NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of cyanoacrylate glue occlusion for varicose veins

Varicose veins in the legs are swollen and enlarged veins. They develop when the small valves inside a vein stop working properly, allowing blood to pool in the vein. This can cause pain, aching and swelling in the legs, and skin problems including inflammatory dermatitis and ulceration. In cyanoacrylate glue occlusion, medical glue is injected into the affected vein to close it and prevent blood pooling in the vein.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in February 2014 and updated in April 2015.

Procedure name

- Cyanoacrylate glue occlusion for varicose veins

Specialist societies

- The Vascular Society of Great Britain and Ireland
- British Association of Sclerotherapists
- British Society of Interventional Radiology.

Description

Indications and current treatment

Varicose veins are a sign of underlying venous insufficiency and affect 20–30% of adults. 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 discoloration, inflammatory dermatitis and ulceration. Great saphenous vein insufficiency is the most common form of venous insufficiency in people presenting with symptoms.

Many people have varicose veins that do not cause any symptoms or need treatment on medical grounds. However, some people will need treatment for the relief of symptoms or if there is evidence of skin discolouration, inflammation or ulceration. Treatment options include endothermal ablation, ultrasound guided foam sclerotherapy, and surgery (usually stripping and ligation of the great and small saphenous veins, and phlebectomies).

What the procedure involves

Cyanoacrylate glue occlusion for varicose veins aims to close the veins by adherence then fibrosis of the lumen, without the need for tumescent anaesthesia (infusion of a large volume of dilute local anaesthetic around and along the entire length of vein to be treated) and with reduced need for postoperative compression therapy.

The procedure is done using local anaesthesia. An introducer sheath is inserted into the distal great saphenous vein and, using ultrasound guidance, a delivery catheter is advanced into position before the saphenofemoral junction. The proximal vein is compressed and medical glue is delivered in measured doses through the tip of the catheter to seal the vein. This is repeated step-wise as the catheter is withdrawn, using ultrasound imaging to monitor the procedure. The procedure may also be done in a similar fashion for the small saphenous vein.

Clinical assessment

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 – telangiectasias 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.

Outcome measures

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 a 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 the current version having an additional category for compression, with a maximum score of 30 (indicating severe disease).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to cyanoacrylate glue occlusion for varicose veins. The following databases were searched, covering the period from their start to 5 March 2015: 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	Cyanoacrylate glue occlusion.
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 IP overview

This IP overview is based on approximately 406 patients from 1 randomised controlled trial, 4 case series and 1 case report[1–5].

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.

Table 2 Summary of key efficacy and safety findings on cyanoacrylate glue occlusion for varicose veins

Study 1 Morrison N (2015)

Details

Study type	**Randomised controlled trial (VeClose)**
Country	USA
Recruitment period	2013
Study population and number	Patients with symptomatic incompetent great saphenous veins **n=222 (108 cyanoacrylate glue occlusion versus 114 radiofrequency ablation)**
Age and sex	Sex: 79% female
Patient selection criteria	Age 21–70 years, symptomatic moderate to severe varicosities (CEAP class C2 to C4b), incompetence of the great saphenous vein with reflux time of at least 0.5 seconds assessed in the standing position. Exclusion criteria: haemodynamically significant reflux of the small saphenous or anterior accessory great saphenous vein, prior treatment of the target vein, symptomatic peripheral arterial disease, a history of deep vein thrombosis or pulmonary embolism, or aneurysm of the target vein >12 mm in diameter.
Technique	Sapheon Closure System was used (Sapheon Inc., USA). A single small bandage was applied and venous occlusion was confirmed by duplex ultrasound. Radiofrequency ablation was done using ClosureFast.
Follow-up	**3 months**
Conflict of interest/source of funding	Study was sponsored by Sapheon Inc., USA.

Analysis

Follow-up issues: All patients were available for follow-up at 3 days. 96% (212/222) of patients had a 3-month visit, of which 7 (3%) were out of the 3-month study window (the allowed window was ±4 weeks).

Study design issues: The primary end point was complete closure of the target great saphenous vein, defined as doppler ultrasound examination showing closure along the entire treated vein segment with no segments of patency exceeding 5 cm at the 3-month visit. Closure was confirmed by an independent vascular ultrasound core laboratory. The primary end point was analysed using an intent-to-treat approach. Adjunctive treatments were withheld until after the month 3 visit.

