groin infection	0	2 (4)	0.03
Haematoma	0	1.5(3)	0.06

[a] treated by anti-coagulant therapy.

Late complications (at 2 years)

Complications	UGFS (n=213)	Surgery (n=177)	p value
Hyperpigmentation	5.6 (12)	1.1 (2)	0.02
Telangiectatic matting	2.8 (6)	1.1 (2)	0.24

Comments

Follow up issues:
- 8.6 % (20/233) patients in the UGFS and 11.9% (27/227) of patients in the surgery group were lost to follow-up.

Study design issues:
- Adequate method of randomisation (computer-generated block randomisation). Method of allocation concealment or blinding not reported. Intention-to-treat analysis not carried out.
- EQ-5D was used to assess health-related quality of life. VAS scale (part of EQ-5D) was used to rate health state from worst possible (0) to best possible (100).

Study population

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Follow-up: 2 years Conflict of interest/source of funding: The authors declared no conflict of interest.	**Patient satisfaction** Complete reduction in venous complaints was reported in 59.6% of patients in the UGFS group and 66.1% of patients in the group having surgery (p=0.21). **Retreatment** UGFS: 40 patients had a repeat session (5 had more than 2 sessions) Surgery: 8 were referred for UGFS because reoperation was technically difficult and 2 patients had re-exploration of the groin. In both groups, if recurrence was not 'serious' it was managed conservatively with stockings.		**issues:** • Study included patients in CEAP class C2–C5.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details

Kalodiki E (2011)[3]

Randomised controlled study

UK

Recruitment period: 2003–4

Study population: patients with symptomatic primary VV because of GSV incompetence

n=**73 (82 legs: 39 foam combined with SFL vs 43 surgical stripping)**

Age: mean 48 years

Sex: 67% female legs

Patient selection criteria: primary symptomatic varicosities involving GSV without previous treatment. History of or risk factors for DVT, known allergies to sclerosants excluded.

Technique: SFL performed using local anaesthesia. 6 ml of 3% STS (mixed with air) was injected into the refluxing vein under US guidance. Thigh length compression stockings were applied following the procedure and patients were advised to wear stockings continuously for 2 weeks and daytime only

Key efficacy findings

Number of patients analysed: 33 legs vs 26 legs

Venous status :

	Foam % (n)	**Surgery** % (n)
Reflux		
Above the knee	33 (11)	26.9 (7)
Below the knee	42.4 (14)	34.6 (9)
Obliteration		
Above the knee	57.6 (19)	53.8 (14)
Below the knee	24.2 (8)	38.5 (10)

Reflux (assessed using US) defined as: reverse flow greater than 0.5 seconds after manual calf compression and release manoeuvres. All patients with reflux received additional UGFS.

Clinical severity

	Foam	Surgery	p between groups
VCSS score			
Preoperative	4.5 (2–15)	5 (2–12)	0.36
5 years	1(2)[a]	2.5(4)[a]	0.35
VSDS score			
Preoperative	1.0 (1.0)	1.0 (1.3)	0.52
5 years	0.25 (1.0)[b]	1.0 (1.0)	0.39

Data reported as median (IQR). [a]p value for change not reported. [b]p<0.0005

Quality of life

	Foam	Surgery	p between groups
AVVQ score (median, IQR)			
Preoperative	12.3(10.4)	16.3(14.7)	Not reported
5 years	7.3(10.1)	5.5(23.9)	0.02

Key safety findings

No thromboembolism, arterial injection, anaphylaxis or neurologic events were observed but 1 patient reported a migraine and another patient reported an 'aura' (no further details) when they presented for additional UGFS session (treatment session was rescheduled).

Adverse event	**Foam (n=39)**	**Surgery (n=43)**
Mild pigmentation	6	2
Significant pigmentation	1 (persisted at 5 years)	0
Groin infection	2	2
Superficial thrombophlebitis	3	0
Vasovagal attack	1	0
Saphenous nerve injury	0	2
Skin ulcer	0	1
Urinary retention	0	1

Comments

Follow-up issues:

- Loss to follow-up reported in both groups. Reasons not reported.

Study design issues:

- Randomisation method was 'adequate', allocation concealment was with sealed envelopes, but the blinding of the outcome assessor is unclear.
- In patients with bilateral VV, the most symptomatic limb was randomised. If VV developed in the contralateral limb, this limb was assigned to the same procedure.
- Technical efficacy assessed at all veins (GSV, AASV, large tributaries, and incompetent perforating veins)

