NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of cyanoacrylate glue occlusion for varicose veins

Varicose veins are enlarged veins, usually in the legs. They develop when small valves inside a vein stop working properly, allowing blood to collect in the vein. This can cause discomfort and lead to skin problems such as discolouration, inflammation and ulceration. In this procedure, medical glue (cyanoacrylate) is injected into a vein. This closes the vein (occlusion) and stops it filling with blood, aiming to improve symptoms.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure 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 March 2019 and updated in October 2019.

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
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

Varicose veins are a sign of underlying venous insufficiency. Primary valvular incompetence is the most common underlying cause of varicose veins. The saphenous veins are the most frequently affected vessels. 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.

NICE's clinical guideline describes the diagnosis and management of varicose veins. Interventional treatment options include endothermal ablation (such as radiofrequency ablation and endovenous laser ablation therapy), foam sclerotherapy, mechanochemical ablation 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 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 at different positions as the catheter is withdrawn, using ultrasound imaging to monitor the procedure. The procedure may also be done in a similar way for the small saphenous vein.

Clinical assessment

The clinical, etiological, anatomic and pathophysiologic (CEAP) 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-item questionnaire covering multiple elements of varicose vein disease, including pain, patient satisfaction and limitations on daily activity, on a scale of 0 to 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).

Efficacy summary

Saphenous vein occlusion rate

Saphenous vein occlusion rates of at least 95% at 6 months after the cyanoacrylate closure (CAC) procedure were reported in 2 systematic reviews[1, 2]. Also, 9 studies described occlusion rates[3-9, 11, 13], which were more than 97% at 1 month post-procedure[3, 6, 8, 9, 11], more than 96% at 6 months[3, 4, 6, 13], more than 94% at 12 months [3-7, 9, 13], and more than 92% at 24 months[3, 4, 8] and was 95% at 36 months[3]. Although there was a trend of better occlusion rates in CAC than in radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and/or mechanochemical ablation (MOCA), these differences were not statistically significant at 6 months after the procedure[3-7, 13]. These findings will be discussed further in each study.

In a systematic review of 7 studies (n=918), an average occlusion rate of 97% at 6-month follow up was reported[2]. In a systematic review and meta-analysis of 15 studies (n=1645) comparing CAC with MOCA, pooled anatomic success (defined as closure and absence of reflux on duplex ultrasound (DUS) imaging in the treated segment of the great saphenous veins [GSV] with a minimum follow up of 6 months) for CAC was 95% (in 7 studies, 95% confidence interval [CI], 92.0% to 97.6%, I^2=69.45%, p=0.003) at 6 months and 89% (in 4 studies, 95% CI, 84.2% to 93.9%, I^2=46.11%, p=0.135) at 1 year; and for MOCA the pooled anatomic success rates were 95% (in 5 studies, 95% CI, 91.3% to 98.0%, I^2=59.60%, p=0.042) at 6 months and 94% (in 3 studies, 95% CI, 91.5% to 96.8%, I^2=0%, p=0.501) at 1 year respectively[1].

In a randomised controlled trial (RCT) of 222 patients with incompetent GSVs, the closure rates at months 6, 12, 24 and 36 were slightly higher with CAC (99%, 97%, 95% and 94% respectively) than with RFA (96%, 96%, 94% and 92% respectively), with noninferiority shown at each time period[3]. The closure rate at month 1 was statistically significantly higher with CAC (100%) than with RFA (87%, p<0.0001)[3]. In an RCT of 456 patients with GSV or small saphenous vein (SSV) incompetence (also included in a systematic review[2]), the occlusion rates were reported at 12 months and 24 months (12 months: CAC 95%, RFA 93% and EVLA 94%, p=0.72; 24 months: CAC 93%, RFA 91% and EVLA 92%, p=0.89)[4]. In an RCT of 400 patients with symptomatic GSVs incompetence, the occlusion rates reported at months 3, 6 and 12 were 99%, 97% and 97% of patients in the CAC group respectively and 97%, 96% and 94% of patients in the EVLA group respectively (p values >0.05)[13].

In a non-randomised comparative study of 339 patients with incompetent GSVs (also included in a systematic review[2]), the total occlusion rates were 99% and 97% in the CAC and EVLA groups respectively (p=0.659) at 12-month follow-up[5].

In a non-randomised comparative study of 310 patients (also included in 2 systematic reviews[1, 2]), the occlusion rates were reported at 6 months (CAC 97% and EVLA 92%, p=0.127) and 12 months (CAC 96% and EVLA 93%, p=0.138)[6]. At 1-month follow-up, the closure rate was statistically significantly higher in the CAC group (97%) than the EVLA group (87%, p=0.001)[6]. In a non-randomised comparative study of 244 patients with incompetent GSVs**,** complete occlusion rates of GSVs were seen in more than 99% of CAC patients compared with 97% of RFA patients (p=0.072) at the 12-month DUS[7].

In a case series of 573 patients, the occlusion rates were 100% at 1 month after the procedure and 99% at 24 months[8]. In a case series of 538 patients, the occlusion rates were more than 99% at 1-month follow up and 99% at 12-month follow up[9]. In a case series of 50 patients, an occlusion rate of 100% was reported at both 7 days and 1 month after the procedure[11].

Recanalisation

Recanalisation happened in small numbers of patients (less than 5%) at different follow-up times[3, 5-8, 13] and the probability of recanalisation was lower in patients who had CAC compared with patients who had RFA or EVLA[3, 5-7, 13], but not for 1 RCT[4]. The detailed information for each study follows.

In the RCT of 222 patients, by 3 months there were 3 recanalisations in the CAC group compared with 9 in the RFA group[3]. At 24 months, there were 5 recanalisations in the CAC group compared with 12 in the RFA group; the cumulative recanalisation rate was less than 5% compared with 12% respectively (p=0.0739). In the RCT of 400 patients, at months 3, 6 and 12, partial recanalisation was seen in 3, 3 and 1 patients in the CAC group respectively, and in 4, 4 and 3 patients in the EVLA group respectively[13]. Of these, at 12 months, 1 patient in the CAC group and 2 patients in the EVLA group turned total recanalisation[13].

In the non-randomised comparative study of 339 patients, at 6 months, partial recanalisation of more than 5 cm at the mid-GSV level was reported in 1 patient in both CAC and EVLA groups[5]. Also, total recanalisation was reported in 2 patients in the EVLA group. No additional recanalisation was seen at 12 months. In the non-randomised comparative study of 310 patients, at months 1, 6 and 12, the incidence rates of small recanalisation of more than 5 cm at GSV were 2% at each follow-up in the CAC group and 3% in the EVLA group[6]. In the non-randomised comparative study of 244 patients, partial recanalisation and minimal reflux were found in 1 patient in the CAC group and in 5 patients in the RFA group on colour doppler ultrasound (CDUS) examinations at 12 months[7]. In the case series of 573 patients, partial recanalisation of more than 5 cm at the

saphenofemoral junction (SFJ) was seen in 6 patients during the 24-month period[8].

In contrast, although there was no recanalisation in patients who had the CAC procedure to the SSVs (5%, 9/186), all recanalisation happened in the GSVs (95%, 159/168) at 2 years after the procedure in the RCT of 456 patients[4].

Adjunctive treatments

The proportions of patients having adjunctive treatments were reported in 3 studies[1, 3, 13] and in particular a high rate (more than 60%) of sclerotherapy at 6 months was highlighted in 1 study[3].

In the RCT of 222 patients, at the 6-month visit, 66% (69/104) of patients in the CAC group and 64% (69/108) of patients in the RFA group (p=0.774) had sclerotherapy; 17% (18/104) and 19% (21/108) of patients respectively had phlebectomy (p=0.726)[3]. The rates of additional adjunctive sclerotherapy and phlebectomy treatments decreased from 12 months to 36 months after both CAC and RFA treatments with phlebectomy being done in 4% (3/72) of patients in the CAC group but none (0/73) in the RFA group (p=0.120)[3]. In the RCT of 400 patients, at months 3, 6 and 12, foam sclerotherapy was done in 2%, 5% and 21% of patients who had CAC treatment respectively, and in 3%, 5% and 25% of patients who had EVLA treatment respectively (p values >0.05)[13]. At the same follow-ups, mini phlebectomy was done in 1%, 4% and 3% of patients in the CAC group respectively and in 0%, 4% and 2% of patients in the EVLA group respectively (p values >0.05). In the systematic review and meta-analysis of 15 studies (n=1645), 7 studies (4 MOCA and 3 CAC studies) reported the rates of adjunctive treatment: 4% to 74% of patients, although it was unclear the exact range for adjunctive treatment in the CAC studies[1].

Symptom relief

Before and after the CAC procedure, a statistically significant reduction (improvement) in VCSS was reported in 9 studies[3-9, 11, 13]. When compared with RFA and EVLA, 1 RCT found that the VCSS reduction was statistically significant lower after the CAC procedure[4]. However, a systematic review reported that a clinically relevant reduction was more common than a statistically significant reduction after the procedure[1]. More information in each study will be presented subsequently.

In the RCT of 456 patients, the mean VCSS decreased in CAC, RFA and EVLA groups after the procedure and these decreases were statistically significant apart from those between years 1 and 2 (p<0.001)[4]. When comparing between groups, VCSS at 6 months and 2 years were statistically significantly lower in the

CAC group (4.1 and 2.7 respectively) than in the RFA (4.8 and 3.7 respectively) and EVLA groups (4.6 and 3.5 respectively, p<0.001).

In the RCT of 222 patients, VCSS declined over time for all patients, by month 3, VCSS had improved about 3.5 points from baseline (p<0.01), with no differences between the CAC and RFA groups and with maximum improvement being seen at month 6 and persisting to month 36 in both groups[3]. In the RCT of 400 patients, at 1-year follow up, VCSS statistically significantly declined from 5.7±2.1 to 1.2±0.8 (p<0.001) for patients who had CAC treatment and from 5.8±1.9 to 1.3±0.9 (p<0.001) for patients who had EVLA treatment, but there was no statistically significant difference in the VCSS scores between the groups at each follow up (p=0.875)[13].

In the non-randomised comparative study of 339 patients, the mean VCSS declined from 7.53±1.03 to 2.79±1.05 (p<0.001) in the CAC group and from 7.73±1.58 to 2.83±1.21 (p<0.001) in the EVLA group, but there was no statistically significant difference between groups (p=0.882) [5]. In the non-randomised comparative study of 310 patients, both CAC and EVLA groups had a statistically significant decrease in VCSS postoperatively (p<0.001), but there was no statistically significant difference between the groups at 1, 6 and 12 months[6]. In a non-randomised comparative study of 244 patients, all patients had a statistically significant improvement in VCSS scores postoperatively (p<0.001)[7]. The mean VCSS scores at baseline and at 12 months were 5.75±1.23 and 1.03±0.96 respectively for the CAC group and 5.79±1.19 and 1.11±0.94 respectively in the RFA group (p=0.921 between groups).

In the case series of 573 patients, the mean VCSS statistically significantly improved from 5.8±1.0 at baseline to 0.6±0.6 at a follow up of 24 months (p<0.0001)[8]. In the case series of 538 patients, the mean VCSS statistically significantly improved from 5.43±0.87 at baseline to 0.6±0.75 at 12 months (p<0.0001)[9]. In the case series of 50 patients, the mean revised VCSS statistically significantly improved from 6.5±2.4 at baseline to 1.8±1.4 at 1-month follow-up (p<0.001)[11].

However, in the systematic review and meta-analysis of 15 studies (n=1645), a statistically significant reduction in the scores after the treatment was only reported in 1 study (from a mean score of 4.3 at baseline to 1.1 at 1 year, p<0.0001), whereas 5 studies described a clinically relevant reduction[1]. In the systematic review of 7 studies (n=918), the average VCSS was 7.9 (in 753 patients, 5 studies) at baseline, and a VCSS decline was seen, ranging from 2.7 to 7.3 at different follow-up times, but there was no discussion about whether these declines were statistically significant[2].

Quality of life

A statistically significant or clinically relevant reduction in the AVVQ scores post-treatment was reported in 2 systematic reviews[1, 2]. For the remaining studies included in table 2, a statistically significant reduction after the CAC procedure at different follow-up intervals was reported in 7 studies[3, 6-9, 11, 13], of which, 4 studies compared the procedure with RFA or with EVLA but did not find a statistically significant difference between the treatments[3, 6, 7, 13]. These reductions will be detailed in each study.