Study population issues: Baseline characteristics were similar between the 2 treatment groups.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: 222 (108 versus 114) **Procedural success** At the end of the procedure, 1 patient in each group had residual flow along the treated segment. At day 3, closure was 100% in both groups. Closure rates at 1-month follow-up: • cyanoacrylate glue=100% • RFA=86% (p<0.01 for both non-inferiority and superiority). Using the predictive method for imputing missing data, 3-month closure rates were 99% for cyanoacrylate glue occlusion and 96% for RFA. All primary end point analyses, which used various methods to account for the missing data rate (14%), showed evidence to support the study's non-inferiority hypothesis (all p<0.01). **Mean VCSS** By month 3, VCSS had improved approximately 3.5 points from baseline (p<0.01) with no differences between treatment groups. By month 3, AVVQ improved by approximately 8 points (p<0.01) with no differences between treatment groups. The CEAP classification improved by approximately 0.5 points per group (p<0.01) with no difference between the groups.	**Adverse events** 4 mild adverse events occurred during the RFA procedure (1 lightheadedness, 1 nausea, 2 vasovagal symptoms) 1 mild adverse event of lightheadedness occurred after cyanoacrylate glue occlusion. Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4, respectively, on a 10-point scale; p=0.11). Patients with adverse events during 3-month follow-up: • cyanoacrylate glue=34 • RFA=29. Adverse events rated as probably or definitely related to cyanoacrylate occlusion devices: • moderate access site infection, n=1 • mild paraesthesia in treatment zone, n=1 • moderate paraesthesia in treatment zone, n=1 • mild phlebitis in the treatment zone, n=6 • moderate phlebitis not in the treatment zone, n=1 • mild superficial vein thrombophlebitis, n=3. Adverse events rated as probably or definitely related to RFA study devices: • moderate access site burn, n=1 • mild paraesthesia in treatment zone, n=2 • mild phlebitis in the treatment zone, n=2 • moderate phlebitis in the treatment zone, n=1 • mild phlebitis not in the treatment zone, n=1. No device- or procedure-related serious adverse events occurred in either group and no post-procedural thrombus extensions into the common femoral vein were identified by duplex in any patient.
Abbreviations used: AVVQ, Aberdeen Varicose Vein Questionnaire; CEAP, clinical, etiological, anatomic and pathophysiologic; RFA, radiofrequency ablation; VCSS, Venous Clinical Severity Score.	

Study 2 Almeida JI (2014)

Details

Study type	**Case series (prospective)**
Country	USA
Recruitment period	Not reported
Study population and number	Patients with symptomatic incompetent great saphenous veins **n=38**
Age and sex	Age: median 51 years (range 26–77) Sex: 76% (29/38) female
Patient selection criteria	Age 21–76 years; venous reflux disease in the great saphenous vein diagnosed by clinical symptoms and confirmed by duplex ultrasound imaging; candidate for surgical closure of a segment of the great saphenous vein; CEAP classification ≥C2; ability to walk unassisted; life expectancy ≥18 months. Exclusion criteria included previous surgical procedure associated with the venous segment to be treated; known sensitivity to cyanoacrylate adhesive; diameter of index vein <3 mm or >12 mm; formal duplication of the saphenous trunk in the index vein; tortuous great saphenous vein, which would limit catheter placement; hypercoagulable state; local or systemic infection; incompetent perforators in the treatment length; insulin-dependent diabetes; history of right ventricular failure; leg obesity; significant femoral or popliteal vein insufficiency; history of superficial or deep thrombophlebitis; additional procedures in the treatment leg likely to be needed within 6 months; varicosities secondary to pelvic or abdominal tumour; significant arterial insufficiency.
Technique	Sapheon Closure System was used (Sapheon Inc., USA). Single adhesive bandage applied. No compression stockings or bandages were used.
Follow-up	**24 months**
Conflict of interest/source of funding	Study was funded by Sapheon Inc., USA. Two authors are stockholders of Sapheon and one is also a consultant of the company.

Analysis

Follow-up issues: All patients were available for follow-up at 1, 3 and 6 months; 36 of the 38 patients reached 12-month follow-up and 24 patients were seen at 24 months.