Study population

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
for an additional week. Follow-up: median 5 years Conflict of interest/source of funding: not reported	Study reported that the minimal important difference for AVVQ score is 2.40, and the difference observed at 5 years was not clinically significant. SF-36: there was no significant difference in the changes on the physical (p=0.72) or mental (p=0.35) scores between the treatment groups. The actual SF-36 scores are not reported here, as they were presented on a graph.		**issues:** • Study reported CEAP classification (C_{2-6}) was similar between groups. **Other issues:** • This study is a follow-up of Bountouroglou (2006) which is included in the Jia (2006)[1] systematic review. Some details provided under study design issues are based on quality assessment of the Bountouroglou (2006) study in the systematic review.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Bradbury AW (2010)[4] **Case series** UK Recruitment period: 2004–9 Study population: patients with symptomatic SVR (CEAP C_{2-6}). 28% of legs had had at least 1 prior operation. n=**977 (1252 legs)** Age: mean 54 years Sex: 64% (810/1252) female Patient selection criteria: symptoms and signs secondary to venous hypertension as a result of significant reflux in one or more segments. Patients with significant post-thrombotic deep venous disease or an ankle-brachial pressure index of less than 0.8 were excluded. Technique: Using local anaesthesia, 2 to 2.5 ml 1% or 3% STS (mixed with air) foam was injected. Bandages and stockings: 5–7 days then stockings alone: 1 additional month. Follow-up: from less than1 month to 68 months Conflict of interest/source of funding: not reported.	Number of patients analysed: 977 **Repeat treatment** 12.9% (161/1252) legs had a further session of UGFS at a mean of 17 months after initial treatment. In 109 legs, retreatment was because of complete or partial recanalisation and because of new SVR in 52 legs. **Freedom from intervention** **Time point (year) / Number of segments at risk / % free from retreatment** 0 / 1417 / 100 1 / 1079 / 96 2 / 680 / 92 3 / 360 / 88 4 / 125 / 85 5 / 25 / 81	**Complications (1-month follow-up)** **Complication / n / Timing** Headache / 3 / Immediately after treatment; resolved in 24 hours after treatment with analgesia Transient visual disturbance / 5 / During or shortly after treatment (twice in 1 patient) Pain in the treated leg / 3 / Related to musculoskeletal and/or stocking, further details not reported Facial rash / 1 / 24 hours after treatment and disappeared spontaneously. Allergy (to the stocking) / 1 / 'Likely' related to an area of pressure erythema and settled spontaneously. Symptomatic DVT / 3 / During first month after treatment; treated with heparin and warfarin PE / 1 / 5 weeks after treatment; treated by an anticoagulant. **Repeat treatment** 4 patients had repeat treatment with UGFS within 1-month follow-up. **Death** 6 patients died after treatment. Cause of death: 1 patient died of rectal carcinoma (at 9 months after treatment), 2 of old age (at 2 and 4 years) and 1 after revisional hip arthroplasty, 1 from colon cancer and 1 from cardiac and renal failure (all 3 patients died 3 years after treatment)	**Follow-up issues:** • 11% (141 legs) were not assessed at 1 month follow-up.1 patient requiring repeat treatment crossed over to another treatment modality. **Study design issues:** • Patients referred consecutively from general practice. **Study population issues:** • Patients with reflux in one or more veins including: GSV AASV, SSV, vein of the popliteal fossa. • SVR was in association with CEAP clinical grade 2–3 (n=868), 4 (n=232) or 5/6 (n=152). **Other issues:** • 15 patients were treated with 0.5% STS; in combination with 1% and/or 3% foam.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Chapman-Smith P (2009)[5] **Case series** New Zealand Recruitment period: not reported Study population: patients treated for GSV reflux. 30% had surgical treatment prior to UGFS. n=**146 (203 limbs)** Age: mean 57 years Sex: 66% female Patient selection criteria: All patients (CEAP C_{1-6}) who attended an initial ultrasound assessment with confirmed GSV reflux. Technique: 0.25 to 3 ml of 3% STS mixed with air injected into GSV under US guidance. Procedure performed weekly until ultrasound demonstrated closure of all refluxing varicosities and tributaries. Compression stockings were worn immediately after treatment for up to 2 weeks. Follow-up: 5 years Conflict of interest/source of funding: None	Number of patients analysed: **203 limbs** **Recurrence rates (at 5-year follow-up)** **Ultrasound recurrence** / % (n=23): Venous closure: 35 Any ultrasound recurrences: 30 New VV: 17 Combined (ultrasound recurrence and new VV): 17 **Clinical recurrence** / % (n=23): No venous symptoms: 74 Minimal venous symptoms: 22 Significant venous symptoms: 4 Significant venous symptoms: visible or palpable varices, aching, oedema or venous skin changes. **Repeat treatment** 43% required additional UGFS treatment between 6 weeks and 6 months and 23% between 6 and 12 months. **Patient assessment** Patients reported that their treatment was successful, improved symptoms and allowed an immediate return to activity. Patients also reported that they would repeat the procedure if required and preferred UGFS to surgery.	No incidence of anaphylaxis, fatality, stroke, sepsis, arterial injection, nerve damage, hypertrichosis, DVT or pulmonary embolism observed. **Adverse event** / **% (of limbs treated)**: Matting and staining: 3.9 Pain (no further details provided): 3 Persistent swelling: 2 Superficial thrombophlebitis: 10.3 (1-year follow-up); 4 (2-year follow-up) Transient migrainous scotomata (lasting for 20 minutes with no sequelae): 1 Transient tongue of thrombus in the common femoral vein: 1 Absolute figures not reported. Symptoms such as aching limb pain and cramps were reported to have resolved on the day of treatment (no further details reported). Further details on timing and how complication was treated not reported for any adverse events.	**Follow-up issues:** • No loss to follow-up reported. **Study design issues:** • Consecutive enrolment of patients • Patient assessment using a self-reported questionnaire at each follow-up visit: self-graded changes in venous symptoms and cosmesis, pain, preference of UGFS to surgery, whether they would undergo repeat procedure if indicated, and if UGFS was a successful treatment. **Study population issues:** • CEAP: 45% C_2, 38% C_4, 11% C_3, 3% C_6, 1.5% C_1 and C_5, 0% C_0.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Gillet J-L (2008)[6] Ma RWL (2011)[7] Bush (2007)[8] Forlee (2006)[9] Hahn (2010)[10] Picard (2010)[11] Study type: **case series and case reports reporting cerebrovascular/ neurological events** France, Australia, USA, Ireland, Germany,	**Gillet (2008)** A case series of 1025 patients treated by UGFS for GSV and SSV incompetence, investigating side effects and complications after treatment with POL or STS foam. Patients with symptomatic PFO or history of DVT or PE were excluded. Mean age was 54 years and 76% were female. Intervention: median 4 cc^3 0.5% to 3% POL or STS mixed with air or oxygen. Effects: One TIA occurred in a 52-year-old woman after injection into the SSV. Patient presented with a dyarthria (for 30 seconds) and paraesthesia of left hand (for 30 minutes). Complete clinical recovery occurred within 30 minutes and further screening revealed a PFO combined with an interatrial septal aneurysm. **Ma (2011)** Case report 1: a 56-year-old woman with recurrent VVs Intervention: 15 ml 3% STS (mixed with air) for GSV, SSV, and intersaphenous veins. UGFS sessions over a period of 9 months (the patient was also treated by EVLA). Effect: Two days after treatment with foam to treat tributaries of GSV, the patient had a right MCA stroke causing dysphasia and paralysis of the left limb and face. Patient made a complete recovery within 1 hour. No visual disturbances were observed. MRI confirmed ischaemic changes but no air bubbles were identified. TOE revealed a PFO (subsequently closed percutaneously). No further neurological or thrombotic events were reported at 1-year follow-up. Case report 2: a 59-year-old woman with right lower limb VVs with history of stroke, previously treated by EVLA (with no complications). Intervention: UGFS with 4ml 1.5% STS for GSV and posterior arch vein. This was followed by ambulatory phlebectomy for treating remaining calf varicosities. Effects: Within seconds of lifting the leg after completion of ambulatory phlebectomy, patient became unresponsive, exhibited an altered mental stated with slurring of speech, disorientation, a dense left arm and leg hemiplegia and an extensor plantar response. CT angiogram confirmed a right MCA air embolus. Patient was treated with tissue plasminogen activator 2 hours later resulting in improvement in mental and neurological status, with a left-sided weakness and droop in the face fully resolved by discharge. TOE revealed a small PFO. CT confirmed resolution of right MCA air embolus and no further neurological or thrombotic events were reported at 3 month follow-up. Case report 3: a 64-year old woman with bilateral incompetence of GSV and SSV. Intervention: 15 ml 1.5% STS foam over a 6-month period in combination with EVLA. Effects: After the second round of treatment, the patient had a right MCA stroke presenting with dysphasia and left limb and facial paralysis 1 day after the procedure. A CT or MRI did not reveal air bubbles. A TOE confirmed a PFO (closed percutaneously) and no further neurological or thrombotic events were reported at 2-year follow-up. **Bush (2007)** Case report 1: a 72-year-old woman with symptomatic saphenous insufficiency of the left leg and 2 incompetent Cockett's		**The following study was included in the previous guidance (IPG 314):** Bush (2007)[8] **The following studies have previously not been seen by the Committee:** • Gillet (2008); Ma (2011); Forlee (2006); Han (2010); Picard (2010) • Forlee (2006) (included in the Jia (2006) systematic review[1]) reported stroke in 1 patient under 'arterial events'.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
	perforators. The patient had no significant medical history. Intervention: 2 cm^3 of 2% Storadecol foam (Tessari method) in each perforator. Effects: the patient was discharged but was found slumped in her chair 25 minutes after the injection. She was able to communicate with slurred speech, but she couldn't move her extremities. When she arrived at the emergency room she had bilateral weakness but more pronounced on her left side. A CT scan revealed air in her vertebral artery. Within 3 hours, the patient's condition had resolved and she had no atrial defect (echogram). A very small shunt was identified after injection with a solution of agitated blood and saline (by TOE). Case report 2: a 35-year-old woman with reticular veins and spider telangiectasia previously treated with foamed STS on 2 occasions. Intervention: this treatment consisted of 10 cm^3 of foam injected over 20 minutes (concentration not stated). Effects: when sitting up to reach for her hose (not otherwise described), the patient fell off the bed, hitting her head on a side table. She was unconscious for 30 seconds, with a spastic appearance in her right hand. She was unable to move her left leg or arm, but was able to answer questions. Later she developed seizure activity in her right upper extremity, her eyes deviated to the right, and she had 'purse-lip type breathing'. A CT scan revealed air in the right venous circulation and an air bubble in the middle cerebral artery. The patient had hyperbaric oxygen therapy. The patient's neurological exam was reported as entirely normal 2 weeks after the incident. **Forlee (2006)** Case report: A 61-year-old man with GSV incompetence. Intervention: 20 ml 0.5% POL foam. Effects: Patient developed right hemiparesis shortly after foam injection. After 10 minutes, power in the right upper limb improved (returning to normal in 2 weeks) and his speech return to normal. TOE revealed a PFO. At 2-week follow-up fine motor coordination remained mildly impaired. **Hahn (2010)** Case report: A 48-year-old woman with incompetent SSV. Intervention: Two sessions of UGFS with 0.5% and 1% POL foam. Effects: The first session was tolerated without complications. Five days after the second session, the patient reported she felt 'like a blow against the head', with subsequent hemiparesis and speech impairment. Ischaemic stroke was confirmed by CT. Paradoxical embolism over a large PFO (subsequently closed successfully) was confirmed following a bubble test. The patient was treated by neurological rehabilitation. At 4-month follow-up she had fully recovered with only occasional slight fatigue. **Picard (2010)** Case report: A 33-year-old man with symptomatic varicose GSV. Intervention: single injection of 0.5% POL. Effects: Four hours after the procedure the patient felt nauseous and developed intense vertigo. A right cerebellar infarction was confirmed by MRI 5 days after the procedure. The neurological examination showed a left lower facial paresis, mildly dysarthric speech, and haemiataxia with hypermetria of the right arm and leg. TOE revealed a PFO with an associated atrial septal aneurysm. A right-to-left shunt was confirmed with colour flow duplex scan.		