In the systematic review and meta-analysis of 15 studies (n=1645), 3 CAC studies reported a statistically significant (2 studies) or clinically relevant reduction (1 study) in AVVQ scores at 6-month after treatment compared with baseline[1]. In the systematic review of 7 studies (n=918), 2 studies reported an AVVQ decline of 10.6 and 11 points at 30 days after the treatment, and 1 study highlighted a chronic venous insufficiency quality-of-life questionnaire (CIVIQ) decrease of 25.5 points at 30-day follow-up time[2].

In the RCT of 222 patients, AVVQ score statistically significantly improved by about 8 points ($p<0.01$) by month 3 and remained improved throughout the 36-month period[3]. However, there was no statistically significant difference between CAC and RFA treatment groups ($p=0.45$). In the RCT of 400 patients, the mean CIVIQ scores showed statistically meaningful improvement for the CAC group (baseline 40.6±17.8 versus 1-year follow up 12.3±2.5, $p<0.001$) and for the EVLA group (baseline 41.4±18.3 versus 1-year follow up 12.8±2.6, $p<0.001$), but there was no statistically significant difference in the CIVIQ scores between the groups ($p=0.928$)[13].

In the non-randomised comparative study of 310 patients, both CAC and EVLA groups had a statistically significant decrease (improvement) in AVVQ scores postoperatively ($p<0.001$), but there was no statistically significant difference between the groups at 1, 6 and 12 months[6]. In a non-randomised comparative study of 244 patients, all patients had statistically significant improvement in AVVQ scores postoperatively ($p<0.001$). The mean AVVQ scores at baseline and at 12 months were 17.43±6.38 and 4.93±1.56 respectively for the CAC group and 18.21±6.93 and 5.13±1.49 respectively in the RFA group ($p=0.752$ between groups)[7].

In a case series of 573 patients, the mean AVVQ scores statistically significantly improved from 19.7±6.4 at baseline to 4.4±1.1 at a follow-up of 24 months ($p<0.0001$)[8]. In the case series of 538 patients, the mean AVVQ scores statistically significantly improved from 18.32±5.2 (range 9 to 30) at baseline to 4.61±1.42 (range 1 to 8) at 12 months ($p<0.0001$)[9]. In the case series of

50 patients, the mean AVVQ scores statistically significantly improved from 17.3±7.9 at baseline to 8.9±6.6 at 1-month follow up (p<0.001)[11].

Patient satisfaction

Patient satisfaction was measured in 2 studies[3, 11]. In the RCT of 222 patients, 66% (146/222) completed a treatment satisfactory questionnaire at 36 months. Patients reported being 'somewhat satisfied' with the treatment to a similar extent in both groups. However, the proportions of patients who were 'very satisfied' were 85% (61/72) in the CAC group and 78% (58/74) in the RFA group (p=0.30)[3]. In the case series of 50 patients, 98% (49/50) were 'completely' or 'somewhat' satisfied, and 2% (1/50) 'unsatisfied' with the procedure at 1 month[11].

Return to work

Time to return to work was reported in 2 studies[4, 11] and time to return to daily activity in 1 study[13]. In the RCT of 456 patients, the mean time to return to work was statistically significantly shorter after CAC (1.04 days) compared with RFA (1.56 days) and EVLA (1.31 days, p<0.001), and the proportions of patients returning to work on day 1 were 96% (161/168) of CAC patients, 50% (75/149) of RFA patients and 75% (105/139) of EVLA patients[4]. In the case series of 50 patients, the mean time to return to work was 0.2 days ±1.1 days[11]. In the RCT of 400 patients, the mean time to return to daily activity was statistically significantly shorter for patients in the CAC group (1.5±0.6 days) compared with patients in the EVLA group (2.9±1.8, p<0.001)[13].

Safety summary

Sensitivity or hypersensitivity reactions

Hives were reported in 2 case series[10, 11]. In the case series of 160 patients, hives happened in 4 patients at day 1 to day 3 after hypersensitivity-type phlebitis (PLAR) in treated areas and these patients had no history of allergies[10]. In 2 of the cases, it involved the upper trunk and scalp areas. In the case series of 50 patients, total body hives was reported in 1 patient and this case improved after treatment with antihistamines and a short course of oral corticosteroids[11].

Allergic contact dermatitis was reported in a single case report and this allergic reaction was caused by the VenaSeal adhesive (containing n-butyl-2-cyanoacrylate)[12].

PLAR, which was defined as any unusual skin condition that develops suddenly (such as erythema, itching, swelling, and pain or tenderness) over the treated veins several days after the CAC treatment, was identified in a case series of

160 patients[10]. In this study, PLAR happened in 25% (69/271) of the treated saphenous veins after a mean follow-up of 13.6 days, and the occurrence of PLAR was statistically significantly higher for GSV (93%) than for SSV (7%, p<0.001). Accompanying symptoms in the 69 treated veins that experienced PLAR were erythema (92%), itching (91%), swelling (66%), and pain/tenderness (49%).

Sensitivity happened in 12% (14/116) of patients in the CAC group compared with 22% (28/128) in the RFA group (p=0.038) in the non-randomised comparative study of 244 patients[7].

A foreign body reaction with granulomatous inflammation was reported at 5.5 years after CAC treatment in a single case report[14]. In this case, the vessel was occluded with collagenised mature fibrous tissue and polymer remnants, which were encapsulated by multinucleated giant cells. Focal areas of granulomatous inflammation were present in the vein wall extending to the adventitia.

Phlebitis

Small proportions (1% to 7%) of patients, who developed phlebitis after the CAC procedure, were reported in 8 studies[3-9, 13], and a slightly higher rate (20%) was highlighted in a case series[11]. The phlebitis rate was compared between patients who had CCA, RFA or EVLA[3-6, 13] and a statistically significantly less rate post CAC treatment was only found in a RCT[5].

Phlebitis happened statistically significantly less in CAC patients (2% [3/150]) compared with EVLA patients (8% [15/189], p=0.015) in the non-randomised comparative study of 339 patients[5]. Patients with phlebitis in the CAC group were fully recovered after an average of 4 days (3 days to 5 days), whereas patients with the condition in the EVLA group had 14 days of antibiotic (sulbactam-ampicillin) and non-steroidal anti-inflammatory medications in 8% of the patients[5].

Phlebitis happened in 7% (11/168) of patients in the CAC group, in 13% (19/149) in the RFA group and in 9% (13/139) in the EVLA group (p=0.17) in the RCT of 456 patients[4]. Phlebitis was reported in 4% of patients who had CAC treatment compared with 7% of patients who had EVLA treatment (p=0.328) at 1-week visit in the RCT of 400 patients[13]. Phlebitis was reported in 5% (7/154) of patients in CAC group compared with 8% (12/156) in EVLA group (p=0.248) in the non-randomised comparative study of 310 patients[6].

Procedure- or device-related phlebitis was reported in 6% (7/108) of patients who had CAC and in 4% (4/114) of patients who had RFA at 3 months in the RCT of 222 patients[3]. Phlebitis was reported in 2% (10/573) and 1% (6/538) of patients respectively in the case series of 573 and 538 patients[8, 9]. Phlebitis in the treatment area or side branches happened in 20% (10/50) of the patients in the

case series of 50 patients[11]. The phlebitis was resolved by 1 month in all but 1 patient, who had P1 phlebitis in the target vein[11].

Thrombophlebitis and vein thrombosis

Thrombophlebitis and/or deep venous thrombosis were reported in 2 studies[1, 7]. In the systematic review and meta-analysis of 15 studies (n=1645), thrombophlebitis was reported in 6 CAC studies ranging from less than 1% to 18%, and deep venous thrombosis was described in 4 CAC studies ranging from 0 to 4%[1]. In the non-randomised comparative study of 244 patients, thrombophlebitis happened in 2% (2/116) of patients in the CAC group compared with 3% (4/128) in the RFA group (p=0.685) [7].

Superficial vein thrombosis was reported in 2% of the 666 patients (in 5 studies) and treated conservatively with medical therapy in the systematic review of 7 studies (n=918)[2].

Thrombus extension

Thrombus extension, that protruded 2 mm into the saphenofemoral junction, happened in 1 patient at the 7-day DUS in the case series of 50 patients[11]. This patient was asymptomatic and did not have anticoagulation. The thrombus extension was no longer evident at the 1-month DUS.

Pain during or following the procedure

Postoperative pain was reported in 5% of 519 patients in 3 included studies in the systematic review of 7 studies (n=918)[2]. Also, pain (mainly mild pain) was reported during and/or after the CAC procedure in 10 studies[3-11, 13]. Of these, 6 studies compared this complication in patients who had CAC with patients who had RFA or EVLA[3-7, 13] and 4 of the 6 studies reported that statistically significant less pain was experienced in the CAC group[4, 6, 7].

In the RCT of 456 patients, there was a statistically significant difference in pain sensation between the CAC and RFA groups, and between the CAC and EVLA groups (p=0.000, no pain [CAC 61%, RFA 0 and EVLA 0], mild pain [CAC 31%, RFA 50% and EVLA 48%], moderate pain [CAC 8%, RFA 36% and EVLA 44%], severe pain [CAC 0, RFA 14% and EVLA 9%])[4]. However, there was no statistically significant difference between the groups in terms of postoperative analgesic consumption (p=0.147). In the RCT of 400 patients, postoperative mean pain score was statistically significantly lower in patients who had CAC treatment (2.8±3.1) compared with patients who had EVLA treatment (5.4±3.7, p<0.001) at 1-week follow up[13]. In the non-randomised comparative study of 310 patients, the mean score of periprocedural pain was statistically significantly

less in CAC group (3.1±1.6) than in EVLA group (6.5±2.3, p<0.001) [6]. In the non-randomised comparative study of 244 patients, severe pain was statistically significantly lower in the CAC group than in the RFA group (4% compared with 13%, p=0.042) [7].

In the RCT of 222 patient, main pain ratings during venous access were similar between the CAC group (1.6) and the RFA group (2.0, p=0.13); mean intraprocedural pain ratings were also low and similar in both groups (2.2 compared with 2.4, p=0.11)[3]. There was no difference between treatment groups in pain experienced in the 24 hours before the day 3 visit (0.93 in each group, p=0.36). However, moderate pain in right medial thigh was reported in 1 CAC patient at day 221. In the non-randomised comparative study of 339 patients, 5% (7/150) reported postoperative pain at the SFJ or entry levels during days 1 to 3 in the CAC group compared with 9% (17/189) experienced pain during days 4 to 7 in the EVLA group (p=0.123) [5].

Mild pain was reported, (mean scores 2.8±1.2, 2.19±0.94 and 2.1±1.8) during the procedure in the case series of 573, 538 and 50 patients respectively[8, 9, 11]. Although mild pain happened after the procedure in the case series of 160 patients, the pain score was statistically significantly higher in patients with PLAR (1.54±2.07) than patients without PLAR (0.41±0.89, p<0.001) at day 10[10].

Pigmentation

Pigmentation happened in 1% of the 354 cases (in 3 studies) in the systematic review of 7 studies (n=918)[2] and hyperpigmentation was described ranging from 2% to 3% (in 3 studies) in the systematic review and meta-analysis of 15 studies (n=1,645)[1].

Pigmentation happened less in patients who had CAC than in patients who had EVLA or RFA, but no statistically significant difference was found in 1 RCT[13] and 2 non-randomised comparative studies[6, 7]. In the RCT of 400 patients, pigmentation was reported in 4% of patients in the CAC group compared with 6% of patients in the EVLA group at 1-week follow-up (p=0.554)[13]. At 3-month follow up, pigmentation was seen in 1% of patients in the CAC group and 2% of patients in the EVLA group (p=0.087). In the non-randomised comparative study of 310 patients, temporary skin pigmentation developed in 1% (2/154) of patients who had CAC and in 2% (3/156) of patients who had EVLA (p=1), and all decreased statistically significantly, becoming almost invisible over the 1-year follow up[6]. In a non-randomised comparative study of 244 patients, a pigmentation increase was reported in 2% (2/116) of patients in the CAC group compared with 3% (4/128) in the RFA group (p=0.685) at superficial small parts close to the entry point[7].