Study design issues: Single centre (4 different physicians). VCSS scores were recorded at baseline and at all follow-up visits by the same physician.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **38** **Procedural success** Complete closure of the great saphenous vein immediately after the procedure and at 48-hour follow-up (diagnosed by duplex ultrasound imaging)=100% (38/38). Recanalisation of >5 cm length=7.9% (3/38, at 1, 3 and 6 months respectively; 1 complete recanalisation and 2 partial recanalisations with lengths of 10 cm and 7 cm). 12-month occlusion rate=92.1%. 24-month occlusion rate=92%. 97.3% of treated great saphenous veins were free from full-length recanalisation at 12-month follow-up. **Mean VCSS** The mean score improved from 6.1±2.7 at baseline to 1.5±1.4 at 12 months (n=36, p<0.001). At baseline, 42% of legs were without oedema compared with 84% of legs at 6 months after treatment and 65% at 24 months. Proportion of patients with no visible varicosities: • baseline=0% (0/38) • 6 months=47% (17/38) • 12 months=50% (18/36) • 24 months=35% (actual numbers not stated). Proportion of patients with only minimal varicosities (VCSS subdomain scores of 0 or 1): • baseline=24% • 6 months=84% • 12 months=75% • 24 months=65% (actual numbers not stated). Proportion of patients free from pain: • baseline=13% • 6 months=84% • 24 months=64% (actual numbers not stated).	**Adverse events** • Phlebitis of tributaries adjacent to the treated great saphenous vein=15.8% (6/38; patients had mild pain and erythema, which persisted for an average of 5 days [range 3–14]). This was treated with oral non-steroidal anti-inflammatory agents. • Low-grade cellulitis=2.6% (1/38, resolved with oral antibiotics). • Superficial thrombophlebitis=2.6% (1/38, in a solitary varix remote from saphenous treatment area; resolved spontaneously). • Hyperpigmentation=2.6% (1/38, still visible at 24-month follow-up). 21.1% (8/38) of patients had thread-like thrombus extensions across the saphenofemoral junction seen on ultrasound imaging at the 48-hour follow-up. Mean protrusion length into the common femoral vein=12.6±9.9 mm (range 3.5–35 mm). At 6-month follow-up, all thrombus extensions had resolved without clinical sequelae.
Abbreviations used: VCSS, Venous Clinical Severity Score.	

Study 3 Proebstle TM (2015)

Details

Study type	**Case series (prospective) (eSCOPE)**
Country	Germany, UK, Denmark, the Netherlands
Recruitment period	2011–12
Study population and number	Patients with symptomatic incompetent great saphenous veins **n=70**
Age and sex	Age: mean 48 years (range 22–72) Sex: 79% (55/70) female
Patient selection criteria	Age ≥18 and ≤70 years, symptomatic primary great saphenous vein incompetence diagnosed by clinical symptoms, with or without visible varicosities, and confirmed by duplex ultrasound imaging, CEAP classification C2, C3, or C4, maximum vein diameter on standing ≥3 mm and ≤10 mm and ability to walk unassisted. Exclusion criteria included anticoagulation, previous deep vein thrombosis, previous superficial thrombophlebitis in great saphenous vein, previous venous treatment on target limb and known hypercoagulable disorder.
Technique	Sapheon VenaSeal System was used (Sapheon Inc., USA). Single adhesive bandage applied and venous occlusion confirmed by duplex ultrasound. Patients were discharged and instructed to resume normal activities, avoiding strenuous activities for 1 day.
Follow-up	**12 months**
Conflict of interest/source of funding	The study was funded by Sapheon Inc., USA.

Analysis

Follow-up issues: 97% (68/70) of patients were available for the 12-month follow-up visit.

Study design issues: The study's primary end point was the proportion of patients with complete occlusion of the target vein at 6-month duplex ultrasound evaluation. Complete occlusion was defined as no segments of patency longer than 10 cm.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **70** **Procedural success** All patients had a technically successful procedure. Immediately after the procedure, all but 1 patient had complete closure of the target great saphenous vein. This patient had foam sclerotherapy to achieve full occlusion. Partial recanalisation at 12 months=7.4% (5/68, defined as patency in the treated segment by duplex ultrasound examination of >10 cm): 2 of these recanalisations were observed at 48 hours follow-up, 2 at 3 months and 1 at 6 months). None of the patients with recanalisation appeared to become clinically symptomatic, and all had junctions with large tributaries. 12-month complete occlusion rate=92.9% (95% CI 87.0–99.1%, by life-table methods). **Mean VCSS** The mean score improved from 4.3 at baseline to 1.1 at 12 months (p<0.0001). Before treatment, 1.4% of legs were free from visible varicosities. At 3 months after treatment, 41.4% of legs were free from visible varicosities. The proportion of patients free from oedema and pain increased from 41.4% and 32.9% at baseline to 90.0% and 82.1%, respectively. Quality-of-life scores (EQ-5D) improved at all follow-up visits to near-maximum levels (p=0.0009). AVVQ score also improved significantly from 16.3 at baseline to 6.7 at 12 months (p<0.0001).	**Adverse events** • Post-procedure phlebitic reaction along the treated vein or its tributaries (defined as reddening of the overlying skin and pain on palpation)=11.4% (8/70, median onset of symptoms was 6 days after procedure and median duration was 6.5 days). • Pain without phlebitic reaction=8.6% (5/70, median duration of 1 day, starting at a median of 0 days after the procedure). • Localised infection at the access point=1.4% (1/70). • Minor access site bruising=1.4% (1/70). • Glue extension measuring 6 mm beyond the saphenofemoral junction=1.4% (1/70, this was recognised immediately after the procedure and still present at the 12-month follow-up. Heparin was given for 2 weeks with spontaneous resolution.
Abbreviations used: AVVQ, Aberdeen Varicose Vein Questionnaire; CI, confidence interval; VCSS, Venous Clinical Severity Score.	