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Regan JD (2011)[12] Hansen (2007)[13] Hill (2008)[14] Parsi (2010)[15] Wright (2010)[16] Ceulen (2008)[17] Rush (2008)[18] Study type**: case series and case reports of systemic bubble embolism** Australia, Canada,UK, USA, Netherlands Conflict of interest: Regan (2011) – Study was sponsored by manufacturers of Varisolve (BTG International). Authors received consulting fees or were employees of BTG International.	**Regan (2011)** Case series: Patients (n=82) with GSV incompetence. 66% of the patients were female and mean age was 45 years. Patients with right-to-left shunt were included to evaluate the safety of cerebral arterial bubbles. Intervention: ultra-low nitrogen (≤0.8%) POL endovenous microfoam (Varisolve) injection under ultrasound guidance. Compression stocking worn continuously for 2 weeks. Effects: MCA bubble emboli were detected in 73% (60/82) of patients and 'most' emboli were detected within 15 minutes of the injections. 82% had 15 or fewer bubbles; and the highest number of bubbles in 1 patient was 382. Patients with MCA bubbles were observed using MRI for at least 1 post-treatment scan (1, 7, 28 days). No new neurological symptoms were detected. One patient with 3 MCA emboli described 'twinkling lights' in peripheral vision lasting 20 seconds (1 hour after procedure). **Hansen (2007)** Case series: A study of 20 patients with suspected PFO or who described respiratory or cerebral symptoms (including migraine and visual disturbance). Effects: Transthoracic echocardiography demonstrated bubbles in the left heart in 65% (13/20) of patients immediately after the procedure. Five patients with a positive test also had emboli in their MCA, demonstrated on transcranial Doppler. The 7 patients without bubbles in the left heart reported visual disturbance, migraine, shortness of breath, dizziness and numbness. **Hill (2008)** A study that assessed techniques to reduce sclerosant foam migration during UGFS. Intervention: 20 patients treated by UGFS while lying supine (mean volume of foam 5.1 ml); 19 patients with leg elevated (mean volume of foam 4.8 ml) and 19 patients injected while leg elevated but no manual compression at SFJ (mean volume of foam 4.1 ml). Air-based foam was used in a majority of the patients. Effects: Incidence of emboli in the right heart after injection was reported in all patients with the leg flat and occlusive pressure at the SFJ, 45% (16/19) of patients with leg elevated with SFJ compression, and 47% (9/19) of patients in legs elevated and no SFJ compressions. **Parsi (2010)** A study of 5 patients with incompetent saphenous veins which assessed modifications to technique to reduce foam migration. None of the patients had a known PFO. Intervention: Maximum 2.5 ml of 3% STS foam (Fibro-vein) was used in all procedures. The standard technique was injecting into the left GSV. Variation to techniques were: filtering the foam, delivering subsequent injection of filtered foam, preparation of foam using CO_2 ,leg elevation before the procedure, leg elevation after the procedure and immobilisation after the procedure. Compression stocking were fitted after cardiac monitoring. Effects: Bubbles entered the right heart in less than 60 seconds and continued for up to 50 minutes despite all treatment modifications. None of the patients developed any neurological or cardiac symptoms.		**The following studies were included in the overview in the previous guidance (IPG 314):** • Published reports: Hansen (2007) and Hill (2008). Ceulen (2008) and Rush (2008) are not peer-reviewed publications, but are included here because they report serious adverse events. **The following studies have not previously been seen by the Committee:** Regan (2011); Parsi (2010); Wright (2010) • Regan (2011) noted that results of the study cannot be generalised to foams compounded using 'bedside' methodologies, since the

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
	Wright (2010) Case series: 221 patients tested for right-to-left shunts, 59% (130/221) tested positive (39% were positive at rest and 52% after Valsalva manoeuvre). 82 patients with symptomatic GSV incompetence were treated. Mean age was 46 years and 76% were women Intervention: maximum of 20 ml, 1% POL (Varisolve) mixed with O_2 or CO_2 Effects: 89% (54/82) of patients with right-to-left shunts compared with 29% (6/82) patients without a right-to left shunt had high intensity transient signals on transcranial Doppler ultrasound. No patients had symptoms or signs of cerebral embolisation. Despite the large volumes of microfoam injected, the number of bubbles was similar to that during the diagnostic test. **Ceulen (2008)** A commentary was published revealing transient scotomas in a 51-year-old man and migraine in a 33-year-old woman following a single injection of 5 ml of 1% POL foam (air:liquid, 4:1). The patients presented with symptomatic varicose GSV and were 'healthy'. The injection was administered with the leg elevated and manual compression on the SFJ until full vasospasm. The authors noted that all 33 patients had foam microemboli in both the right atrium and ventricle between 45 seconds and 15 minutes after injection. In 5 patients, microemboli were also detected in the left atrium and ventricle, but there were no neurological signs. All 5 patients were later revealed to have right-to-left shunt through a PFO on echocardiographic examination (tested because of the possibility of right-to-left shunt in the first 2 patients). **Rush (2008)** A commentary on the Ceulen report (above) revealed that intracardiac gas emboli were discovered in all 45 patients treated with low nitrogen (less than 0.8%) POL microfoam (Varisolve, Provensis). Pretreatment screening revealed a 40% prevalence of right-to-left shunt. Cerebral emboli and extensive monitoring in 36 of these patients revealed no cerebral lesions or abnormalities on the perimetry or assessment of cardiac markers.		composition of these foams is substantially different. • Bush (2007)[8] and case report 2 from Nitecki and Bass (2007)[19] included in table 2 also reported foam embolism.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Nitecki S and Bass A (2007)[19] **Case reports of local arterial injury** Israel n=3 Study population: patients with venous insufficiency Technique: UGFS Follow-up: over approximately 7 years at 3 centres Conflict of interest/source of funding: not reported	The incidence of arterial injury during UGFS was reported to be 0.25% (3/1200). The cause was said to be chemical and irreversible and resulted in tissue loss. Case report 1: a 16-year-old woman with Klippel-Trenaunay syndrome with varicosities and venous lakes from buttocks and in right limb. Intervention: 3% POL foam injected into 2 toe arteries. Effects: rapid development of dry gangrene in both toes where the foam was injected. This was treated with conservative treatment (dressing, antibiotic, analgesics) and was under observation at the time of the report. Case report 2: a 23-year-old man with C_4 varicosities and atrophie blanche. Intervention: 3% POL foam prepared with the Tessari method directed under direct vision into a Cockett 3 perforator (the study states that this was UGFS, but also that it was injected under direct vision). Effects: severe pain and 'ice cold' foot as a result of bubble embolisation through small arteriovenous shunts to the posterior tibial artery and its branches resulted in gangrene. The foot was treated with thrombolytic therapy, mechanical thrombectomy and hyperbaric oxygen followed by partial foot amputation and free muscle flap transfer. At 15-month follow-up, the patient was 'ambulating and active'. Case report 3: a 54-year-old man with C_4 varicosities. Intervention: 3% POL foam. Effects: deep pain as a result of incorrect placement of the needle into the superficial femoral artery. Duplex scanning revealed a double saphenous system with a subfascial position of the main trunk. This led to the development of gangrene, which required below-knee amputation.		**This study was included in the overview of the previous guidance (IPG 314)** • This study is a report of 6 cases out of approximately 1200 patients treated by UGFS (and 4800 treated by surgery) over 7 years from 3 medical centres. Three other cases are not reported here because they had complications as a result of surgery.