Ecchymosis or hematoma

Ecchymosis or haematoma was reported in 2 CAC studies ranging from 1% to 2% in the systematic review and meta-analysis of 15 studies (n=1645)[1], and haematoma was reported in less than 1% of the 431 patients (in 3 studies) in the systematic review of 7 studies (n=918)[2]. For the remaining studies included in table 2, ecchymosis rates ranging from less than 1% to 32% after the CAC procedure were reported in 6 studies[3, 4, 6, 8, 9, 13]. Of these, a statistically significant lower rate was found after the CAC treatment compared with RFA or EVLA[3, 4, 6, 7, 13].

Ecchymosis severity at day 3 was lower in the CAC group (p<0.01), and was absent in more patients after CAC (68%) than after RFA (48%, p<0.01) in the RCT of 222 patients[3]. Ecchymosis was reported in 5% (9/168) of patients who had CAC, in 18% (27/149) of patients who had RFA and in 4% (6/139) of patients who had EVLA, with a statistically significant difference between the CAC and RFA groups (p<0.001) in the RCT of 456 patients[4]. Ecchymosis happened statistically significantly less in patients who had CAC treatment (12%) compared with patients who had EVLA treatment (26%, p<0.001) at 1-week visit in the RCT of 400 patients[13]. Ecchymosis was statistically significantly less in CAC group (14%) than in EVLA group (56%) at day 3 (p<0.001) in the non-randomised comparative study of 310 patients[6]. Ecchymosis was statistically significantly lower in CAC group (12%) than in RFA group (20.3%, p=0.044) in the non-randomised comparative study of 244 patients[7].

Ecchymosis rates at day 3 were 1% (8/573) and 1% (5/538) in the case series of 573 and 538 patients respectively[8, 9].

Access site infection or cellulitis

Access site infection or cellulitis was described in 2 stuides[1, 7]. In the systematic review and meta-analysis of 15 studies (n=1645), access site infection or cellulitis was reported in 3 CAC studies, ranging from 1% to 3%[1]. In the non-randomised comparative study of 244 patients, cellulite was reported in 2% of patients who had CAC patients compared with 2% patients who had RFA (p=0.998)[7].

Nerve injury or paraesthesia

Nerve injury or paraesthesia was stated in 3 studies[1, 3, 13]. In the systematic review and meta-analysis of 15 studies (n=1645), nerve injury or paraesthesia was reported in 3 CAC studies ranging from 0 to 2%[1]. In the RCT of 222 patients, paraesthesia happened in 2% (2/108) of patients who had CAC and in 1% (1/114) of patients who had RFA at 3 months[3]. In the RCT of 400 patients, paraesthesia was reported statistically significantly less in patients who had CAC

treatment compared with patients who had EVLA treatment at 1 week (CAC 3% versus EVLA 11%, p<0.001) and 3 months (CAC 1% versus EVLA 7%, p<0.001)[13].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, 4 specialist advisers listed the following anecdotal adverse events: hypersensitivity reactions, phlebitis, glue extension, granuloma formation or discharge and sepsis. They considered that the following were theoretical adverse events: hypersensitivity reactions, phlebitis, glue extension or discharge, deep vein thrombosis, pulmonary embolism, granuloma formation, failure of procedure and recurrence.

The evidence assessed

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 15 October 2019: 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 the literature 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 4,432 patients from 2 systematic reviews[1, 2], 3 randomised controlled trials[3, 4, 13], 3 non-randomised comparative studies[5-7], 4 case series[8-11] and 2 case reports[12, 14].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

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

Study 1 Vos CG (2017)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Study period	Search date: not reported Publication years for the included studies: 2012 and 2017
Study population and number	**n=1,645 (15 studies; 691 patients in 7 studies on MOCA versus 954 patients in 8 studies on CAC)** Patients with GSV incompetence (GSV reflux >500 milliseconds)
Age and sex	Mean 38 years to 70 years; 38% to 81% female
Patient selection criteria	Inclusion criteria: articles were prospective studies that included patients having treatment for GSV incompetence, described the primary outcomes, had a minimum follow up of 6 months with duplex ultrasound imaging, and were published between January 1966 and December 2016. Exclusion criteria: full text not available, case reports, retrospective studies, small series (n<10), reviews, abstracts, animal studies, studies of small saphenous vein incompetence, and recurrent GSV incompetence.
Technique	CAC used Sapheon VenaSeal or Biolas VariClose, and the procedural technique involved local anaesthesia, ultrasound-guided puncture of the GSV, and positioning of the catheter tip 3 cm to 5 cm proximal to the SFJ. Then, the SFJ was compressed by the probe, and the first 10 cm were treated, followed by compression of 5 seconds (in 3 studies) or 3 minutes (in 5 studies). The latter 5 studies injected 2 boluses of 0.08 ml to 0.09 ml of cyanoacrylate adhesive in the 1st segment, 1 cm apart, the other studies used the standard dose of 0.03 ml per cm. One study applied a slightly higher dose of 0.05 ml per cm. Postprocedural compression therapy was not applied in 4 studies, used for the first 24 hours in 2 studies and not reported in 2 studies.
Follow-up	**CAC: 0 to 2 years** **MOCA: 1 week to 3 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Most studies had only a short follow up of 6 months to 1 year. The authors reported that losses to follow-up were not described in 1 study and were too high in 5 studies.

Study design issues: This review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews and meta-analyses. This review evaluated the reported efficacy of MOCA and CAC for GSV incompetence, with the primary outcome being anatomic success (defined as closure and absence of reflux on DUS imaging in the treated segment of the GSV with a minimum follow up of 6 months) and secondary outcomes being initial technical success (referred to successful completion of the procedure with occlusion of the GSV on DUS imaging), VCSS, AVVQ, and complications. Two authors independently searched the literature using a suitable search strategy, screened the papers, extracted data and assessed the methodological quality of the relevant articles using the Methodological Index for Non-Randomised Studies (MINORS) score, with a global ideal score of 16 for noncomparative studies and 24 for comparative studies. Discrepancies were solved by discussion and/or consulting the third author. The 15 chosen studies included 2 RCTs and 13 prospective observational cohorts. Of these, 14 studies were of moderate methodologic quality and 1 RCT had good methodologic quality. Blinding and prospective calculation of study size were infrequently reported.

Study population issues: There was an overlap between 6 studies, however, the studies described different durations of follow up and presented unique data for at least 1-time interval. Also, each cohort was included only once in all pooled analyses and overlapping data were excluded from these analyses. Baseline VCSS and AVVQ scores varied between studies, which implies differences in severity of disease of included patients in the studied cohorts. In respect of adjunctive treatment (for example concomitant phlebectomy or sclerotherapy), 7 studies (4 MOCA and 3 CAC) reported the rates of adjunctive treatment, 7 studies (3 MOCA and 4 CAC) did not use adjunctive treatments and 1 CAC study did not report. For CAC, there were minor differences in technique, especially concerning the first segment distal to the SFJ.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 1,645 (691 MOCA patients [7 studies] versus 954 CAC patients [8 studies])

Adjunctive treatment:
- 7 studies (3 CAC and 4 MOCA studies) reported the rates of adjunctive treatment: 4% to 74% of the patients

Initial technical success for CAC:
- 100% in 3 studies
- Not reported in 5 studies

Initial technical success for MOCA:
- 100% in 3 studies
- 99% in 2 studies
- 98% in 1 study
- Not reported in 1 study

Closure rates for CAC:
- 6 months in 7 studies: 94.8% (95% CI, 92.0% to 97.6%, I^2=69.45%, p=0.003)
- 1 year in 4 studies: 89.0% (95% CI, 84.2% to 93.9%, I^2=46.11%, p=0.135)
- 2 year in 1 study: 92.0%

Closure rates for MOCA:
- 6 months in 5 studies: 94.7% (95% CI, 91.3% to 98.0%, I^2=59.60%, p=0.042)
- 1 year in 3 studies: 94.1% (95% CI, 91.5% to 96.8%, I^2=0%, p=0.501)
- 2 years in 3 studies: range 89.5% to 95.0%
- 3 years in 1 study: 86.5%

VCSS: After CAC treatment, 6 CAC studies reporting VCSSs highlighted a statistically significant (1 study) or clinically relevant reduction (5 studies) in the scores. Similarly, 6 MOCA studies reporting VCSSs described a statistically significant (2 studies) or clinically relevant reduction (4 studies) in these scores. Similarly,

VCSS for CAC, mean±SD
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>1 year</th><th>2 years</th></tr>
<tr><td>Study 1</td><td>6.1±2.7</td><td>-</td><td>1.5±1.4</td><td>-</td></tr>
<tr><td>Study 2</td><td>6.1±2.7</td><td>1.3±1.2</td><td>1.3±1.3</td><td>2.5</td></tr>
<tr><td>Study 3</td><td>4.9±1.2</td><td>1.4±0.8</td><td>-</td><td>-</td></tr>
<tr><td>Study 4</td><td>6.9±3.5</td><td>1.8±1.7</td><td>1.7±1.0</td><td></td></tr>
</table>
</td><td>
Complications in the CAC studies:
- Thrombophlebitis: range 0.5% to 18% in 6 studies
- Hyperpigmentation: range 1.6% to 3% in 3 studies
- Deep venous thrombosis: range 0 to 3.5% in 4 studies
- Access site infection or cellulitis: range 1.4% to 3% in 3 studies
- Ecchymosis or hematoma: range 1.4% to 1.6% in 2 studies
- Nerve injury or paraesthesia: range 0 to 2% in 3 studies
</td></tr>
</table>

Study 5	5.5±2.6	1.5±1.8	-	-
Study 6*	4.3	1.1	-	-

*p<0.0001

AVVQ: 3 CAC studies reported a significant (2 studies) or clinically relevant reduction (1 study) in AVVQ scores post treatment compared with baseline values, whereas 3 MOCA studies reporting AVVQ scores described a significant reduction in AVVQ scores after treatment compared with baseline.

AVVQ for CAC, mean±SD

	Baseline	**3 months**	**6 months**	**1 years**
Study 1**	23.7±11.1	5.8±5.6	1.8±1.7	1.7±1.0
Study 2	18.9±9.0	11.6±7.5	10.2±7.2	-
Study 3**	16.3±8.0	7.6±6.3	6.3±8.5	6.7±6.4

**A statistically significant reduction in mean AVVQ score compared with baseline but p value was not reported.

Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; CAC, cyanoacrylate closure; CI, confidence interval; MOCA, mechanochemical endovenous ablation; SD, standard deviation; VCSS, venous clinical severity score.

Study 2 Bissacco D (2019)

Details

Study type	**Systematic review**
Country	7 studies in Turkey
Study period	First search in January 2017 and updated in December 2017 Average enrolment period: 13.4 months (range 7 to 18 months)
Study population and number	**n=918 (1,000 limbs [947 GSV and 53 SSV], 7 studies)** Patients with superficial vein insufficiency
Age and sex	Average 43.2 years; 49.7% female
Patient selection criteria	Inclusion criteria: Studies included patients having Variclose system (Biolas, Ankara, Turkey) for superficial vein insufficiency (either GSV, SSV, and/or perforator veins). Studies describing cohorts that did not solely use CAC treatments could only be included if the data for patients with CAC could be specifically extracted from the study results. English language was applied as restriction, while no time restrictions were used. Exclusion criteria: Case reports, review, meta-analysis, article with <6-month follow-up data, abstracts and congress presentations.
Technique	CAC treatment with a particular type of device (Variclose Vein Sealing System®, Biolas Inc., Ankara, Turkey). In terms of the CAC used, 5 studies declared 0.03 ml of CAC per cm of treated vein was injected during catheter pullback, 1 study reported the injection rate was 0.05 ml per cm, and 1 study described only the total amount of CAC used to treat the entire vein segment for GSV (0.91 ml ±0.12 ml) and SSV (0.58 ml ±0.11 ml) procedures. Concomitant phlebectomies were done in 1 study in 24% of cases and foam sclerotherapy was associated to the CAC procedure in 1.4% of case in 1 study.
Follow up	**Average 14 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Losses to follow up were not discussed in the review.

Study design issues: This study reviewed published evidence regarding an n-butyl-cyanoacrylate injection device for great (GSV) and small (SSV) saphenous vein incompetence in terms of occlusion rate, postoperative complications and quality of life improvement. The search was done following the recommendations of Preferred Reporting Items for Systematic Reviews and Me-ta-Analyses (PRISMA) guidelines. If more than 1 study reported the same patient cohort, only the most recent and complete manuscript was included in the review. Two reviewers independently selected potentially relevant papers and then independently extracted data. In case of discrepancies in article or data extract, a third searcher was consulted to find an agreement. However, the quality assessment of the included studies was not described in the review. The included articles consisted of 2 prospective and 5 retrospective studies; so, there was a lack of RCTs. A meta-analysis was not applied because of heterogeneity between studies and poor published data, and results were presented as weighted average, based on the number of patients involved in each single analysis. Anatomical success was defined as closure and absence of reflux on colour Doppler ultrasound scan analysis. Postoperative pain was defined according to the visual analogue scale or as requiring analgesics/local cooling or limitation of daily life activities, although 1 study did not define it.