Study 4 Lawson J (2013)

Details

Study type	**Review of 4 case series (2 have been excluded because they are summarised above [studies 2 and 3])**
Country	Germany, Denmark, UK, the Netherlands
Recruitment period	2011–2
Study population and number	Patients with varicose veins Case series 1 (author's personal communication with Dr Ulf Zierau, Germany): **n=65** (43 great saphenous veins, 22 short saphenous veins) Case series 2 (author's personal experience): **n=10 procedures** (8 great saphenous veins, 2 anterior accessory saphenous veins)
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	All procedures used the VenaSeal Sapheon closure system (Sapheon Inc, USA). No compression stockings or dressing applied.
Follow-up	Case series 1: **3 months** Case series 2: **3–6 months**
Conflict of interest/source of funding	None declared by the author (case series 1 was sponsored by Sapheon).

Analysis

Follow-up issues: Details of follow-up assessment are not provided.

Study design issues: The review summarises 4 case series, 2 of which have been published in peer-reviewed literature; 1 was reported to the author as a personal communication; and 1 reports data from the author's own experience.

Study population issues: Baseline characteristics and patient selection criteria are not described.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **65 patients (case series 1); 10 procedures (case series 2)** **Case series 1** **Primary closure** Occlusion rate at 3-month follow-up=99% **Case series 2** **Primary closure** All 8 great saphenous veins were occluded at a follow-up from 3–6 months. All 8 great saphenous veins were closed to the saphenofemoral junction with no or minimal stump length. In 1 patient with double anterior accessory saphenous vein insufficiency, 1 side was only partially occluded 3 days after the procedure and recanalised totally 2 months after the procedure.	**Adverse events** **Case series 1** • Postoperative erysipeloid-phlebitic skin reaction=15% (10/65, occurred within 8–12 days after the procedure; resolved quickly after conservative compression therapy). No patients had sensory loss. 'There was no discomfort, no serious pain or hypaesthesia.' **Case series 2** • Self-limited thrombophlebitis=40% (4/10, occurred within 2–7 days after the procedure). • Hypersensitive reaction=10% (1/10, patient had simultaneous occlusion of both incompetent anterior accessory saphenous veins; reaction probably caused by subcutaneous delivery of the adhesive). 'There were no serious adverse events.'
Abbreviations used: VCSS, Venous Clinical Severity Score.	

Study 5 Lane TRA (2013)

Details

Study type	**Case report**
Country	UK
Recruitment period	2012
Study population and number	Patient with complicated varicose vein disease, with recurrent bleeding from extensive varicosities, and a history of atrial fibrillation treated with warfarin. **n=1**
Age and sex	73-year-old male
Patient selection criteria	Not reported
Technique	Sapheon VenaSeal closure system (Sapheon Inc., USA) was used to occlude the right leg great saphenous vein. The patient was advised to continue with compression hosiery in the long term because of pre-existing deep venous incompetence.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Study design issues: Assessment included VCSS and AVVQ – this questionnaire combines into a single score a patient's answers to a number of health questions of particular relevance to varicose veins (including the distribution of their varicose veins, pain, ankle swelling, use of support stockings, interference with social and domestic activities and the cosmetic aspects of varicose veins). The score ranges from 0 to 100, where 0 is 'best' and 100 is 'worst'.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 1

The patient was advised to continue warfarin anticoagulation (the international normalised ratio at treatment was 2.3).