Abbreviations used: AASV, anterior accessory saphenous vein; AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP; clinical, etiological, anatomic and pathophysiologic classification; CI, confidence interval; DVT, deep vein thrombosis; EVLA, endovascular laser ; GSV, great saphenous vein; I^2, measure of heterogeneity; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PE, pulmonary embolism; PFO, patent foramen ovale; POL, polidocanol; RCT, randomised controlled trial; RFA, radiofrequency ablation; RR, relative risk; SFL: saphenofemoral ligation; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; SVR, superficial venous reflux; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; UGFS, ultrasound-guided foam sclerotherapy; US, ultrasound; VCSS, Venous Clinical Severity Score; VCSD, Venous Segmental Disease Score ;VV, varicose vein

Study details	Key efficacy findings	Key safety findings	Comments
Scurr (2007)[20] Brzoza (2007)[21] Guex JJ (2010)[22] **Case reports and data from registry of allergic reaction to foam** Poland, UK, France n=1 in each study Technique: UGFS Conflict of interest: not stated	**Scurr (2007)** Case report1: a 62-year-old woman with a body mass index of greater than 35, angina, hypertension and mild asthma with hay fever presented with a large anterolateral thigh vein (CEAP classification:C_2primary superficial vein reflux); she reported allergies to pollen and perfume but not to conventional medications. Intervention: 4 ml of 3% STD foam (Fibrovein, STD Pharmaceuticals). A compression bandage was applied after the procedure. After 6 months, a persistent patent and incompetent vein warranted further treatment (12 ml of 1% STD). Effects: within 20 minutes of the procedure, the patient reported a hot sensation in her mouth and appeared flushed. After administration of 10 mg of intravenous chlorphenamine, her tongue and lips swelled, her breathing became 'wheezy', she developed tachycardia (120 beats/min) and became hypotensive (79/50 mmHg). She was resuscitated by being given high-flow oxygen and epinephrine (1:1000 solution 0.5 ml), and then she was given intravenous fluids and hydrocortisone (100 mg). She did not lose consciousness or require intubation but did stay in critical care overnight before being discharged after 24 hours without any further events. **Brzoza (2007)** Case report 2: a 49-year-old woman with a 10-year history of bilateral leg varicoses, and a history of arterial hypertension (treated with cilazapril), but no drug allergy or personal or family history of allergic disease. Intervention: 1% STD. Effects: within 10 minutes of injection, she developed a generalised itch with an urticarial rash and nausea. She did not faint, but had tachycardia (150 beats/min) and a weak pulse (blood pressure 60/30 mmHg). Bronchospasm and laboratory abnormalities were not found and a chest X-ray and electrocardiogram were normal. She was treated with epinephrine, hydrocortisone, phenazoline, and intravenous fluids, and had a full recovery with no further events. (The authors noted that a skin test was not done before the procedure; they did state that the patient could have had a reaction to the benzyl alcohol but a skin test proved negative.) **Guex (2010)** A registry of 1605 patients (3357 patient years) who had received at least 1 POL injection. Allergic reaction was reported in 1 female patient treated by 0.33% POL for spider veins. Onset of adverse reaction was 'medium' (less than 4 weeks after treatment) and 2 instances of the event occurred in the patient. No further details reported.		**The Scurr (2007) and Brzoza (2007)studies were included in the previous guidance (IPG 314)** • Scurr (2007) stated that those performing the procedure should be trained in resuscitation techniques and have appropriate resuscitation equipment available. • Brzoza (2007) highlighted that there have been reports of allergic reactions in sclerosants previously (a German study reported an incidence of 0.2% allergic reaction). • An interim report of Guex (2010) is included in the Jia (2006)[1]systematic review.

Efficacy

Venous occlusion

A randomised controlled trial (RCT) of 73 patients (82 legs), in which foam sclerotherapy plus saphenofemoral ligation (n=39) was compared with standard surgery (n=43), reported above-the-knee vein obliteration in 58% (19/33) of legs in patients treated in the foam plus saphenofemoral ligation group and 54% (14/26) of legs in patients treated by standard surgery alone at 5-year follow-up (p=0.19). Below-the-knee vein obliteration was reported in 24% (8/33) of legs in patients treated by foam plus saphenofemoral ligation and 39% (10/26) of legs in patients treated by standard surgery alone at 5-year follow-up (p=0.34)[3].

A meta-analysis of 2 RCTs (included in a systematic review) with 340 patients reported that foam sclerotherapy was not significantly more efficacious (n=174) than liquid (n=166) in occluding the vein (relative risk [RR] 1.5; 95% confidence interval [CI] 0.6 to 3.6, I^2=95%, indicating significant heterogeneity), with follow-up ranging from 1 to 10 years[1]. A meta-analysis of 2 different RCTs (included in the systematic review) including 324 patients reported that surgery involving stripping (n=117) was more efficacious than foam sclerotherapy (n=207) in occluding the vein (RR 0.9; 95% CI 0.7 to 1.1) but this difference was not significant (follow-up ranging from 3 months to 1 year)[1].

In a RCT of 460 patients, (233 patients treated by foam sclerotherapy compared with 227 treated by surgery) reflux irrespective of venous symptoms was significantly more frequent in the group treated by foam sclerotherapy (35%) compared with the patients treated by surgery (21%) at 2-year follow up (p=0.003)[2].

Recurrence rate

In a case series of 146 patients (203 limbs), the clinical recurrence rate (reported in 23 patients) with significant venous symptoms (visible or palpable varices, aching, oedema or venous skin changes) was 4%, the clinical recurrence rate with minimal venous symptoms was 22%, and recurrence with no venous symptoms was 74% at 5-year follow-up[5].

Change in clinical severity

The RCT of 460 patients reported the median Venous Clinical Severity scores (graded from 0 [absent] to 3 [severe]; maximum score 30). The mean change from baseline was –1.49 in the foam sclerotherapy group and –1.75 in the surgery group (p=0.23) at 2-year follow-up[2].

In the RCT of 73 patients the median Venous Clinical Severity scores (graded from 0 [absent] to 3 [severe]; maximum score 30) decreased from 5 to 1 in patients treated by foam sclerotherapy plus saphenofemoral ligation and decreased from 5 to 3 in patients treated by surgery alone at 5-year follow-up (p=0.36 between groups; p values for change within groups not reported)[3].

The RCT of 73 patients reported a significant improvement in the median Venous Segmental Disease score from 1 at baseline to 0.3 ($p<0.005$) in patients treated by foam sclerotherapy plus saphenofemoral ligation, and no change from baseline in patients treated by surgery, at 5-year follow-up. The difference between the groups was not significant at 5-year follow-up ($p=0.39$)[3].

Quality of life

The RCT of 73 patients reported that the median Aberdeen Varicose Vein Questionnaire scores (range 0–100, with higher scores indicating more severe effects) decreased from 12 at baseline to 7 in patients treated by foam sclerotherapy plus saphenofemoral ligation, and from 16 at baseline to 6 in patients treated by surgery. The difference between the groups was statistically significant but not considered 'clinically significant' at 5-year follow-up ($p=0.02$)[3].

Safety

Cerebrovascular/neurological events

A transient ischaemic attack after injection was reported in 1 patient in a case series of 1025 patients. Complete clinical recovery occurred in 30 minutes[6].

Stroke was reported in a case report of 3 patients, all of whom were subsequently diagnosed with a patent foramen ovale. In 1 patient treated by foam sclerotherapy and ambulatory phlebectomy, middle cerebral arterial bubbles were detected immediately after the procedure (treated with tissue plasminogen activator), and in the other 2 patients middle cerebral arterial ischaemic change was confirmed (1 day after the procedure in 1 patient and 2 days after the procedure in the other patient)[7]. All 3 patients recovered completely with no further neurological or thrombotic events reported at follow-up ranging from 3 months to 2 years[7].

Transient visual disturbance was reported in 5 patients (twice in 1 patient) during or shortly after treatment in a case series of 977 patients treated by foam sclerotherapy[4].

A grand mal epileptic seizure was reported in 1 patient 40 minutes after injection (based on an unpublished report included in the systematic review; no further details available)[1].

Bubble embolisation

Bubble embolisation was reported in 73% (60/82) of patients in a case series of 82 patients with right-to-left shunts. 'Most' bubbles were detected within 15 minutes of the foam injection and no new neurological symptoms were detected at follow-up (1, 7 and/or 28 days)[12].

A case series of 5 patients using a modified technique reported that in all patients bubbles entered the right side of the heart in less than 60 seconds and continued

for up to 50 minutes. None of the patients developed any neurological or cardiac symptoms[15].

Pulmonary embolism

Pulmonary embolism (treated by an anticoagulant) was reported in 1 patient in the case series of 977 patients treated by foam sclerotherapy at 5 weeks after treatment[4].

Deep vein thrombosis

Symptomatic deep vein thrombosis was reported in 3 patients during the first month after treatment by foam sclerotherapy (treated by heparin and warfarin) in the case series of 977 patients[4].

Myocardial Infarction

Myocardial infarction was reported in 1 patient 30 minutes after injection (based on an unpublished report included in the systematic review; no further details available)[1].

Thrombophlebitis

Thrombophlebitis was reported in 7% (17/230) patients treated by foam sclerotherapy within 1 week of the procedure compared with 0% patients treated by surgery in an RCT of 430 patients ($p<0.001$)[2].