Study population issues: No patient had treatment for both GSV and SSV incompetence in the same surgical session. In 1 study, the diameters of the GSV and SSV were mixed. Anatomical and pathophysiological classifications of chronic venous disorders (CEAP) were used in all studies to assess disease severity. One study used CAC in patients with an active venous ulcer (C6).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 918 (1000 limbs [947 GSVs and 53 SSVs])

Procedure characteristics
<table>
<tr><th>Characteristics</th><th>Average</th></tr>
<tr><td>GSV diameter, mm</td><td>7.2[a]</td></tr>
<tr><td>SSV diameter, mm</td><td>6.6[b]</td></tr>
<tr><td>Treated segment length, cm</td><td>29.5</td></tr>
<tr><td>Procedure time, minutes</td><td>11.7</td></tr>
<tr><td>Surgical time, minutes (range)</td><td>5.4 to 25</td></tr>
</table>
[a]In 767 veins
[b]In 42 veins

In 2 retrospective non-randomised trials that compared CAC with EVLA, there was a statistically significantly shorter procedural time in CAC group (15 minutes ±2.5 minutes) than in the EVLA group (33.2 minutes ±5.7 minutes, p<0.001).

VCSS scores in 723 patients in 5 studies:
- Average VCSS at baseline: 7.9
- 2 studies reported a VCSS decline at 30 days of 3.3 and 4 points.
- 2 studies reported a VCSS decline at 6 months and 12 months of 6 and 5 points, and 7.3 and 6 points, respectively.
- 1 study reported a VCSS decline at months 3, 6, 12 and 30 of 3.9, 4.2, 2.9 and 2.7 points, respectively.

Quality of life:
- 2 studies reported an AVVQ decline at 30 days of 10.6 and 11 points.
- 1 study reported a CIVIQ decline at 30 days of 25.5 points.
- 1 study reported a CEAP classification reduction at 30 days of 2.2 points.

Occlusion rate (complete recanalisation rate):
- 1 week: 99.9% of 761 cases (in 5 studies)
- 1 month: 99.1% of 661 cases (in 5 studies)
- 3 months: 97.8% of 277 cases (in 3 studies)
- 6 months: 97.3% of 1000 cases (in 7 studies)
- 12 months: 96.8% of 534 cases (in 4 studies)
- 30 months: 94.1% of 180 cases (in 1 study)
</td><td>
Complications:
- Pain: 4.8% of 519 cases (in 3 studies)
- Bruising: 0.8% of 569 cases (in 4 studies)
- Hematoma: 0.2% of 431 cases (in 3 studies)
- Pigmentation: 0.8% of 354 cases (in 3 studies)
- SVT: 2.1% of 666 cases (in 5 studies) and treated conservatively with medical therapy.
</td></tr>
<tr><td colspan="2">Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; CAC, cyanoacrylate closure; CEAP, clinical, aetiology, anatomy and pathophysiology classification; CIVIQ, chronic venous insufficiency questionnaire; EVLA, endovenous laser ablation; GSV, great saphenous vein; SSV, small saphenous vein; SVT, superficial vein thrombosis; VCSS, venous clinical severity score.</td></tr>
</table>

Study 3 Morrison N (2015, 2017, 2019) and Gibson (2018)

Details

Study type	**Randomised controlled trial (VeClose)**
Country	US (10 centres)
Recruitment period	2013
Study population and number	**n=222 (108 CAC versus 114 RFA)** Patients with incompetent great saphenous veins
Age and sex	CAC: Mean 49.0 years; 77% (83/108) female RFA: mean 50.5 years; 82% (93/114) female
Patient selection criteria	Inclusion criteria: Adult patients with symptomatic venous reflux and varicosities who had clinical–aetiology–anatomy–pathophysiology (CEAP) classifications of C2 to C4b and GSV incompetence with a reflux time of ≥0.5 seconds assessed in the standing position using duplex ultrasound, ability to walk unassisted, ability to attend follow-up visits, and ability to understand the needs of the study and to provide informed consent. Exclusion criteria; Patients were excluded if they were asymptomatic, had clinically significant reflux of the SSV or anterior accessory GSV, previous treatment of venous disease in target limb, symptomatic peripheral arterial disease, a history of deep venous thrombosis, pulmonary embolism, or aneurysm of the target GSV with a diameter of >12 mm, their life expectancy <1 year, active treatment for malignant disease other than nonmelanoma skin cancer.
Technique	Endovenous treatment of the GSV with the CAC device (VenaSeal Closure System manufactured by Medtronic Minneapolis, MN, USA) was done, following the instructions for use. With proximal GSV compression using the ultrasound probe, 2 x 0.1 ml aliquots of cyanoacrylate were delivered 1 cm apart with additional hand compression at the treated segment for 3 minutes. Subsequent 0.1 ml aliquots were delivered at 3 cm intervals along the target treatment area, and compression with the ultrasound probe and free hand was done for 30 seconds at each treated segment. Additional aliquots of 0.1 ml of adhesive were delivered in dilated areas. Manual compression over the vein during the polymerisation phase is used to eliminate as much blood as possible from the vein to achieve complete adhesion of the cyanoacrylate to the vein wall. For residual varicosities or the untreated portion of the GAS, no adjunctive treatments were allowed during the first 3 months in either the ipsilateral or contralateral leg. The decision to do adjunctive procedures, and which procedures would be used was made in consultation between physician and patient at each follow-up visit.
Follow up	**36 months**
Conflict of interest/source of funding	Five authors were investigators in this study and received payments to cover study-related activities. In addition, 3 of them are consultants to Medtronic but do not have stock or options in Medtronic. Another author was an investor in Sapheon which was acquired by Covidien and is now an employee of Medtronic. This trial was originally funded by Sapheon, then by Covidien, and currently by Medtronic.

Analysis

Follow-up issues: Patients were followed up at day 3 and at 1, 3, 6, 12, 24 and 36 months for clinical assessments. At 36 months, losses to follow up were 36 patients in the CAC group and 40 patients in the RFA group, therefore, 67% (72/108) of patients and 65% (74/114) were evaluated, respectively. The lack of data for approximately one-third of patients in each group was due to patient dropout (although the reasons for dropout were unclear) or the data could not be collected in the time period dictated by the study period.

Study design issues: Multicentre, prospective, randomised controlled trial without blinding. Randomisation was stratified by study centre and random block sizes of 4 or 6 were used, and assignments were obtained through automated telephone service connected to a password protected randomisation table. The first 2 patients at each site (non-randomised) were used as roll-in cases and were treated with CAC to train and ensure familiarity with the procedure. These cases were analysed and reported separately. This RCT evaluated the efficacy (in terms of closure rates, symptom scores and quality of life measurements) and safety of cyanoacrylate closure for the treatment of incompetent GSVs in

comparison with radiofrequency ablation through a 36-month period. Intention-to-treat analysis was only applied to analyse the complete closure of the target GSV at 3 months (in Morrison 2015), per-protocol analysis used for analysing the remaining outcomes.

The complete closure of the target great saphenous vein was determined using duplex ultrasound examination (including colour flow, compression, and pulsed Doppler) showing closure along the entire treated target vein segment with no discrete segments of patency exceeding 5 cm in length. Closure was confirmed by an independent vascular ultrasound core laboratory (VasCore, Boston, Mass). Recanalisation was defined as patency along the treated segment exceeding 5 cm in length. Time to recanalisation was calculated as the number of days from treatment to first instance of recanalisation. Patients completed a brief questionnaire about treatment satisfaction, including “very dissatisfied”, “somewhat dissatisfied”, “somewhat satisfied” and “very satisfied” with the treatment provided.

Study population issues: There was no statistically significant difference between the 2 treatment groups in terms of age, gender, BMI, primary symptoms, GSV diameter, CEAP classification, VCSS, AVVQ and EQ-5D health thermometer at baseline. Most patients (87%) were in the CEAP classifications C2 or C3 at baseline. However, there was a slight predominance of current and former smokers in the CAC groups (p=0.02).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **222 (108 CAC versus 114 RFA).**

Procedure characteristics

Characteristics	CAC	RFA	P
Treatment zone maximum diameter, mm (mean, range)	5.9 (2 to 12)	6.2 (1.5 to 11)	0.19
GSV treatment length, cm (mean, range)	32.8 (8 to 61)	35.1 (6.5 to 84.5)	0.17
Stump length, cm (mean, range)	22.5 (0 to 83)	18.9 (0 to 330)	0.38
Cyanoacrylate glue delivered, ml (mean, range)	1.2 (0.4 to 2.3)	-	-
Procedure duration, minutes (mean, range)	24 (11 to 40)	19 (5 to 46)	**<0.01**
Volume lidocaine, ml (mean, range)	1.6 (0.2 to 6)	2.7 (0.2 to 10)	0.1

Adjunctive treatments for persistently incompetent untreated GSV segments and residual varicosities.

Adjunctive treatments	CAC	RFA	P
Month 6			
sclerotherapy	66.3% (69/104)	63.9% (69/108)	0.774
Phlebectomy	17.3% (18/104)	19.4% (21/108)	0.726
Month 12 to 36			
Phlebectomy	4.2% (3/72)	0	0.120

GSV closure rate at different time points as judged by the investigator

Timepoints	CAC	RFA	P*	P**
Day 3	100% (108/108)	99.1% (113/114)	0.0001	1.00
Month 1	100% (105/105)	87.3% (96/110)	<0.0001	<0.0001
Month 3	99% (10.3/104)	95.4% (103/108)	<0.0001	0.22
Month 3 (ITT)***	99%	96%	<0.01	<0.07
Month 6	99% (100/101)	96.2% (101/105)	0.0001	0.37
Month 12	96.8% (92/95)	95.9% (93/97)	0.0015	1.00
Month 24	95.3% (82/86)	94.0% (79/84)	0.0034	0.75
Month 36	94.4% (68/72)	91.9% (68/74)	0.0050	0.75

Safety

Pain and ecchymosis

Complications	CAC	RFA	P
Pain, mean			
During venous access	1.6	2.0	0.13
intraprocedural	2.2	2.4	0.11
In the 24 hours before day 3	0.93	0.93	0.36
Ecchymosis at day 3, %			
Absence	67.6	48.2	**<0.01**
<25%	26.9	33.3	
25% to 50%	2.8	14	
50% to 75%	1.9	3.5	
75% to 100%	0.9	0.9	

AEs at month 3

AEs	CAC, % (n)	RFA, % (n)	P
Procedure-related adverse events[a]	25 (27)	27 (31)	0.76
Device-related adverse events[a]	12 (13)	6 (7)	0.16

[a]Judged by investigator to be probably or definitely related.

Events rated as probably or definitely related to CAC devices at 3 months:

- Moderate access site infection: n=1
- Mild paraesthesia in the treatment zone: n=1
- Moderate paraesthesia in the 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.

Events rated as probably or definitely related to RFA devices at 3 months:

- Mild access site burn: n=1
- Mild paraesthesia in the 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

AEs between 3 and 36 months

AEs	Related to device	Related to procedure	Severity	Days to AE

*One-sided p-value for noninferiority comparing CAC and RFA with 10% margin.

**Two-sided p-value comparing CAC and RFA using Fisher's exact test.

***With use of the predictive model for missing data interpretation, closure rates were 99% and 96% in the CAC and RFA groups respectively (p<0.01 for noninferiority, p<0.07 for superiority).

Recanalisation, n

Recanalisation	CAC	RFA
3 months	3	9
24 months	5	12

Kaplan-Meier analysis showed that the cumulative recanalisation rate was <5% versus 12% (p=0.0739).

Survival free from recanalisation

- At 12 months: 97% in the CAC group versus 90.7% in the RFA group (p=0.08 for superiority, p<0.0001 for noninferiority).
- At 24 months, 94.6% in the CAC group versus 87.8% in the RFA group (p< 0.0001 for 10% noninferiority).

Overall, when compared with the RFA group, the CAC group showed a numerically higher rate of freedom from recanalisation throughout the study period of 36 months, i.e. the probability of recanalisation was lower, even though the difference was not statistically significant (log-rank, p=0.1006).