<table>
<tr><th>Follow-up</th><th>VCSS</th><th>AVVQ</th></tr>
<tr><td>Baseline</td><td>14</td><td>15.4</td></tr>
<tr><td>8 weeks</td><td>7</td><td>4.6</td></tr>
<tr><td>6 months</td><td>10</td><td>25.5</td></tr>
</table>

On postoperative clinical and duplex ultrasound at 8 weeks, the great saphenous vein was occluded and the mild deep venous incompetence had resolved. The patient’s symptoms were much improved, with no further episodes of bleeding varicosities.

At 6 months, the varicosities had not returned but significant oedema and symptoms had recurred. On repeat venous duplex imaging, the great saphenous vein was recanalised and incompetent. Two 2 cm sections of the vein in the mid-thigh remained completely occluded. The deep venous incompetence remained absent.

Repeat treatment with foam sclerotherapy was arranged.</td><td></td></tr>
<tr><td colspan="2">Abbreviations used: AVVQ, Aberdeen Varicose Vein Questionnaire; VCSS, Venous Clinical Severity Score.</td></tr>
</table>

Efficacy

Primary closure rate

A randomised controlled trial of 222 patients with varicose veins treated by cyanoacrylate glue occlusion or radiofrequency ablation reported closure rates of 100% and 86% respectively at 1-month follow-up ($p<0.01$)[1].

A case series of 38 patients reported complete closure of the great saphenous vein in 100% (38/38) of patients at 48-hour follow-up (diagnosed by duplex ultrasound imaging)[2]. The closure rates at 12- and 24-months follow-up were 92%: there were 2 partial recanalisations and 1 complete recanalisation[2]. A case series of 70 patients reported a 12-month survival free from recanalisation of 93%[3].

A case series of 65 saphenous veins (43 great saphenous veins and 22 short saphenous veins) reported a closure rate of 99% at 3-month follow-up[4]. A case series of 10 veins (8 great saphenous veins and 2 anterior accessory saphenous veins) reported that all 8 great saphenous veins were closed at follow-up (3–6 months): in 1 patient with double anterior accessory saphenous vein insufficiency, 1 side was only partially closed 3 days after the procedure and had recanalised totally 2 months after the procedure[4].

A case report of a patient who was being treated with an anticoagulant at the time of the procedure reported complete closure of the great saphenous vein at 8 weeks but extensive recanalisation was seen at 6 months[5].

Symptom relief

The randomised controlled trial of 222 patients reported an improvement in the VCSS of approximately 3.5 points from baseline at 3-month follow-up ($p<0.01$), with no differences between the 2 treatment groups[1]. In the same study, the score on the AVVQ improved by approximately 8 points from baseline at 3-month follow-up ($p<0.01$), with no differences between the treatment groups. The CEAP (clinical, etiological, anatomic and pathophysiologic) classification improved by approximately 0.5 points per group from baseline at 3-month follow-up ($p<0.01$).

The case series of 38 patients reported an improvement in the mean VCSS from 6.1±2.7 at baseline to 1.5±1.4 at 12-month follow-up ($n=36$, $p<0.001$). At baseline, 42% of legs were without oedema compared with 84% and 65% of legs at 6-month and 24-month follow-up respectively. Before treatment, all legs showed clinically relevant varicosities. At 6-month follow-up, 47% of legs were free from visible varicosities. At 12- and 24-month follow-up, 50% and 35% of legs were free from varicosities respectively (absolute numbers not reported)[2]. In the same study, the proportion of patients free from pain increased from 13% at baseline to 84% at 6-month and 64% at 24-month follow-up. The case series of 70 patients reported an improvement in the mean VCSS from 4.3±2.3 at baseline to 1.1±1.3 at 12-month follow-up[3].

Safety

Thrombus extensions

Thread-like thrombus extensions across the saphenofemoral junction were reported in 21% (8/38) of patients in the case series of 38 patients (seen on ultrasound imaging at the 48-hour follow-up). At 6-month follow-up, all thrombus extensions had resolved without clinical sequelae[2]. Thrombus extension into the common femoral vein was reported in 1 patient in the case series of 70 patients; this resolved without progression[3].