Allergic reaction

Facial rash was reported in 1 patient in the case series of 977 patients treated by foam sclerotherapy. The rash appeared 24 hours after treatment and disappeared spontaneously[4].

Pigmentation

Mild pigmentation was reported in 15% (6/39) of limbs treated by foam sclerotherapy and in 5% (2/43) of limbs treated by surgery in the RCT of 73 patients (82 legs)[3].

Skin pigmentation was reported in 6% (12/213) of patients treated by foam sclerotherapy compared with 1% (2/177) of patients treated by surgery in the RCT of 430 patients at 2-year follow-up[2].

Localised phlebitis

Persistent swelling was reported in 2% of limbs in the case series of 146 patients treated by foam sclerotherapy (203 limbs)[5].

Systemic complications

Complications including coughing, chest tightness/heaviness, panic attack, malaise and vasovagal fainting occurred at a rate of 0–3% across the studies in the systematic review (follow-up ranged between 1 month and 5 years)[1].

Infection
Groin infection was reported in 2 patients treated by foam sclerotherapy and 2 patients treated by surgery in the RCT of 73 patients at median 5 year follow-up[3].

Headache
Headache was reported in 3 patients immediately after the procedure in the case series of 977 patients (resolved in 24 hours after treatment by analgesia)[4].

Validity and generalisability of the studies

- Studies included in table 2 were restricted to those presenting long-term data on efficacy and new safety data.
- The studies used a variety of sclerosants, usually polidocanol or sodium tetradecyl sulphate, at different concentrations (ranging from 0.5 to 3%). The method of foam preparation varied.
- The use of compression after the procedure also varied in the studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedures guidance 314 (2009). Available from www.nice.org.uk/IPG314
- Endovenous laser treatment of the long saphenous vein. NICE interventional procedures guidance 52 (2004). Available from www.nice.org.uk/IPG52
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedures guidance 37 (2004). Available from www.nice.org.uk/IPG37
- Radiofrequency ablation of varicose veins. NICE interventional procedures guidance 8 (2003). Available from www.nice.org.uk/IPG8

Clinical guidelines

- Varicose veins in the legs: the diagnosis and management of varicose veins. NICE clinical guideline. Publication expected July 2013.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Sam Stuart, British Society of Interventional Radiology; Prof. Alison Halliday, Mr Tim Lees, and Mr Isaac.Nyamekye, The Vascular Society

- Two Specialist Advisors reported performing this procedure regularly, 1 Specialist Advisor reported performing this procedure at least once and 1 reported having never performed this procedure.
- Three Specialist Advisors considered foam sclerotherapy to be an established procedure and 1 considered it to be a minor variation of an existing procedure. Two Specialist Advisors noted that more than 50% of specialists are engaged in this area of work, 1 noted that 10 to 50% are engaged in this area of work and 1 Specialist Advisor noted that fewer than 10% of specialists are engaged in this area of work.
- Open varicose vein surgery, standard sclerotherapy, laser ablation or radiofrequency ablation were considered to be comparator procedures.
- The Specialist Advisors listed the following as key efficacy outcomes: occlusion rates, clinical reduction in varicose veins, duplex confirmed vein occlusion (at 6 weeks, 6 months and 5 years), long-term vein complication, recurrence rates, recurrence of leg ulceration, mobility, improvement in pain and swelling, patient satisfaction and improvement in quality of life.
- Adverse events listed in the literature: stroke, skin ulceration, transient ocular events, and deep vein thrombosis. Anecdotal adverse events: allergic reaction, neuropathy, temporary visual disturbance, localised phlebitis, brown staining of skin, skin damage, blistering/ulceration of skin, pain and swelling. Theoretical adverse events: allergic reaction, bruising, deep vein thrombosis, extravasation (resulting in pain), infection, nerve damage, oedema, phlebitis, pulmonary embolism, skin pigmentation, skin damage, skin irritation, temporary dry cough, thrombophlebitis and stroke.
- The Specialist Advisors noted uncertainties about the efficacy of this procedure, in that it may not be as long-lasting as surgery and that it can take a long time for thrombosed veins to disappear, and there may be long-term recurrence of varicose veins.
- In relation to uncertainty or controversy on how the procedure is done, 1 Specialist Advisor noted that there has been some suggestion that CO_2 should be used rather than air, but because of practical issues it is likely that air will continue to be used routinely.
- One Specialist Advisor noted that this procedure is already in widespread use and all Specialist Advisors noted that if found to be safe and efficacious, it is likely the procedure will be carried out in most or all district general hospitals. Specialist Advisors noted that in terms of numbers of patients eligible for the procedure and the use of resources, the potential impact of this procedure on the NHS was considered to be moderate.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- It is unclear whether a higher concentration of foam will increase the risk of adverse events.
- The Wright (2010)[16] paper included in table 2 noted that of 221 participants tested for right-to-left shunts, 59% (130/221) were positive for right-to-left shunt at rest or after the Valsalva manoeuvre. The authors noted that this is significantly higher than the reported 26% of patent foramen ovale in the general population.
- Ongoing trials:
  - NCT00529672: Randomised controlled trial; Magna: Surgery versus non-invasive therapy (ultrasound-guided sclerotherapy with foam and endovenous laser therapy) for varicose veins; Location: Netherlands; Estimated enrolment: 240; Estimated study completion date: May 2011.
  - NCT00621062: Randomised controlled trial; RAFPELS: New endovenous procedures (foam sclerotherapy, radiofrequency ablation and endovenous laser ablation) versus conventional surgery for varicose veins due to great saphenous vein incompetence; Location: Sweden; Estimated enrolment: 600; Estimated study completion date: August 2013.
  - ISRCTN 51995477: Randomised controlled trial; CLASS: Comparing foam sclerotherapy, alone or in combination with endovenous laser therapy, with conventional surgery as a treatment for varicose veins; Location: UK; Estimated enrolment: 1016; Estimated closure date: July 2012.

References

1. Jia X, Mowatt G, Burr JM et al. (2006) Systematic review of the safety and efficacy of foam sclerotherapy for venous disease of the lower limbs. Available from www.nice.org.uk

2. Shadid N, Ceulen R, Nelemans P et al. (2012) Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. British Journal of Surgery. 99(8): 1062–70. doi: 10.1002/bjs.8781. Epub 2012 May 25.

3. Kalodiki E, Lattimer CR, Azzam M et al. (2012) Long-term results of a randomized controlled trial on ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation vs standard surgery for varicose veins. Journal of Vascular Surgery 55 (2): 451–7

4. Bradbury AW, Bate G, Karl P et al. (2010) Ultrasound-guided foam sclerotherapy is a safe and clinically effective treatment for superficial venous reflux. Journal of Vascular Surgery 52 (4): 939–45

5. Chapman-Smith P and Browne A (2009) Prospective five-year study of ultrasound-guided foam sclerotherapy in the treatment of great saphenous vein reflux. Phlebology 24 (4): 183–8

6. Gillet J-L, Guedes JM, Guex J-J et al. (2009) Side-effects and complications of foam sclerotherapy of the great and small saphenous veins: A controlled multicentre prospective study including 1025 patients. Phlebology 24 (3): 131–8.

7. Ma RWL, Pilotelle A, Paraskevas P et al. (2011) Three cases of stroke following peripheral venous interventions. Phlebology 26 (7): 280–4

8. Bush RG, Derrick M and Manjoney D (2008) Major neurological events following foam sclerotherapy. Phlebology 23: 189–92

9. Forlee MV, Grouden M, Moore DJ et al. (2006) Stroke after varicose vein foam injection sclerotherapy. Journal of Vascular Surgery 43 (1): 162–4.