Change in VCSS, AVVQ and EQ-5D

Symptom scores and QoL	CAC****	RFA	p
VCSS mean (SD), n			
Baseline	5.5 (2.6), 108	5.6 (2.6), 114	0.60
Day 3	4.9 (1.3), 108	5.0 (1.9), 114	
Month 1	2.3 (1.7), 105	2.6 (2.0), 110	
Month 3	1.9 (1.6), 104	2.0 (2.0), 108	
AVVQ mean (SD), n			
Baseline	18.9 (9.0), 107	19.4 (9.9), 111	0.53
Month 1	11.9 (7.1), 102	12.6 (8.3), 109	
Month 3	11.6 (7.5), 104	10.7 (8.6), 108	
EQ-5D TTO mean (SD), n			
Baseline	0.935 (0.113), 108	0.918 (0.116), 114	0.34
Month 1	0.965 (0.113), 105	0.961 (0.106), 110	
Month 3	0.965 (0.095), 104	0.965 (0.083), 108	

****There was a statistically significant difference between baseline and month 3 for VCSS and AVVQ, p<0.01 and for EQ-AD TTO, p=0.01.

CAC				
Chronic phlebitis	PR	DR	Mild	92
Pain in right medial thigh	NR	PR	Moderate	221
Erythema in medial thigh	Unknown	Unknown	-	477 & 721
Late onset of phlebitis	NR	PR	-	976
Scar	DR	DR	-	1175
Left leg calf pain	NR	Unknown	-	1241
RFA				
DVT non-index leg	DR	DR	Moderate	172
EHIT	DR	DR	Moderate	172
Left groin discomfort	PR	PR	Mild	97
Phlebitis	PR	PR	Mild	106

VCSS of the 2 groups were comparable at baseline and declined over time for all subjects with no statistically significant difference between the groups. Maximum improvement in the VCSS was seen at month 6 and persisted to month 36 in both groups.

There was no statistical difference between CAC and RFA treatment groups in both **AVVQ (p=0.45) and EQ-5D health thermometer as assessed by VAS (p=0.42)** which remained improved throughout the 36-month period.

Patient satisfaction at months 24 and 36

Patient satisfaction	CAC, % (n)	RFA, % (n)	P
24 months			
Very satisfied	79.1 (68/86)	75.0% (63/84)	-
Somewhat satisfied	9.3 (8/86)	22.6 (19/84)	-
Consider having the treatment again	82.6% (71/86)	77.4 (65/84)	-
36 months			
Very satisfied	84.7 (61/72)	78.4 (58/72)	0.30
Somewhat satisfied	To a similar extent in both groups		

Abbreviations used: AEs: adverse events; AVVQ, Aberdeen varicose vein questionnaire; CAC, cyanoacrylate closure; DR, definitely related; EHIT, endovenous heat-induced thrombosis; EQ-5D, EuroQoL-5 dimension; GSV, great saphenous vein; NA, not applicable; NR, not related; PR, probably related; QoL, quality of life; RFA, radiofrequency ablation; SD, standard deviation; TTO, time trade-off; VAS, visual analogue score; VCSS, venous clinical severity score.

Study 4 Eroglu E (2018)

Details

Study type	**Randomised controlled trial**
Country	Turkey
Recruitment period	2014 to 2015
Study population and number	**n=456 (168 CAC, 139 RFA and 149 EVLA)** Patients with great saphenous vein (GSV) or small saphenous vein (SSV) incompetence
Age and sex	CAC: mean 47.7 years; 58.3% (98/168) female RFA: mean 44.9 years; 56.4% (84/149) female EVLA: mean 45.9 years; 52.2% (73/139)
Patient selection criteria	Inclusion criteria: Patients had a GSV exceeding 5.5 mm in diameter or an SSV exceeding 4 mm in diameter 2 cm below the saphenofemoral or saphenopopliteal junctions in standing position, combined with reflux exceeding 0.5 seconds, according to the ESVS guideline. Exclusion criteria: Patients were under the age of 18 years, with obstruction in the deep venous system, had previously used another invasive treatment method (thermal and chemical ablation, or surgery), with cardiac and renal failure, immobile or had secondary varicose veins, hypercoagulability status, and local or systemic infection.
Technique	Endovenous ablation was done on patients using the VariClose Vein Sealing System (Biolas, FG Group, Turkey). The 4F delivery catheter was positioned 3 cm distal to the SFJ or SPJ. The delivery catheter was adjusted for the injection of 0.03 ml of CAC per cm. No simultaneous phlebectomy was done on any patients either during the procedure or during subsequent follow up. However, foam sclerotherapy of varicose tributaries was done in 18 patients from all groups.
Follow up	**2 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at 2 days, and 1, 6, 12 and 24 months. The proportions of patients lost to follow up were 4% (7/168) in the CAC group, 14.8% (26/149) in the RFA group and 20.5% (36/139) in the EVLA group during a 2-year follow up. The reasons for lost to follow up were categorised as ‘moved to another city’ and ‘no reason’.

Study design issues: Randomised clinical trial. Patients were blindly assigned into N-butyl cyanoacrylate (CAC), RFA, and EVLA groups using block randomisation with sealed envelopes. A radiologist in a blinded manner did DUS and assessed whether or not incompetence was present in the saphenous vein, perforator veins or deep veins. This study compared early and 2-year results for CAC, RFA, and EVLA in terms of effectiveness and side effects in treating varicose veins, with the primary outcome being the ablation rates and the secondary outcome being incidence of complication and patient satisfaction. Pain experienced during the procedure was measured as none (0), mild pain (1), moderate pain (2) or severe pain (3). Per-protocol analysis was used. The operator’s training and experience of the procedure was not described.

Study population issues: There was no statistically significant difference between the groups in terms of sex, age, the leg scheduled for the procedure, the vein involved CEAP classification, vein diameter, depth beneath the skin and vein length at baseline. More than half of the patients in all groups had C3 disease.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **456 (168 CAC, 149 RFA and 139 EVLA)**

Procedure characteristics

Characteristics	CAC	RFA	EVLA	P
Vessels undergoing procedures				**0.003**[*]
GSV, % (n)	94.6 (159)	98.0 (146)	88.5 (123)	
SSV, % (n)	5.4 (9)	2.0 (3)	11.5 (16)	
Duration of procedure, minutes (mean±SD)	15.3±2.6	27.3±7.7	35.0±5.2	**0.000**[**]

[*]The variation derived from EVLA group

[**]In all group

Occlusion rates, %

Occlusion rates	CAC	RFA	EVLA	P
6 months	98.1	94.1	95.1	0.14
1 year	94.7	92.5	94.2	0.72
2 years	92.6	90.9	91.5	0.89

The **occlusion rates** in the CAC group presented a statistically significant difference between 6 months and 2 years (p<0.005).

Recanalisation:

- No recanalisation in patients having procedures to the SSV.
- All recanalisation occurred in the GSV.

Foam sclerotherapy of varicose tributaries: n=18 from all groups, without difference between the groups.

Mean VCSS, p<0.001

Mean scores	CAC	RFA	EVLA
Preprocedural VCSS	7.6	7.7	7.8
6 months	4.1	4.8	4.6
1 year	3	3.8	3.6
2 years	2.7	3.7	3.5

Intergroup comparisons - VCSS values in the CAC group were statistically significantly lower at 6 months and 2 years than in the other groups (p<0.001), while values differed between all 3 groups 1 year after the procedure.

Within groups - VCSS decreased in all groups following the procedure and that these decreased were statistically significant apart from those between years 1 and 2 (p<0.001).

Safety

Complications seen, % (n)

Complications	CAC	RFA	EVLA	P
Pain				**0.000**[a]
No pain	61.3	0	0	
Mild pain	31.0	50.3	47.5	
Moderate pain	7.7	35.6	43.9	
Severe pain	0	14.1	8.6	
Ecchymosis	5.4 (9)	18.1 (27)	4.3 (6)	**<0.001**[b]
DVT	0	0.7 (1)	0	0.36[c]
Bleeding	0	1.3 (2)	0	0.13[c]
phlebitis	6.5 (11)	12.8 (19)	9.3 (13)	0.17

[a]There was a statistically significant difference in pain sensation between the CAC and RFA groups, and between the CAC and EVLA groups.

[b]Statistically significant difference was found between the CAC and RFA groups (p<0.001) and between the RFA and EVLA groups (p<0.001).

[c]The chi-square test does not apply.

Number of analgesics used daily, % (n)

No. of analgesics used daily	CAC	RFA	EVLA	P
1	37.5 (63)	34.2 (51)	24.5 (34)	0.147
2	48.2 (81)	47.7 (71)	56.1 (78)	
3 or more	14.3 (24)	18.1 (27)	19.4 (27)	

Days of return to work, % (n)

Days of return to work	CAC	RFA	EVLA	p
1	95.8 (161)	50.3 (75)	75.5 (105)	**0.000**[***]
2	4.2 (7)	35.6 (53)	17.3 (24)	
3[****]	0	13.4 (20)	7.2 (10)	
4 or later [****]	0	0.7 (1)	0	

[***]All groups differed statistically significantly.

[****]Columns 3 and 4 were combined for the statistical analysis to be valid.

Abbreviations used: CAC, cyanoacrylate closure; EVLA, endovenous laser ablation; GSV, great saphenous vein; RFA, radiofrequency ablation; SSV, small saphenous vein; VCSS, evolution of the venous clinical severity score.

Study 5 Koramaz I (2016)

Details

Study type	**Non-randomised comparative study**
Country	Turkey
Recruitment period	2013 to 2014
Study population and number	**n=339 (150 CAC versus 189 EVLA)** Patients with incompetent great saphenous veins
Age and sex	CAC: Mean 45.09 years; 50.7% [76/150] female EVLA: Mean 47.08 years; 49.7% [94/189] female
Patient selection criteria	Inclusion criteria: Age ≥20 years and ≤70 years; vein diameter at the GSV ≥5.5 mm and ≤15 mm; reflux in GSV >0.5 seconds; CEAP classification between C2 and C5; patients attended the follow up examinations and were sufficiently mentally healthy to consent to the operation. Exclusion criteria: Tortuous GSV; symptomatic peripheral arterial disease history or an ABI <0.9; history of DVT or PE; life expectancy <2 years; active thrombophlebitis in the deep or superficial veins; significant femoral or popliteal venous insufficiency and perforator vein insufficiency; known sensitivity to cyanoacrylate adhesives; aneurysm >15 mm in the target vein; previously treated GSV; existence of malignant disease; pregnancy; and immobilisation.
Technique	CAC treatment used VariClose Vein Sealing System; Biolas, Ankara, Turkey. The 4F delivery catheter was positioned 3 cm distal to the SFJ. The VariClose delivery system was set up for the injection of 0.03 ml of n-butyl cyanoacrylate per centimetre. The remaining refluxing tributaries were treated with microphlebectomy at the same session. There was no concurrent treatment of the small saphenous vein or anterior accessory saphenous vein.
Follow up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up immediately after the treatment and then at 1 week, 6 months and 1 year.

Study design issues: Retrospective, comparative study of 339 patients having treatment for incompetent GSVs, including 150 patients having treatment with CAC ablation and 189 patients with 1470 nm EVLA. This study compared both anatomic and clinical results of CAC with EVLA at 12-month follow up. Lack of experience or learning curve of the procedure was discussed as 1 patient in the VVSS group experienced a partial recanalisation at the SFJ level in the 1st week after the procedure and this patient was the second patient to have the procedure.

Skin burn was defined as reddening of the skin area involving 20% or more of the treated part or blistered skin involving 20% or less of the treated area. No pain was regarded as having tolerable pain but needing no additional analgesics, and having pain was referred to requiring additional analgesics or topical cooling or affecting patient's activities of daily life. Having bruising was defined as specific colour or darker bruising involving 20% or more of the treated area or markedly dark bruising involving 20% or less of the treated areas. Procedural success was defined as complete occlusion of the treated vein segment or a partial recanalisation of <5 cm. Clinical recovery was assessed by comparing the VCSS values before and after the procedures.