Phlebitis

Phlebitis was reported in 16% (6/38) of patients in the case series of 38 patients: the patients had mild pain and erythema which persisted for an average of 5 days. Superficial thrombophlebitis that resolved spontaneously was reported in 1 patient in the same case series[2]. A mild phlebitic reaction was reported in 11% (8/70) of patients in the case series of 70 patients, with a median duration of 6.5 days[3]. Self-limited thrombophlebitis was reported after 40% (4/10) of procedures in the case series of 10 veins[4]. 'Mild' phlebitis in the treatment zone was reported in 6% (6/108) of patients treated by cyanoacrylate glue occlusion in a randomised controlled trial of 222 patients[1]. 'Moderate' phlebitis not in the treatment zone was reported in 1 patient treated by cyanoacrylate glue occlusion in the same study and 'mild' superficial vein thrombophlebitis was reported in 3% (3/108) of patients.

Hypersensitivity reactions

A postoperative erysipeloid-phlebitic skin reaction was reported after 15% (10/65) of procedures in the case series of 65 patients; all resolved quickly after conservative compression therapy[4]. A hypersensitivity reaction was reported in 1 patient in the case series of 10 veins: the patient had simultaneous occlusion of both incompetent anterior accessory saphenous veins and the reaction was thought to be caused by subcutaneous delivery of the adhesive[4].

Cellulitis

Low-grade cellulitis that resolved with oral antibiotics was reported in 1 patient in the case series of 38 patients[2].

Hyperpigmentation

Hyperpigmentation was reported in 1 patient in the case series of 38 patients: this was still visible at 24-month follow-up[2].

Infection

Moderate access site infection was reported in 1 patient treated by cyanoacrylate glue occlusion in the randomised controlled trial of 222 patients[1].

Paraesthesia

Moderate and mild paraesthesia were each reported in 1 patient treated by cyanoacrylate glue occlusion in the randomised controlled trial of 222 patients[1].

Validity and generalisability of the studies

- Two of the 4 case series are reported in a review article, which describes the studies very briefly; it does not include patient characteristics or patient selection criteria.

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 procedure guidance 440 (2013). Available from http://guidance.nice.org.uk/IPG440
- Endovenous mechanochemical ablation for varicose veins. NICE interventional procedure guidance 435 (2013). Available from http://guidance.nice.org.uk/IPG435
- Endovenous laser treatment of the long saphenous vein. NICE interventional procedure guidance 52 (2004). Available from http://guidance.nice.org.uk/IPG52
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedure guidance 37 (2004). Available from http://guidance.nice.org.uk/IPG37
- Radiofrequency ablation of varicose veins. NICE interventional procedure guidance 8 (2003). Available from http://guidance.nice.org.uk/IPG8

NICE guidelines

- Varicose veins in the legs: the diagnosis and management of varicose veins. NICE clinical guideline 168 (2013). Available from http://guidance.nice.org.uk/CG168

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 is not intended to represent the view of the society.

Mr S Ashley, Mr R Bulbulia, Professor S Das, Mr S Dimitri, Mr P Dunning, Mr P Tisi, Mr A Tiwari, Mr F Torella, Mr L Wijesinghe (The Vascular Society of Great Britain and Ireland); Dr S D'Souza, Dr D West (British Society of Interventional Radiology).

- One of the specialist advisers performs the procedure regularly; none of the other advisers have performed the procedure.
- Eight advisers considered the procedure to be definitely novel and of uncertain safety and efficacy; 2 advisers considered it to be a minor variation on an existing procedure that is unlikely to affect that procedure's safety and efficacy; and 1 adviser considered the procedure to be the first in a new class of procedures.
- Comparators for this procedure would be endovenous laser and radiofrequency ablation, varicose vein stripping and foam sclerotherapy.
- Theoretical adverse effects include deep vein thrombosis, embolisation of glue to the lungs, phlebitis, thrombophlebitis, allergic reaction, skin staining, scarring, ulceration, haematoma, infection, thrombus extension into the common femoral vein, cerebrovascular complications giving rise to transient or permanent neurological sequelae, and pain.
- Anecdotal adverse events include inadvertent injection into subcutaneous space, muscle or perivenous space, nerve injury, superficial thrombophlebitis, and local soft tissue inflammatory or allergic reaction.
- Adverse events reported in the literature: phlebitis, thrombophlebitis, deep vein thrombosis, pulmonary embolism, ulceration, blistering, bleeding, discomfort, thrombus extension into the saphenofemoral junction, and allergic reaction.
- Key efficacy outcomes: complete closure of long or short saphenous vein (on duplex ultrasound), long-term recanalisation, improvement in leg symptoms, improvement in quality of life, cosmetic improvement, ulcer healing, skin change improvement, recurrence rates and patient satisfaction.
- There is uncertainty about the long-term efficacy of the procedure.