10. Hahn M, Schulz T, Junger M (2010) Late stroke after foam sclerotherapy. Vasa 39 (1): 108–10.

11. Picard C, Deltombe B, Duru C et al. (2010) Foam sclerotherapy: A possible cause of ischaemic stroke? Journal of Neurology, Neurosurgery and Psychiatry 81 (5): 582–3

12. Regan JD, Gibson KD, Rush JE et al. (2011) Clinical significance of cerebrovascular gas emboli during polidocanol endovenous ultra-low

nitrogen microfoam ablation and correlation with magnetic resonance imaging in patients with right-to-left shunt. Journal of Vascular Surgery 53 (1) 131–7

13. Hansen K, Morrison N, Neuhardt DL et al. (2007) Transthoracic echocardiogram and transcranial Doppler detection of emboli after foam sclerotherapy of leg veins. Journal for Vascular Ultrasound 31: 213–6

14. Hill D, Hamilton R and Fung T (2008) Assessment of techniques to reduce sclerosant foam migration during ultrasound-guided sclerotherapy of the great saphenous vein. Journal of Vascular Surgery 48: 934–9

15. Parsi K (2010) Venous gas embolism during foam sclerotherapy of saphenous veins despite recommended treatment modifications Phlebology 26:140–7

16. Wright DD, Gibson KD , Barclay J (2010) High prevalence of right-to-left shunt in patients with symptomatic greate saphenous incompetence and varicose veins Journal of Vascular Surgery 51(1): 104–7

17. Ceulen RP, Sommer A and Vernooy K (2008) Microembolism during foam sclerotherapy of varicose veins. New England Journal of Medicine 358: 1525–6

18. Rush JE and Wright DD (2008) More on microembolism and foam sclerotherapy. New England Journal of Medicine 359: 656–7

19. Nitecki SS and Bass A (2007) Inadvertent arterial injury secondary to treatment of venous insufficiency. Vascular 15: 49–52

20. Scurr JH, Fisher RK, Wallace SB et al. (2007) Anaphylaxis following foam sclerotherapy: a life threatening complication of non invasive treatment for varicose veins. European Journal of Vascular and Endovascular Surgery Extra 13: 87–9

21. Brzoza Z, Kasperska-Zajac A, Rogala E et al. (2007) Anaphylactoid reaction after the use of sodium tetradecyl sulfate: a case report. Angiology 58: 644–6

22. Guex JJ, Schliephake DE, Otto J (2010) The French polidocanol study on long-term side effects: a survey covering 3,357 patient years. Dermatologic Surgery 36 (supplement): 1003.

Appendix A: Additional papers on ultrasound-guided foam sclerotherapy for varicose veins

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bhogal RH, Moffat CE, Coney P et al (2012) Can foam sclerotherapy be used to safely treat bilateral varicose veins? Phlebology 27 (1):19-24.	N=112 Follow up=2 weeks	81% of legs had occlusion after bilateral foam sclerotherapy. Complications included DVT, staining and anaphylaxis.	Studies with longer follow-up included in table 2.
Blaise S, Bosson JL, Diamand JM (2010) Ultrasound-guided sclerotherapy of the great saphenous vein with 1% vs. 3% polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. European Journal of Vascular and Endovascular Surgery; 39(6):779-86.	N=243 (73 1% vs 70 3% polidocanol [POL]) Follow up= 3 years	Three asymptomatic thrombo-embolic events (2%) occurred. Local side effects (principally pigmentation and matting)6% in the 1% POL group and 9% in the 3% POL group. No difference in clinical severity and quality of life scores.	Studies with longer follow-up included in table 3.
Brunken A, Rabe E, Pannier F. Changes in venous function after foam sclerotherapy of varicose veins. Phlebology 2009 Aug; 24(4):145-50.	N=53 Follow up= mean 128 days	No deep vein thrombosis detected after sclerotherapy. In 14.9% (10 cases) symptomatic phlebitis with hyperpigmentation in the treated vein developed after treatment.	Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns.
Chien-Hsun Chen MD., Cheng-Sheng Chiu MD, Chih-Hsun Yang MD. (2012) Ultrasound-Guided Foam Sclerotherapy for Treating Incompetent Great Saphenous Veins—Results of 5 Years of Analysis and Morphologic Evolvement Study. Dermatologic Surgery DOI: 10.1111/j.1524-4725.2012.02408.x. 2012.	N=233 Follow up=5 years	Occlusion was achieved for 89.6% of the incompetent veins in 2 sessions. No complications were observed.	Studies with similar length of follow-up included in table 2.
Darvall KA, Bate GR, Sam RC et al. (2009) Patients' expectations before and satisfaction after ultrasound guided foam sclerotherapy for varicose veins. European Journal of Vascular and	N=351 Follow up = 6 months	Survey on patient expectations and satisfaction. A quarter of patients had their expectation exceeded and 10 to 25% were left with unmet expectations.	Studies with longer follow-up reporting patient satisfaction included in table 2.

Endovascular Surgery 38(5):642-7.			
Darvall KAL, Sam RC, Bate GR et al.(2010) Changes in health-related quality of life after ultrasound-guided foam sclerotherapy for great and small saphenous varicose veins Journal of Vascular Surgery 51(4):913-20	N=296 Follow up=12 months	There were improvements in generic and disease-specific health-related quality of life outcomes.	Studies with longer follow-up included in table 2.
Darvall KA, Bate GR, Adam DJ, Bradbury AW. Recovery after ultrasound-guided foam sclerotherapy compared with conventional surgery for varicose veins. British Journal of Surgery 2009 Nov;96(11):1262-7.	N=332 Follow up=4 weeks	Foam sclerotherapy was associated with less pain and analgesia requirement, time off work and quicker return to driving compared with patients undergoing conventional varicose vein surgery.	Studies with longer follow-up included in table 2.
Darvall KA, Bate GR, Silverman SH et al. (2009) Medium-term results of ultrasound-guided foam sclerotherapy for small saphenous varicose veins. British Journal of Surgery; 96(11):1268-73.	N=82 Follow up=12 months	Ultrasound-guided foam sclerotherapy was an effective treatment for small saphenous varicose vein, with abolition of reflux and visible varicose veins and improvement in HRQL for at least 12 months.	Studies with longer follow-up included in table 2.
Darvall KA, Bate GR, Adam DJ et al (2010) Duplex ultrasound outcomes following ultrasound-guided foam sclerotherapy of symptomatic primary great saphenous varicose veins. European Journal of Vascular and Endovascular Surgery;40(4):534-9.	N=278 Follow up=12 months	A single session of ultrasound-guided foam sclerotherapy eradicated reflux in above and below knee of great saphenous veins.	Studies with longer follow-up included in table 2.
Figueiredo M, Araujo S, Barros N, Jr. et al. (2009) Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. European Journal of Vascular and Endovascular Surgery 38(6):758-63.	N=60 (27 foam vs 29 stripping) Follow up=6 months	The vein had been obliterated in 90% of the foam sclerotherapy group compared with 78% of the surgery group. No serious adverse events	Studies with longer follow-up included in table 2.
Figueiredo M, de Araujo SP, Figueiredo MF et al. (2012) Late follow-up of saphenofemoral junction ligation combined with ultrasound-guided foam sclerotherapy in patients	n=35 FU=ranged from 45 to 68 months	Total and partial recanalisation in 19 patients (treatment failure) and occlusion in 13 patients (treatment success). 1 patient died because of myocardial	Larger studies included in table 2.

with venous ulcers. Annals of Vascular Surgery 26(7): 977-81.		infarction 12 months after the procedure. Superficial thrombophlebitis (n=13), mild pigmentation (10), groin infections (6) and deep vein thrombosis (3) were observed.	
Hahn M, Schulz T, Junger M (2008) Outcome four years after transcatheter foam sclerotherapy of the greater saphenous vein. Phlebologie 37: 237–40	N=20 Follow up= 4 years	Recurrence rate was 40%. Transient minor side effects were noted. All but 1 patient was satisfied.	Larger studies included in table 2.
Hamahata A, Yamaki T, Sakurai H. (2011) Outcomes of ultrasound-guided foam sclerotherapy for varicose veins of the lower extremities: A single center experience. Dermatologic Surgery 37(6):804-9.	N=104 Follow up= 2 years	No adverse events observed. Primary and secondary success rates were 62.2% and 75.8%.	Studies with longer follow-up included in table 2.
Hamahata A, Yamaki T, Osada A. et al. (2011) Foam sclerotherapy for spouting haemorrhage in patients with varicose veins. European Journal of Vascular and Endovascular Surgery 41 (6): 856-8.	N=5 Follow up=17 months	5 cases of haemorrhage from varicose veins in patients. Patients were subsequently treated by foam sclerotherapy. There was no recurrence of haemorrhage in any patient.	Larger studies included in follow-up.
Hamel-Desnos CM, Guias BJ, Desnos PR, et al. (2010) Foam sclerotherapy of the saphenous veins: randomised controlled trial with or without compression. European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery 39(4):500-7.	N=60(foam sclerotherapy with compression vs without compression) Follow up=28 days	Patient satisfaction scores were high for both groups. Side effects included pain, inflammation, ecchymosis, induration, pigmentation and matting.	Larger studies with longer follow-up included in table 2.
Hamel-Desnos C, Ouvry P, Benigni JP et al. (2007) Comparison of 1% and 3% polidocanol foam in ultrasound guided sclerotherapy of the great saphenous vein: a randomised, double-blind trial with 2 year-follow-up. 'The 3/1 Study'. European Journal of Vascular and Endovascular Surgery 34: 723–9	N= 148 (74 in each group: 3% vs 1% POL) Follow up= 2 years	Elimination of venous reflux was 68% for 1% POL and 69% for 3% Pol.	Studies with longer follow-up included in table 2.
Hartmann K, Harms L, Simon M. Reversible neurological deficit after	N=1 Follow up= not reported	Photopsiae immediately following foam injection and speech disturbance	Safety outcomes included in table 2.