Study population issues: There was no statistically significant difference between the 2 groups in terms of age, gender, CEAP class, VCSS and GSV diameter at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **339 (150 CAC versus 189 EVLA)**

Procedure characteristics

Characteristics	CAC	EVLA	P*
GSV diameter, mm (mean±SD)	6.88±1.80	7.15±1.77	0.065
Length of the ablated GVS, cm (mean±SD)	31.97±6.84	31.64±6.26	0.974
Procedure duration, minutes (median, range)	7 (4 to 11)	18 (14 to 25)	**<0.001**

*Mann-Whitney U test

Recanalisation

Recanalisation	CAC, n	EVLA, n
Partial recanalisation >5 cm at the SFJ level		
Within the first week	1	2
Partial recanalisation >5 cm at the mid-GSV level		
6 months	1	1
Total recanalisation		
6 months	0	2

Occlusion rates at 12 months: 98.7% (148/150) in the VVSS and 97.4% (184/189) in the EVLA group (p=0.659)

VCSS values

VCSS scores	CAC	EVLA	P*
Pretreatment VCSS, (mean±SD)	7.53±1.03	7.73±1.58	0.493
Posttreatment VCSS, (mean±SD)	2.79±1.05	2.83±1.21	0.882
P**	<0.001	<0.001	

*Mann-Whitney U test

**Wilcoxon signed rank test

Safety

Complications

Complications	CAC, % (n)	EVLA, % (n)	P
Pain (first week)	4.7 (7)[a]	9.0 (17)	0.123[b]
Burns	-	2.1 (4)	0.133[c]
Pigmentation	-	5.9 (11)	**0.002**[c]
Bruising	-	2.6 (5)	0.069[c]
Paraesthesia	-	1.6 (3)	0.258[c]
Phlebitis	2.1 (3)[d]	7.9 (15)	**0.015**[c]
DVT	-	1.6 (3)	0.258[c]

[a]Postoperative pain was seen at the SFJ or entry levels during the first 3 days.

[b]Chi-square test

[c]Fisher exact test

[d]The patients with phlebitis fully recovered after an average of 4 days (3 to 5 days).

Abbreviations used: CAC, n-butyl cyanoacrylate; EVLA, Endovenous laser ablation; GSV, great saphenous vein; SFJ, sapheno-femoral junction; VCSS, Venous Clinical Severity Score.

Study 6 Bozkurt AK (2016)

Details

Study type	**Non-randomised comparative study**
Country	Turkey
Recruitment period	2013 to 2014
Study population and number	**n=310 (154 CAC versus 156 EVLA)** Patients with incompetent great saphenous veins
Age and sex	CAC: Mean 42.5 years; 51.3% (79/154) female EVLA: Mean 40.2 years; 50.6% (79/156) female
Patient selection criteria	Inclusion criteria: Primary varicosities with C2 to C4b patients (clinical, etiological, anatomical and pathophysiological classification [CEAP]) and a sapheno-femoral junction (SFJ) incompetence and GSV reflux lasting longer than 0.5 seconds on duplex scanning. Exclusion criteria: A history of deep vein thrombosis, reflux of femoral vein going beyond the knee, hemodynamically significant reflex of the short saphenous or great saphenous anterior accessory vein, congenital vasculopathies, thrombophilia, severe systemic disease, pregnancy, breast feeding, noncompliant patients for follow up, and GSV diameter >15 mm.
Technique	CAC procedure used the VariClose Vein Sealing System (Biolas, Ankara, Turkey). The 4F catheter tip was positioned 3 cm distal to the SFJ, and 0.03 cc of polymer was given in every centimetre. All procedures were done under local anaesthesia using standard sterile technique. Miniphlebectomy or foam for residual side branches was done on 24% (37/154) of patients in CAC group and on 21.2% (33/156) in EVLA group after 3 months.
Follow up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at day 3 and then months 1, 6 and 12. Losses to follow up at months 1, 6 and 12 months was 1, 8, and 3 patients in CAC group and 1, 10 and 4 in EVLA group respectively.

Study design issues: This prospective, independent study compared the safety and efficacy of CAC with EVLA for the treatment of venous insufficiency. The primary endpoint of the study was complete occlusion of the target GSV defined as Doppler ultrasound examination but not confirmed by an independent ultrasound core laboratory. Any open segment over 5 cm was considered as a recanalised GSV or treatment failure. The secondary endpoints were procedure time, procedural pain, ecchymosis at day 3, changes from baseline in VCSS and AVVQ scores, and all adverse events. The screened patients were alternatively allocated to CAC or EVLA procedure in 2 vascular units. The operator(s) training and experience of the procedure was not discussed.

The procedural pain was rated on a numeric visual analogue scale of 0 (no pain) to 10 (extreme pain). Ecchymosis was confirmed 72 hours after the operation (0, none; 1, involving up to 25% of the treated segment; 2, involving up to 50% of the treated segment; 3, involving up to 75% of the treated segment; and 4, involving all of the treated segment).

Study population issues: The demographic information was comparable between the 2 treatment groups in terms of age, sex, treated vein segments, disease stage by CEAP classification), with no statistically significant differences at baseline. The mean GSV diameter was 7.2 cm in CAC group and 7.1 cm in EVLA group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **310 (154 CAC versus 156 EVLA)**

Procedure characteristics

Characteristics	CAC	EVLA	P
Length of treated segment, cm (mean±SD)	29.8±5.4	29.7±8.1	0.176
Procedure duration, minutes (mean±SD)	15±2.5	33.2±5.7	.001
Miniphlebectomy or foam*, % (n)	24 (37)	21.2 (33)	0.545

*Residual side branch treatment after 3 months

Closure rates, % (n)

Closure rates	CAC (n=154)	EVLA (n=156)	P
Closure – 3rd day			0.184
Total	100 (154)	97.4 (152)	
Partial	0	0.6 (1)	
Recanalisation	0	1.9 (3)	
Closure – 1st month			**0.001**
Total	96.7 (148)	87.1 (135)	
Partial	2 (3)	2.6 (4)	
Recanalisation	1.3 (2)	10.3 (16)	
Closure – 6th month			0.127
Total	96.6 (141)	91.7 (133)	
Partial	2.1 (3)	2.8 (4)	
Recanalisation	1.4 (2)	5.5 (8)	
Closure – 12th month			0.318
Total	95.8 (136)	92.2 (130)	
Partial	2.1 (3)	2.8 (4)	
Recanalisation	2.1 (3)	5 (7)	

Post procedure clinical assessment, mean±SD (n)

Symptom scores and QoL	CAC (n=154)	EVLA (n=156)	P
VCSS			0.997**
Preintervention	5.7±2.3 (154)	5.7±1.2 (156)	
1st month	2.4±0.9 (153)	2.2±0.7 (155)	
6th month	1.3±0.9 (145)	1.2±0.6 (145)	
12th month	0.6±0.7 (142)	0.7±0.5 (141)	
AVVQ			0.062**
Preintervention	18.1±5 (154)	18.8±4.6 (156)	
1st month	7.5±2.1 (153)	7.9±2 (155)	
6th month	4.6±1.4(145)	4.9±1.3 (145)	
12th month	4.6±1.4 (142)	4.9±1.3 (141)	

Safety

Complications

Complications	CAC (n=154)	EVLA (n=156)	P
Pain during procedure, mean±SD	3.1±1.6	6.5±2.3	**<0.001**
Phlebitis, % (n)	4.5 (7)	7.7 (12)	0.248
Ecchymosis			**<0.001**
None, % (n)	85.7 (132)	53.2 (83)	
<25%, % (n)	12.3 (19)	30.1 (47)	
25% to 50%, % (n)	1.3 (2)	12.8 (20)	
50% to 75%, % (n)	0.6 (1)	3.2 (5)	
>75%, % (n)	0	0.6 (1)	
Pigmentation[a], % (n)	1.3 (2)	1.9 (3)	1
Paraesthesia			
Total, % (n)	0	4.5 (7)	**0.015**
Temporary, % (n)	0	3.2 (5)	0.061
Permanent, % (n)	0	1.3 (2)	0.498

[a]All decreased statistically significantly, becoming almost invisible over the 1-year follow up.

p value of repeated measured analysis of variance. Both groups had statistically **significant decrease (improvement) in VCSS and AVVQ scores postoperatively (**p<0.001**), however, there was no statistically significant difference in VCSS and AVVQ scores between the groups at 1st, 6th and 12th month (p>0.05).	
Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; CAC, cyanoacrylate closure; EVLA, endovenous laser ablation; SD, standard deviation; VCSS, venous clinical severity score.	

Study 7 Ovali C (2019)

Details

Study type	**Non-randomised comparative study**
Country	Turkey (single centre)
Recruitment period	2013 to 2016
Study population and number	**N=244 (116 CAC versus 128 RFA)** Patients with incompetent GSVs
Age and sex	CAC: Mean 49.21 years; 58.6% (68/116) female RFA: Mean 46.30 years; 57.0% (73/128) female
Patient selection criteria	Inclusion criteria: patient were aged between 21 years and 70 years with symptomatic varicose veins, had a CEAP classification of C2 to C4b, a GSV diameter at the SFJ while standing of between 5.5 mm and 14 mm, an insufficiency 2 cm distal to the SFJ, reflux in the GSV of 0.5 seconds or greater as determined by CEUS examination, the presence of insufficiency only in vena saphena magna and its branches, ability to walk unassisted, ability to attend follow-up examinations, and mentally competent to approve procedure. Exclusion criteria: patients had a deep venous thrombosis, arteriovenous malformation, severe immobility, severe tortuosity in the VSM, moderate to severe deep venous insufficiency, a VSM dilated at and over 14 mm, presence of old and incipient severe thrombophlebitis, and an inability to follow up despite the surgery, a history of intervention on the GSV to be treated, a duplicate or accessory GSV with venous insufficiency, and those who were pregnant were also excluded.
Technique	CAC was done using VenaBlock (Invamed, Ankara, Turkey; 6F per 90 cm). The CAC patients received local anaesthesia with 2 to 5 ml of lidocaine. The catheter was advanced to about 3 cm distal of the SFJ and 0.03 ml of CA was applied every centimetre. If any unoccluded segment was seen, the procedure was repeated through a separate access point. All patients had treatment with elastic bandages after the procedure and the bandages were opened 2 hours later. No additional procedures such as miniphlebectomy or sclerotherapy were done.
Follow up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at day 3 and then months 1, 3, 6 and 12 after the operation. Losses to follow up was 30 (4 patients at the 3rd month, 13 at the 6th month, and 13 at 12th month), which resulted in 214 complete follow ups at 1 year after the procedure.

Study design issues: This independent retrospective cohort study compared the clinical results of n-butyl-cyanoacrylate embolisation system and RFA. CAC or RFA methods assigned according to patient choice. Both treatments presented by the same physician, without prescreening by another physician, by using exactly same standard descriptions. The operator(s) training and experience of the procedure was not discussed. Adequate sample size determined by a statistical noninferiority (z-test) that resulted in 200 patients total (100 patients per group). Treatment success was defined as compete vein occlusion. Any patency or recanalisation, reflux or open segment >5 cm in length was considered a failure.

Study population issues: There was no statistically significant difference between patients having treatment with RFA or CAC in terms of demographic and clinical features such as age, gender, right/left VSM insufficiency and CEAP classification at baseline. The mean duration of symptoms was 9 years to 10 years and was similar in both groups (p=0.058). Other conditions were noted in patient's history, including rheumatoid arthritis (n=1), psoriatic arthritis (n=3), psoriasis (n=5), malignancy (n=1), hypertension (n=19), and diabetes (n=13), however, it was unclear which group(s) these conditions belonged to. Of the 141 women, 72% (101/141) gave birth between 1 and 6 times.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **244 (CAC n=116 versus RFA n=128)**

Procedure characteristics

Characteristics	CAC	RFA	P
VSM proximal diameter, mm (mean±SD)	7.0±4.23	7.2±2.31	
Treated VSM length, cm (mean±SD)	45±4.33	47.2±8.61	
Procedure duration, minutes (mean±SD)	19.60±7.88	44.80±8.12	0.023

Postoperative outcomes

Outcomes	CAC	RFA	P
Duration of discharge, hours (mean±SD)	5±2.5	45±5.9	0.001
Occlusion in postoperative CDUS VSM, n	116	128	
12-month CDUS recanalisation and reflux, n	1	5	

Means and overall comparisons for survival time**

			95% CI	
	Estimate	SE	Lower bound	Upper bound
CAC	11.971	0.029	11.916	12.027
RFA	11.895	0.049	11.783	12.007
Overall	11.932	0.033	11.867	11.996
Overall comparisons		X^2	Dif	Sig
Log-rank (Mantel-Cox)		3.229	1	0.072

**Estimation is limited to the largest survival time if it is censored.

Kaplan-Meier survival analysis showed that the overall clinical recurrence-free rates after a mean follow up of 11.9 months were 99.5% for CAC and 96.6% for RFA. The standard error of the survival curve point estimates was below 0.05 at all times. The overall mean survival time was 11.932 (95%CI, 11.867 to 11.996). Log-rank testing revealed no statistically significant different between the 2 groups (p=0.072).