- One adviser commented that ‘the attraction of this procedure being so simple obviating the need for general anaesthesia and tumescent anaesthesia drives the need for further information with regard to its safety and efficacy and long-term success so that the procedure can be introduced to the NHS’.
- Five advisers thought that the procedure would have a minor impact on the NHS, in terms of patient numbers and use of resources; 3 advisers thought the impact would be moderate and 3 advisers thought the impact would be major.

Patient commentators’ opinions

NICE’s Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing trials:

- ‘The Sapheon closure system feasibility study’ (NCT01603433; currently recruiting participants); Dominican Republic; study start date=July 2011, estimated completion date=July 2015; estimated enrolment=75.
- Post-market study – ‘European observational study of the Sapheon closure system for the definitive treatment of incompetent great saphenous veins: a prospective single arm multicenter clinical observational study’ (NCT01570101; ongoing but not recruiting participants); Denmark, Germany, UK; study start date=December 2011, estimated completion date=June 2015; estimated enrolment=80.

References

1. Morrison N, Gibson K, McEnroe S et al. (2015) Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). Journal of Vascular Surgery: Venous and Lymphatic Disorders 61: 985–94
2. Almeida JI, Javier JJ, Mackay E et al. (2014) Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology 0268355514532455
3. Proebstle TM, Alm J, Dimitri S et al. (2015) The European multicentre cohort study on cyanoacrylate embolization of refluxing great saphenous veins. Journal of Vascular Surgery: Venous and Lymphatic Disorders 3: 2–7
4. Lawson J, Gauw S, van Vlijmen C et al. (2013) Sapheon: the solution? Phlebology 28 (Suppl. 1): 2–9
5. Lane TRA, Kelleher D, Moore HM et al. (2013) Cyanoacrylate glue for the treatment of great saphenous vein incompetence in the anticoagulated patient. Journal of Vascular Surgery: Venous and Lymphatic Disorders 1: 298–300

Appendix A: Additional papers on cyanoacrylate glue occlusion for varicose veins

The following table outlines the studies that are considered potentially relevant to the IP 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
Anwar M A, Lane T R, Franklin I J, et al. (2014) Cyanoacrylate for the Treatment of Small Saphenous Vein Venous Incompetence. Cureus 6(10): e221. doi:10.7759/cureus.221	n=1	There were no procedure related complications. Follow up at 6 weeks and 4 months showed improvement in symptoms and complete occlusion of SSV with no evidence of DVT.	Case report with no unique safety outcomes.

Appendix B: Related NICE guidance for cyanoacrylate glue occlusion for varicose veins

Guidance	Recommendations
Interventional procedures	**Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedure guidance 440 (2013).** 1.1 Current evidence on the efficacy of ultrasound-guided foam sclerotherapy for varicose veins is adequate. The evidence on safety is adequate, and provided that patients are warned of the small but significant risks of foam embolisation (see section 1.2), this procedure may be used with normal arrangements for clinical governance, consent and audit. 1.2 During the consent process, clinicians should inform patients that there are reports of temporary chest tightness, dry cough, headaches and visual disturbance, and rare but significant complications including myocardial infarction, seizures, transient ischaemic attacks and stroke. **Endovenous mechanochemical ablation for varicose veins. NICE interventional procedure guidance 435 (2013).** 1.1 Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. 1.2 Clinicians wishing to undertake endovenous mechanochemical ablation for varicose veins should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients understand that there is a lack of long-term efficacy data and that the procedure has potential side effects (particularly venous thromboembolism). They should be provided with clear written information, including details of other treatment options available to them. In addition, the use of NICE's information for the public is recommended. • Report adverse events and review and audit clinical outcomes (including long-term efficacy) for all patients having endovenous mechanochemical ablation for varicose veins (see section 3.1). 1.3 Patient selection should be carried out by clinicians who can offer a range of treatment options. 1.4 This procedure should only be carried out by clinicians with specific training in this technique.

	1.5 NICE may review the procedure on publication of further evidence. **Endovenous laser treatment of the long saphenous vein. NICE interventional procedure guidance 52 (2004).** 1.1 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. **Transilluminated powered phlebectomy for varicose veins. NICE Interventional procedure 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. **Radiofrequency ablation of varicose veins. NICE interventional procedure 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.