foam sclerotherapy. European Journal of Vascular and Endovascular Surgery 2009 Nov;38(5):648-9.		for a few minutes was reported 2 hours after sclerotherapy in a patient.	
Islamoglu F(2011)An alternative treatment for varicose veins: ligation plus foam sclerotherapy. Dermatologic Surgery; 37(4):470-9.	N=372 (foam and ligation vs stripping) Follow up=mean 10 months	No significant difference between the groups in relation to effectiveness. Superficial thrombophlebitis in 2 patients in the foam group.	Studies with longer follow-up included in table 2.
Jia X, Mowatt G, Burr JM et al. (2007) Systematic review of foam sclerotherapy for varicose veins. British Journal of Surgery 94: 925-36	N=69	Serious adverse events are rare. There is insufficient evidence to compare the effectiveness of this treatment with other minimally invasive therapies or surgery.	Additional details reported on adverse events included in table 2.
King T, Coulomb G, Goldman A, Sheen V, McWilliams S, Guptan RC. Experience with concomitant ultrasound-guided foam sclerotherapy and endovenous laser treatment in chronic venous disorder and its influence on Health Related Quality of Life: interim analysis of more than 1000 consecutive procedures. International Angiology 2009 Aug; 28(4):289-97.	N=924 Follow up= 2 years	Ultrasound-guided foam sclerotherapy given concomitantly with endovenous laser treatment demonstrated significant improvement in health related quality of life.	Studies with longer follow-up included in table 2.
Leopardi D, Hoggan BL, Fitridge RA, Woodruff PW, Maddern GJ. Systematic review of treatments for varicose veins. [Review] [34 refs]. Annals of Vascular Surgery 2009 Mar; 3(2):264-76.	N=17 studies Follow up= not applicable	Median occlusion rate was 88%, healing of venous ulcers 80.4% and recurrence was 8.1%.	Data from Jia (2006) reported.
Liu X, Jia X, Guo W et al.(2011) Ultrasound-guided foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping: a prospective clinical study. International Angiology; 30(4):321-6.	N=60 (30 foam vs 30 standard stripping) Follow up=3 months	Ultrasound guided sclerotherapy combined with sapheno-femoral ligation involved a shorter treatment time, less postoperative discomfort and resulted in more rapid recovery compared to conventional stripping.	Studies with longer follow-up included in table 2.
Morrison N, Neuhardt DL, Rogers CR et al. (2008) Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. Journal of	N=128 vs 49 (CO_2 vs air based foam)	A study comparing air-based foam with carbon dioxide-based foam reported that the overall side effects following UGFS decreased from 39% (19/49) to 11%	Safety outcomes included in table 2.

Vascular Surgery 47: 830-6		(14/128) when carbon dioxide replaced air in the foam preparation (p < 0.001). Visual disturbance decreased from 8% (4/49) to 3% (4/128), chest tightness from 18% (9/49) to 3% (4/128), and dizziness from 12% (6/49) to 3% (4/128).	
Morrison N, Neuhardt DL, Rogers CR et al. (2010) Incidence of side effects using carbon dioxide-oxygen foam for chemical ablation of superficial veins of the lower extremity. European Journal of Vascular and Endovascular Surgery; 40(3):407-13.	N=100 Follow up= unclear	Complications included itching or leg pain similar to that for air-based foam incidence of visual disturbance was comparable with that for CO2 or air foam and reporting of dizziness was less than that for air-based foam. Lack of reported chest tightness and/or dry cough compared with CO2 or air foam.	No new safety outcomes reported.
Murad MH, Coto-Yglesias F, et al. (2011) A systematic review and meta-analysis of the treatments of varicose veins. Journal of Vascular Surgery; 53(5: Suppl):Suppl-65S.	N=39 studies Follow up=	Studies of foam sclerotherapy, laser and radiofrequency ablation demonstrated short-term effectiveness and safety.	Three studies related to foam sclerotherapy included in this review have been included in the Jia (2006)[1] systematic review included in table 2.
Myers KA, Jolley D, Clough A et al. (2007) Outcome of ultrasound-guided sclerotherapy for varicose veins: medium-term results assessed by ultrasound surveillance. European Journal of Vascular and Endovascular Surgery 33: 116–21	N= 807 Follow up=2 years	Primary success rate was 52.4% and secondary success rate was 76.8%.	Results for foam and liquid sclerotherapy not reported separately.
Nael R and Rathbun S.(2010) Effectiveness of foam sclerotherapy for the treatment of varicose veins. Vascular Medicine; 15(1):27-32.	N= 166 Follow up= median 24 weeks	Complete (65%) or near complete (345) obliteration was achieved in 215(99%) legs after one injection. Active ulcers healed.	Studies with longer follow up included in table 2.
Nesbitt C, Eifell RKG, Coyne P et al (2011) Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for great saphenous vein varices Cochrane Database of Systematic Reviews Issue 10	N= 13 reports of 5 studies	No randomised trials comparing ultrasound-guided foam sclerotherapy met study inclusion criteria.	Studies related to foam sclerotherapy were excluded mainly because evidence related to case series or the comparators were not considered appropriate.

O'Hare JL and Earnshaw JJ (2007) The use of foam sclerotherapy for varicose veins: a survey of the members of the Vascular Society of Great Britain and Ireland. European Journal of Vascular and Endovascular Surgery 34:232-5	N= 609 surgeons surveyed.	Serious complications were few, but 11 surgeons reported a deep vein thrombosis, 2 reported a patient with a stroke and 1 reported a transient ischaemic attack	Safety outcomes included in table 2.
Palm MD, Guiha IC, Goldman MP (2010) Foam sclerotherapy for reticular veins and nontruncal varicose veins of the legs: a retrospective review of outcomes and adverse effects. Dermatologic Surgery; 36:Suppl-33.	N= 425 (retrospective review) Follow up= unclear	No serious adverse events occurred. Complications were minimal to mild and included hyperpigmentation, ulceration , pain and matting.	Safety outcomes identified included in table 2.
Pang KH, Bate GR, Darvall KA et al. (2010) Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. European Journal of Vascular and Endovascular Surgery; 40(6):790-5.	N= 130 Follow up=median 16 months	Healing was observed in 82% following first treatment and 4.9% estimate of recurrence at 2 years.	Studies with loner follow-up included in table 2.
Park SW, Yun IJ, Hwang JJ et al. (2009) Fluoroscopy-guided endovenous foam sclerotherapy using a microcatheter in varicose tributaries followed by endovenous laser treatment of incompetent saphenous veins: technical feasibility and early results. Dermatologic Surgery May;35(5):804-12.	N= 312 (foam followed by endovenous laser treatment). Follow up=6 months	Technical success was achieved in 99% of limbs. No serious complications were noted.	Studies reporting on efficacy and safety of foam sclerotherapy alone with longer follow-up included in table 2.
Rasmussen LH, Lawaetz M, Bjoern B et al. (2011) Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins British Journal of Surgery 98: 1079-87	N=500 (125 foam vs 125 laser, vs radiofrequency vs 125 surgical stripping). All treated by phlebecotmy. Follow-up= 1 year	At 1 year, 5.8%, 4.8%, 16.3% and 4.8% of the great saphenous veins were patent and refluxing in the laser radiofrequency, foam and stripping groups respectively (p,0.001). 1 patient developed pulmonary embolus after foam sclerotherapy.	Studies with longer follow-up included in table 2.
Rathbun S, Norris A and Stoner J (2012) Efficacy and safety of endovenous foam sclerotherapy: meta-analysis for treatment of	N=30 studies	Endovenous foam sclerotherapy was found to be effective with similar vein occlusion rates to laser therapy	Studies included were for treatment of varicose veins, congenital venous malformation and for