Clinical assessment, mean±SD

Symptom scores and QoL	CAC	RFA	P
VCSS			
Preoperative	5.75±1.23	5.79±1.19	0.910*
Postoperative at 12 months	1.03±0.96	1.11±0.94	0.921*
AVVQ			
Preoperative	17.43±6.38	18.21±6.93	0.655*
Postoperative at 12 months	4.93±1.56	5.13±1.49	0.752*

*Pearson exact X^2

Safety

Complications, % (n)

Complications	CAC	RFA	P
DVT	0	0	-
Skin burn	0	0.8 (1)	0.339[a]
Thrombophlebitis	1.7 (2)	3.1 (4)	0.685[a]
Cellulite	1.7 (2)	2.3 (3)	0.998[a]
Paraesthesia	0	2.3 (3)	0.240[a]
Urinary retention	0	2.3 (3)	0.240[a]

[a]Fisher's Exact X^2

Side effects, % (n)

Side effects	CAC	RFA	P
Severe pain	4.3 (5)	12.5 (16)	**0.042**[a]
Ecchymosis	10.3 (12)	20.3 (26)	**0.044**[b]
Sensitivity	12.1 (14)	21.9 (28)	**0.038**[b]
Induration	3.5 (4)	5.5 (7)	0.645[b]
Oedema	0.9 (1)	2.3 (3)	0.360[a]
Pigmentation increase[c]	1.7 (2)	3.1 (4)	0.685[a]
Hematoma	0	0.8 (1)	0.339[a]

[b]Pearson X^2 test

[c]A pigmentation increase occurred at superficial small parts close to the entry point.

Abbreviations used: CAC, cyanoacrylate closure; CI, confidence interval; CDUS, colour doppler ultrasound; DVT, deep venous thrombosis; QoL, quality of life; RFA, radiofrequency ablation; SD, standard deviation; VSM, vena saphena magna.

Study 8 Sarac A (2019)

Details

Study type	**Case series**
Country	Turkey (single centre)
Recruitment period	2015 to 2018
Study population and number	**n=573** Patients with incompetent great saphenous veins
Age and sex	Mean 44.7 years; 76% (436/538) female
Patient selection criteria	Inclusion criteria: patients aged 21 years to 70 years with symptomatic moderate to severe varicosities (C2 to C6 patients CEAP classification), GSV reflux lasting longer than 0.5 seconds with GSV diameter ≥5.5 mm and ≤2 mm assessed in the standing position, ability to walk unassisted, ability to come to follow-up examinations, and mentally healthy to approve procedure. Exclusion criteria: Patients had a history of deep-vein thrombosis or pulmonary embolism, reflux of the femoral vein going beyond the knee, hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, symptomatic peripheral arterial disease, or GSV >20 mm, their life expectancy <1 year, had cancer, and those who were pregnant or immobilisation.
Technique	The VenaBlock Venous Closure System (Invamed, Ankara, Turkey) was used, consisting of a proprietary formula of CAC with dimethyl sulfoxide and a dispensing system. This formula of CAC finishes initial polymerisation reaction in 5 seconds and system has a guiding light at the tip of the catheter to visually show where to put pressure on immediately in order to catch up with the fast polymerisation time. All procedures were done under local anaesthesia with standard sterile technique. The catheter was advanced through the GSV and placed 3 cm away from the SFJ. In vein segments ≤10 mm, 0.03 ml of CAC was applied on every centimetre, whereas in vein segments over 10 mm, double amount (0.06 ml) was applied. if there was any un-occluded segment, the procedure was repeated through separate access by needle with direct injection. No phlebectomy or sclerotherapy was done in the same session of CAC.
Follow up	**2 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at day 3 and then at 1, 6, 12, 18 and 24 months after the procedure. Losses to follow up was 117 patients for 24 months, resulting in 450 patients' data followed up for 24 months.

Study design issues: This prospective study assessed the safety and efficacy of the new VenaBlock CAC of the GSV. The operator(s) training and experience of the procedure was not reported. Treatment success was defined as complete occlusion of the treated GSV. Any patency or recanalisation, reflux, or open segment >5 cm in length was considered a failure.

Study population issues: At baseline, by the CEAP classification, 27% (156/538) of patients were C2, 54% (310) were C3, 8% (46/538) were C4, 6% (37/538) were C5 and 4% (24/538) were C6. The mean (±SD) preprocedural VCSS was 5.8±1.0 (range 4 to 8) and the mean (±SD) preprocedural diameter of GSV at the SFJ in the standing position was 11.7 mm ±3.4 mm (range 5.50 mm to 16 mm) with a mean reflux of 2.3 seconds ±0.9 seconds (range 1 second to 5 seconds).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **538**

Procedural characteristics

Characteristics	mean±SD	Range
Length of treated segment (cm)	30.6±5.3	10 to 45
CAC delivered (ml)*	1.2±0.3	0.4 to 2
Procedure duration (minutes)	10.8±4.7	4 to 35

*It is dependent on treated vein length and diameter.

The GSV was accessed in 55% of the patients above the knee and 45% above the knee level.

Closure rates

Closure rates	% (n)
Closure – 3rd day	**573**
Total	100 (573)
Partial	0
Recanalisation	0
Closure – 1st month	**570**
Total	100 (570)
Partial	0
Recanalisation	0
Closure – 6th month	**536**
Total	99.8 (535)
Partial	0.2 (1)
Recanalisation	0
Closure – 12th month	**511**
Total	99.4 (508)
Partial	0.6 (3)
Recanalisation	0
Closure – 18th month	**488**
Total	99 (483)
Partial	1 (5)
Recanalisation	0
Closure – 24th month	**456**
Total	98.7 (450)
Partial	1.3 (6)
Recanalisation	0

Kaplan-Meier analysis showed that the overall clinical recurrence-free rate after a mean follow up of 23.96 months was 99.38%. The standard error of the survival curve point estimate was below 0.05. Overall mean survival time (95% CI) was (23.92 to 23.99).

Safety

Complications

Complications	mean±SD	%, (n)
Pain during procedure	2.8±1.2	
Ecchymosis		1.4 (8)
Phlebitis		1.8 (10)

Clinical assessment

Symptom scores and QoL	mean±SD (n)
VCSS	
Preoperation	5.8±1.0 (573)
1st month	3.1±0.9 (570)
6th month	1.6±0.8 (535)
12th month	0.9±0.7 (508)
18th month	0.6±0.7 (483)
24th month	0.6±0.6 (450)
AVVQ	
Preoperation	19.7±6.4 (573)
1st month	8.3±3.3 (570)
6th month	5.1±1.9 (535)
12th month	5.0±1.7 (508)
18th month	4.7±1.3 (483)
24th month	4.4±1.1 (450)

Both mean VCSS and AVVQ scores statistically significantly improved at 24 months compared with preintervetion, ($p<0.0001$).

Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; CI, confidence interval; GSV, great saphenous vein; QoL, quality of life; SD, standard deviation; VCSS, venous clinical severity score.

Study 9 Yavuz T (2018)

Details

Study type	**Case series**
Country	Turkey (single centre)
Recruitment period	2016
Study population and number	**N=538** Patients with great saphenous vein incompetency
Age and sex	Mean 44.6 years: 67% (360/507) female
Patient selection criteria	Inclusion criteria: Patients aged 21 year to 70 years with symptomatic moderate to severe varicosities (C2 to C4b patients CEAP classification) and GSV reflux lasting longer than 0.5 seconds with GSV diameter ≥5.5 mm and ≤15 mm assessed in the standing position, ability to walk unassisted, ability to come to follow-up examinations, and mentally healthy to approve procedure. Exclusion criteria: Patients had a history of deep vein thrombosis or pulmonary embolism, reflux of the femoral vein going beyond the knee (high degree of deep vein insufficiency), hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, symptomatic peripheral arterial disease, or GSV >15 mm, their life expectancy <1 year, had cancer, and those who were pregnant or immobilisation.
Technique	n-butyl-2-cyanoacrylate-based treatment used VenaBlock Venous Closure System (Invamed, Ankara, Turkey). All procedures were done under local anaesthesia with standard sterile technique and 0.03 ml of CAC was applied on every centimetre. if there was any un-occluded segment, the procedure was repeated through separate access. No phlebectomy or sclerotherapy was done in the same session of CAC.
Follow up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at day 3 and then months 1, 6 and 12. Thirty-one patients were lost to follow up (11 patients at the 1st month and 20 at the 6th month).

Study design issues: This retrospective study assessed the safety and efficacy of the new VenaBlock CAC of the GSV. Procedural pain was assessed using a scale of 0 (no pain) to 10 (extreme pain). Quality of life survey was completed based on Turkish translated and non-validated version of AVVQ. Treatment success was defined as complete occlusion of the treated GSV. Any patency or recanalisation, reflux, or open segment >5 cm in length was considered a failure. The operator(s) training and experience of the procedure was not described.

Study population issues: at baseline, by the CEAP classification, 33% (176/507) of patients were C2, 63% (339/507) were C3, and 4% (23/507) were C4. The mean preprocedural VCSS was 5.4±0.9 (range 4 to 8) and the mean preprocedural diameter of GSV at the SFJ in the standing position was 6.7 mm ±1.7 mm (range 5.5 mm to 14.6 mm) with a mean reflux of 1.9 seconds ±0.8 seconds (range 1 second to 5 seconds).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **538**

Procedural characteristics

Characteristics	mean±SD	Range
Length of treated segment (cm)	25.69±4.88	10 to 43
n-butyl cyanoacrylate delivered (ml)*	0.87±0.15	0.4 to 1.39
Procedure duration (minutes)	11.75±4.97	5 to 33

*It is dependent on treated vein length.

The GSV was accessed in 52% of the patients above the knee and 48% above the knee level.

Closure rates

Closure rates	% (n)
Closure – 3rd day	**538**
Total	100 (538)
Partial	0
Recanalisation	0
Closure – 1st month	**527**
Total	99.6 (525)
Partial	0.4 (2)
Recanalisation	0
Closure – 6th month	**507**
Total	99.6 (505)
Partial	0.4 (2)
Recanalisation	0
Closure – 12th month	**507**
Total	99.4 (504)
Partial	0.4 (2)
Recanalisation	0.2 (1)

Kaplan-Meier analysis yielded an occlusion rate of 99.4% at the 12-month follow up.

Clinical assessment

Symptom scores and QoL	mean±SD (n)
VCSS	
Preoperation	5.43±0.87 (538)
1st month	2.43±0.75 (527)
6th month	1.03±0.96 (507)
12th month	0.60±0.75 (507)
AVVQ	
Preoperation	18.32±5.24 (538)

Safety

Complications

Complications	mean±SD	%, (n)
Pain during procedure	2.19±0.94	
Burning sensation		70 (378)
Ecchymosis[a]		0.9 (5)
Phlebitis		1.1 (6)

[a]This ecchymosis was related to applying CAC to the entry point at the end of the procedure. Therefore, injection was terminated 2 cm before and from the entry point with help from the guide light for the rest of the patients. No ecchymosis was seen after this procedural change.

1st month	7.12±2.38 (527)	
6th month	4.63±1.46 (507)	
12th month	4.61±1.42 (507)	
Both mean VCSS and AVVQ scores statistically significantly improved at 12 months compared with preintervention (p<0.0001).		
Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; QoL, quality of life; SD, standard deviation; VCSS, venous clinical severity score.		

Study 10 Park I (2019)

Details

Study type	**Case series**
Country	Korea (single centre)
Recruitment period	2016 to 2017
Study population and number	**n=160 (271 incompetent saphenous veins [201 GSV and 70 SSV])** Patients with incompetent saphenous veins
Age and sex	Mean 44.3 years; 64.4% (103/160) female
Patient selection criteria	Inclusion criteria: All veins targeted for treatment needed to show at least 0.5 seconds of reflux in the standing position and have a diameter of at least 3 mm. The preoperative CEAP classification ranged from C1 to C4.
Technique	Cyanoacrylate closure was done on patients using the VenaSeal system (Medtronic, USA). Patients received local anaesthesia. With ultrasound guidance, the catheter was often positioned 5.0 cm distal to the SFJ or SPJ. The saphenous vein was compressed by the ultrasound probe with the left hand 2 cm proximal to the delivery catheter tip. Two injections of about 0.10 ml each of cyanoacrylate glue were administered 1 cm apart at this location, followed by a 3-minute period of local compression with the right hand and then a single injection and 30-second compression were done every 3 cm moving distally. Concomitant procedures (miniphlebectomy and sclerotherapy) were done after the CAC procedure.
Follow up	**1 month**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at 6 hours, 1 day, 10 days, and 1 month after the procedure.