Clinical guidelines	**Varicose veins in the legs: The diagnosis and management of varicose veins. NICE guideline CG168 (2013).** **1.1 Information for people with varicose veins** 1.1.1 Give people who present with varicose veins information that includes: • An explanation of what varicose veins are. • Possible causes of varicose veins. • The likelihood of progression and possible complications, including deep vein thrombosis, skin changes, leg ulcers, bleeding and thrombophlebitis. Address any misconceptions the person may have about the risks of developing complications. • Treatment options, including symptom relief, an overview of interventional treatments and the role of compression. • Advice on: – weight loss (for guidance on weight management see Obesity [NICE guideline CG43]) – light to moderate physical activity – avoiding factors that are known to make their symptoms worse, if possible – when and where to seek further medical help. 1.1.2 When discussing treatment for varicose veins at the vascular service tell the person: • What treatment options are available. • The expected benefits and risks of each treatment option. • That new varicose veins may develop after treatment. • That they may need more than 1 session of treatment. • That the chance of recurrence after treatment for recurrent varicose veins is higher than for primary varicose veins. **1.2 Referral to a vascular service** 1.2.1 Refer people with bleeding varicose veins to a vascular service immediately. 1.2.2 Refer people to a vascular service if they have any of the following. • Symptomatic* primary or symptomatic recurrent varicose veins. • Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency. • Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence. • A venous leg ulcer (a break in the skin below the knee that has

	not healed within 2 weeks). • A healed venous leg ulcer. * Veins found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness and itching). **1.3 Assessment and treatment in a vascular service** **Assessment** 1.3.1 Use duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux, and to plan treatment for people with suspected primary or recurrent varicose veins. **Interventional treatment** 1.3.2 For people with confirmed varicose veins and truncal reflux: • Offer endothermal ablation (see Radiofrequency ablation of varicose veins [NICE interventional procedure guidance 8] and Endovenous laser treatment of the long saphenous vein [NICE interventional procedure guidance 52]). • If endothermal ablation is unsuitable, offer ultrasound‑guided foam sclerotherapy (see Ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedure guidance 440]). • If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery. If incompetent varicose tributaries are to be treated, consider treating them at the same time. 1.3.3 If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days. **Non-interventional treatment** 1.3.4 Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.

Appendix C: Literature search for cyanoacrylate glue occlusion for varicose veins

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	05/03/2015	Issue 3 of 12, March 2015
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	05/03/2015	Issue 1 of 4, January 2015
HTA database (Cochrane Library)	05/03/2015	Issue 1 of 4, January 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	05/03/2015	Issue 2 of 12, February 2015
MEDLINE (Ovid)	05/03/2015	1946 to March Week 1 2015
MEDLINE In-Process (Ovid)	05/03/2015	March 04, 2015
EMBASE (Ovid)	05/03/2015	1974 to 2015 Week 09
PubMed	05/03/2015	n/a
JournalTOCS	05/03/2015	n/a

Trial sources searched on 28/01/2014:

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

Websites searched on 28/01/2014

- National Institute for Health and Clinical Excellence (NICE)
- NHS England
- 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 websites <<add details>>
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp Cyanoacrylates/
2	Cyanoacrylat*.tw.
3	Tissue Adhesives/
4	Acetates/
5	Acetat*.tw.
6	Acrylates/
7	Acrylat*.tw.
8	Tumescentless.tw
9	((CA or cyanoacry* or Medic* or Tissu*) adj4 (adhes* or superglue* or glue* or gum* or resin*)).tw.
10	((CA or cyanoacry*) adj4 (endoven* or ablat*)).tw.
11	or/1-10
12	((venous or vein*) adj3 (incomp* or insuffic*)).tw.
13	((venous or vein*) adj3 ulcer*).tw.
14	telangiect*.tw.
15	((reticular or thread or spider) adj3 (vein* or venous)).tw.
16	(varix or varices or microvaricosity or phlebarteriectasia or phlebectas* or prevaricos* or vein ectasia or venectasia).tw.
17	exp Venous Insufficiency/
18	telangiectasis/
19	or/12-18
20	exp lower extremity/
21	(lower limb* or lower extremit* or leg* or calf or valves or thigh* or membrum inferius).tw.
22	20 or 21
23	19 and 22
24	exp varicose veins/
25	(varicos* adj3 vein*).tw.
26	Saphenous Vein/
27	((saphenous or perforator) adj3 (vein* or vena or incomp* or insuffic*)).tw.
28	GSV.tw.
29	or/23-28

30	11 and 29
31	Venaseal.tw.
32	Sapheon.tw.
33	31 or 32
34	30 or 33
35	animals/ not humans/
36	34 not 35