venous disorders. Phlebology 27(3): 105-17.		but less effective than surgery. Major adverse effects were rare.	venous ulcers. It is unclear if the safety events reported were in patients with varicose veins.
Raymond-Martimbeau P. (2009) Transient adverse events positively associated with patent foramen ovale after ultrasound-guided foam sclerotherapy. Phlebology 24(3):114-9.	N=3259 Follow up= 24h to 2 weeks	Seven patients (0.21%) reported adverse events at their initial session before leaving the clinic or within 20 minutes. Reported complications included visual disturbance, migraine with aura, and chest pain and tightness.	No new safety outcomes reported. Studies with longer follow-up included in table 2.
Reich-Schupke S, Weyer K, Altmeyer P et al. (2010) Stucker M. Treatment of varicose tributaries with sclerotherapy with polidocanol 0.5 % foam. Vasa; 39(2):169-74.	N=76 patients (110 legs) Follow up=14 months	Reflux in varicose tributaries was found in 51.8% of the legs. Hyperpigmentation, local thrombophlebitis, paraesthesia and recurring migraine were observed.	Studies with longer follow-up included in table 2.
Tan VKM and Tan SG (2009) Technique and early results of ultrasound-guided foam sclerotherapy of the long saphenous vein for treatment of varicose veins Singapore Med J 50(20: 284	N= 62 Follow up = 1 day	Complete occlusion in 62 veins. Early complications included skin pigmentation and superficial thrombophlebitis.	Studies with longer follow-up included in table 2.
Tan VKM, Abidin SZ, Tan SG (2012) Medium-term results of ultrasonography-guided, catheter-assisted foam sclerotherapy of the long saphenous vein for treatment of varicose veins. Singapore Medical Journal 53 (2): 91-4	N=62 Follow up= 12 months	Successful occlusion rate was 80% at 12 months. Patient satisfaction was good, with 96% reporting symptom improvement. Minor complications observed.	Studies with longer follow-up included in table 2.
Thomasset SC, Butt Z, Liptrot S et al. (2010) Ultrasound guided foam sclerotherapy: factors associated with outcomes and complications. European Journal of Vascular and Endovascular Surgery; 40(3):389-92.	N=116 Follow up=median 3 months	Complete occlusion of target veins in 79% of patients. Most frequent complications included skin staining, superficial thrombophlebitis and pain.	Studies with longer follow-up included in table 2.
Ukritmanoroat T(2011) Comparison of efficacy and safety between foam sclerotherapy and conventional sclerotherapy: a controlled clinical trial. Journal of the Medical Association of Thailand; 94:Suppl-40.	N=50 (foam and liquid) Follow up= 90 days	Total occlusion of 46 sites and 38 sites in the foam and liquid therapy sites. Pain and hyperpigmentation were significantly higher in the foam group that the liquid group at 15 and 30 days.	Larger studies with longer follow-up included in table 2.
Uncu H (2010) Sclerotherapy: a study	N=100 (50 foam and 50 liquid)	'Complete disappearance' was	Larger studies with longer follow-up

comparing polidocanol in foam and liquid form. Phlebology/Venous Forum of the Royal Society of Medicine; 25(1):44-9.	Follow up= 15 days	reported in 84% of patients in the foam group and 72% in the liquid group. Allergic reaction was reported in 1 patient in the foam group.	included in table 2.
Van den Bos, Arend L, Kockaert M et al. (2009) Endovenous therapies of lower extremity varicosities: A meta-analysis Journal of Vascular surgery 49(1):230-8	N=64 studies Follow up= mean 32 months	Foam therapy was as effective as surgical stripping (Adjusted odds ratio 0.12 (95% CI -0.61 to 0.85). Endovenous laser therapy was significantly more effective than foam (adjusted odds ratio 1.02(95% CI 0.28 to 1.75)	Studies related to foam sclerotherapy included in Jia (2006)[1] systematic review.

Appendix B: Related NICE guidance for ultrasound-guided foam sclerotherapy for varicose veins

Guidance	Recommendations
Interventional procedures	**Radiofrequency ablation for varicose veins. NICE interventional procedures guidance 8 (2003)** 1.1 Current evidence on the safety and efficacy of radiofrequency ablation of varicose veins appears adequate to support the use of this procedure as an alternative to saphenofemoral ligation and stripping, provided that the normal arrangements are in place for consent, audit and clinical governance.
	Transilluminated powered phlebectomy for varicose veins. NICE interventional procedures guidance 37 (2004) 1.1 Current evidence on the safety and efficacy of transilluminated powered phlebectomy for varicose veins includes small numbers of patients and is of limited quality. It does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake transilluminated powered phlebectomy for varicose veins should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present.
	Endovenous laser treatment of the long saphenous vein. NICE interventional procedures guidance 52 (2004). Current evidence on the safety and efficacy of endovenous laser treatment of the long saphenous vein appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. Current evidence on the efficacy of this procedure is limited to case series with up to 3 years follow-up. Clinicians are encouraged to collect longer-term follow up data.

Appendix C: Literature search for ultrasound-guided foam sclerotherapy for varicose veins

IP overview appendix (update search)

IP 244_4 : Ultrasound-guided foam sclerotherapy for varicose veins

Database	**Date searched**	**Version/files**
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/11/12	Issue 10 of 12, October 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	02/11/12	-
HTA database (CRD website)	02/11/12	-
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/10/12	Issue 10 of 12, October 2012
MEDLINE (Ovid)	31/10/12	1946 to October Week 3 2012
MEDLINE In-Process (Ovid)	31/10/12	October 30, 2012
EMBASE (Ovid)	31/10/12	1980 to 2012 Week 43
JournalTOCS	02/11/12	-

Trial sources searched

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

MEDLINE search strategy

1 Telangiectasis/

2 Venous Insufficiency/ use mesz

3 exp vein insufficiency/ use emez

4 ((venous or vein?) adj3 (incomp$ or insuffic$)).tw.

5 ((venous or vein?) adj3 ulcer$).tw.

6 telangiect$.tw.

7 ((reticular or thread or spider) adj3 (vein? or venous)).tw.

8 or/1-7

9 exp Lower Extremity/ use mesz

10 exp leg/ use emez

11 (lower limb$ or lower extremit$ or leg? or calf or valves or thigh?).tw.

12 or/9-11

13 8 and 12

14 saphenous vein/

15 ((saphenous or perforator) adj3 (vein? or incompet$ or insuffic$)).tw.

16 exp varicose veins/ use mesz

17 varicosis/ or leg varicosis/ use emez

18 (varicos$ adj3 vein?).tw.

19 or/13-18

20 Sclerotherapy/

21 Sclerosing Solutions/

22 (sclerotherap$ or sclerosing$ or sclerosant$).tw.

23 or/20-22

24 9002-92-0.rn.

25 sodium tetradecyl sulfate.tw.

26 sodium tetradecyl sulphate.tw.

27 hypertonic saline.tw.

28 ethanolamine oleate.tw.

29 3282-75-5.rn.

30 2272-11-9.rn.

31 (polydocanol or polidocanol).tw.

32 sodium morrhuate.tw.

33 8031-09-2.rn.

34 sotradecol.tw.

35 1191-50-0.rn.

36 (aet?oxysclerol or aethoxyskerol).tw.

37 or/24-36

38 foam/ use emez

39 (foam$ or microfoam$).tw.

40 (tessari or monfreux or double syringe).tw.

41 or/38-40

42 41 and (19 or 23 or 37)

43 varisolve.tw.

44 42 or 43

45 19 and (23 or 37)

46 ae.fs.

47 exp Venous Thrombosis/

48 exp embolism/

49 Ischemic Attack, Transient/

50 cerebrovascular accident/

51 exp Migraine Disorders/ use mesz

52 exp migraine/ use emez

53 (dvt or thrombo$ or embolism).tw.

54 isch?em$.tw.

55 stroke?.tw.

56 migraine?.tw.

57 (visual or vision).tw.

58 or/46-57

59 45 and 58

60 44 or 59

61 animals/ use mesz not humans/ use mesz

62 nonhuman/ use emez not human/ use emez

63 61 or 62

64 60 not 63

65 remove duplicates from 64

66 from 65 keep 1-1467

67 limit 66 to em=201130-201220 [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]

68 from 65 keep 1468-1653

69 limit 68 to ed=20110801-20120531 [Limit not valid in Embase; records were retained]

70 from 65 keep 1654-1664