Study design issues: This prospective observational study was to investigate the clinical features of phlebitis-like abnormal reaction (PLAR) after the CAC treatment and to report its management. PLAR was defined as any unusual skin condition that develops suddenly, such as erythema, itching, swelling, and pain/tenderness, over the treated veins several days after CAC. The operator's training and experience of the procedure was not described.

Study population issues: Of the 160 patients, 69 were treated with 1 vein, 74 treated with 2 veins, 14 treated with 3 veins and 3 treated with 4 veins. In terms of the CEAP classification, there were 19 patients in C1 group, 116 in C2 group, 19 in C3 group, and 6 in C4 group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **160 (201 GSV and 70 SSV)**

Procedure characteristics

Characteristics	% or mean±SD (range)
Length of treated vein, cm	
GSV	44.9±10.4 (10.0 to 70.0)
SSV	17.5±5.3 (5.0 to 30.0)
Glue injection count	
GSV	16.6±4.1 (5 to 30)
SSV	8.3±2.4 (4 to 14)
GSV with suprafascial length >10 cm, % (n)	29.4 (59)
Maximum diameter of treated veins, mm	
All	8.3±4.0 (3.1 to 28.4)
GSV	8.3±4.4 (3.3 to 28.4)
SSV	8.7±2.9 (3.1 to 15.9)

Safety

Comparison of treated veins with versus without PLAR

Characteristics	No PLAR (n=202)	PLAR (n=69)	P
GSV length, cm, mean±SD (range)	45.8±9.5 (14 to 70)	43.4±11.9 (10 to 70)	0.122
Female, n	134	52	0.163
Male, n	6/8	17	
Suprafascial GSV, n	32	27	**0.001**
Subfascial GSV, n	109	33	
GSV, n	137	64	**<0.001**
SSV, n	65	5	

The **mean time of occurring PLAR** was 13.6 days ± 4.6 days after the procedure. PLAR was treated by NSAIDS and/or antihistamine for 5 days to 14 days.

PLAR occurred bilaterally in patients in whom the GSV was treated in both the legs:

- Of the 68 patients having treatment with bilateral GSV, PLAR occurred in 27 patients.
- Of the 27 patients with PLAR, 14.8% (4/27) had unilateral PLAR and 85.2% (23/27) developed bilateral PLAR

Accompanying symptoms in the 69 treated saphenous veins with PLAR:

- Erythema: 92.2%
- Itching: 91.2%
- Swelling: 66.2%
- Pain/tenderness: 48.5%

Hives occurred in 4 patients who had no history of allergies at day 1 to day 3 after PLAR in treated areas, and in 2 of the cases, it involves the upper trunk and scalp areas.

Comparison of pain score (0 to 10) between the PLAR and no PLAR groups

Assessment time	PLAR	No PLAR	P
6 hours	1.67±1.47 (0 to 6)	1.53±1.55 (0 to 8)	0.603
1 day	1.15±1.23 (0 to 5)	0.86±1.06 (0 to 5)	0.134
10 days	1.54±2.07 (0 to 7)	0.41±0.89 (0 to 4)	**<0.001**
1 month	0.26±0.70 (0 to 3)	0.29±0.94 (0 to 5)	0.891

On day 10, the **mean pain score** (2.3±2.3) decreased statistically significantly after the administration of antihistamine (0.6±1.2, p=0.006).

Abbreviations used: GSV, great saphenous veins; NSAIDs, nonsteroidal anti-inflammatory drugs; PLAR, phlebitis-like abnormal reaction; SD, standard deviation; SSV, small saphenous veins.

Study 11 Gibson K (2017)

Details

Study type	**Case series (WAVES)**
Country	US (single centre)
Recruitment period	2015
Study population and number	n=50 (70 target veins) Patients with symptomatic GSV, SSV, and/or accessory saphenous veins incompetence
Age and sex	Mean 49.5 years; 70% (35/50) female
Patient selection criteria	Inclusion criteria: Patients were between 18 years and 80 years with symptomatic varicose veins CEAP clarification C2 to C5, and incompetence of GSV, SSV, and/or ASV. The veins targeted for treatment needed to show at least 0.5 seconds of reflux, measure at least 4 mm but no more than 20 mm in diameter, and contain a refluxing segment of at least 10 cm in length. Treatment of below knee saphenous segments was allowed. Exclusion criteria: Patients were excluded if they were pregnant or breastfeeding, had a history of previous deep venous thrombosis, a current history of active superficial thrombophlebitis in the limb to be treated, previous treatment of target veins, or veins too tortuous to allow passage of the CAC device.
Technique	The CAC technique was done using VenaSeal Closure System (Medtronic Minneapolis, MN, USA). the first adhesive injection was placed 5 cm caudal to the SFJ or SPJ, with ultrasound probe compression held 2 cm above the catheter for 3 minutes. Addition adhesive volume (more than 0.1 cc) was permitted in larger diameters of veins. Women of child-bearing potential had preprocedure pregnancy tests. No concomitant procedures such as microphlebectomy or sclerotherapy were allowed.
Follow up	**1 month**
Conflict of interest/source of funding	This study was an investigator-initiated study funded in part by a research grant from Medtronic, Santa Rosa, CA. The first author was the Principal Investigator on the study and receives fees as a consultant for Medtronic who, in part, funded this study.

Analysis

Follow-up issues: Patients were followed up at 1 week and 1-month postprocedure.

Study design issues: This single-centre, multi-investigator, single-arm prospective study investigated the use of CAC in a cohort with symptomatic venous reflux disease in the GSV, SSV and/or accessory saphenous veins (ASV). All investigators were experienced with endovascular ablation therapies and had training as needed in the US by the manufacturer for physician use of CAC. Of the 5 investigators, 3 were investigators in the VeClose study and had previous experience with the treatment device, and 2 of the investigators were first-time users. After the procedure, the patient rated pain during the procedure in the treated limb using a 10-point numerical pain rating scale. ‘‘Normal activities’’ was defined as a return to a full and usual exercise and leisure activity routine. A phlebitis classification schema was developed: P1 was defined as phlebitis involving the TV, P2 as phlebitis involving tributaries/side branches of the TV, and P3 as a non-specific erythematous reaction. Complete closure of the primary target vein was defined as DUS of the target vein showing no areas of patency - as shown by colour flow and compression – of more than 5 cm in length at 1-month post-treatment.

Study population issues: Most subjects were women (70%) and Caucasian (94%). The most frequent presenting CEAP clinical class was class 2 (36%). GSV as the PTV was in 96% (48/50) of the patients. A single TV was identified in 60% (30/50) of the patients, which was the GSV in all but 1 case (98%). Among the remaining 19 patients with more than 1 TV, 36% (18/50) had 2 TVs, and 2% (1/50) had 3 TVs. Fourteen per cent (7/50) of the patients had maximum GSV diameters of 15 mm to 20 mm.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **50 (70 target veins)**

Procedure characteristics:

Characteristics	Mean±SD (range)
Procedure duration, minutes	
1 treated vein	23±8 (11 to 43)
2 treated veins	34±12 (13 to 54)
3 treated veins	55 (1 case)
All	27±11 (11 to 55)
Subfascial treated vein, cm	42±19 (10 to 77)
Suprafascial treated vein, cm	16±10 (3 to 32)
Maximum diameter, mm	
GSV	10±4 (4 to 20)
Accessory saphenous vein	8±2 (4 to 12)
SSV	5±3 (1 to 13)

Procedure time was slightly shorter for experienced operators (25 minutes ±10 minutes compared with 32 minutes ±12 minutes, p=0.040).

Vein closure:

Duplex-assessed complete closure of the PTV and all TV immediately after the procedure, at seven days, and at 1 month was 100%.

At day 30, CC was achieved in:

- 100% (50/50) of the patients (95% CI, 93.9% to 100%)
- 100% (70/70) of the TV (95% CI, 95.5% to 100%)
- 100% (128/128) treated vein segments (95% CI, 97.5% to 100%)

Mean time to return to work: 0.2 days ±1.1 days

Mean time to resumed normal activities: 2.4 days ±4.1 days

Venous quality of life indices

	Baseline	30 days	P
rVCSS	6.5±2.4 (3 to 14)	1.8±1.4 (0 to 6)	**<0.001**
AVVQ	17.3±7.9 (2.5 to 47.1)	8.9±6.6 (0 to 24.8)	**<0.001**

Patient satisfaction:

- "Completely" or "somewhat" satisfied with the procedure: 98% (49/50)
- Dissatisfaction with the procedure: 2% (1/50)

Multivariable analysis

Dependent variable	Predictors	Coefficient	P
Procedure duration	Physician experience	-0.20	0.034

Safety

Pain

Leg pain (NRS)	Mean±SD (range)	P
During access	2.0±1.9 (0 to 8)	-
During procedure	2.1±1.8 (0 to 8)	-
Day 7	1.6±1.8	0.170
Month 1	0.3±0.8	**<0.001**[a]

[a]Compared with the pain during the procedure and at day 7 after the procedure.

Comparison between the phlebitis and non-phlebitis groups, mean±SD

	Patients with phlebitis	Patients without phlebitis	p
Pain at day 7	4.2±1.9	1.3±1.5	<0.001
Pain at month 1	0.2±0.6	0.3±0.8	0.781
Return to normal activities, days	3.5±3.7	2.1±4.2	0.331
Time to return to work, days	0.1±0.3	0.3±1.2	0.634

Adverse events but not SAE within 1 month

Description	Number of patients
Phlebitis, P1	4
Phlebitis, P2	3
Phlebitis, P3	3
Allergic reaction	1
Gastroenteritis	1
Local access site reaction	1

These adverse events were resolved at 1 month and none of the cases was severe adverse event.

Total body hives: 1 patient developed total body hives within the first week of the procedure. This improved after treatment with antihistamines and a short course of oral corticosteroids, and due to the temporal relationship, was felt by the

	Segments treated	0.40	<0.001
	Number of injections	0.44	<0.001
	Subfascial length treated	0.23	0.31
rVCSS change at 30 days	Baseline rVCSS	1.08	<0.001
	Baseline CEAP	-0.43	0.001
AVVQ change at 30 days	Physician experience	0.30	0.030
	Segments treated	0.46	0.005
	Largest diameter treated	0.45	0.004
	Subfascial length treated	-0.37	0.013
	Suprafascial length treated	-0.40	0.014
Return to work	Age	-2.31	0.028
	Length of incompetent GSV	2.41	0.022
	Baseline CEAP	-2.43	0.021
Return to normal activities	BMI	-0.38	0.002
	Phlebitis postprocedure	0.40	<0.001
	Length of incompetent GSV	-.036	0.003
	Number of injections	2.23	<0.001
	Volume CA delivered	-1.25	<0.001

investigator to be consistent with a cyanoacrylate allergy.

Vasovagal event: 1 patient had a vasovagal event causing nausea and light headedness that persisted throughout the procedure.

Thrombus extension: 1 patient had thrombus extension that protruded 2mm into the saphenofemoral junction at the 7-day DUS. This patient did not have treatment with anticoagulation, was asymptomatic, and the thrombus extension was no longer evident at the 1-month DUS study.

Abbreviations used: AVVQ, Aberdeen varicose vein questionnaire; CEAP, clinical, etiological, anatomic and pathophysiologic classification; GSV, great saphenous veins; NRS, numerical pain rating scale; rVCSS, revised venous clinical severity score; SD, standard deviation; SSV, small saphenous veins.

Study 12 Watts TJ (2019)

Details

Study type	**Case report**
Country	UK
Recruitment period	Not reported
Study population and number	n=1 Patient with right leg deep vein thrombosis-induced venous incompetence
Age and sex	45 years; female
Patient selection criteria	The patient had right leg deep vein thrombosis-induced venous incompetence
Technique	The procedure was done using the VenaSeal closure system (containing n-butyl-2-cyanoacrylate). Patch tests were done 18 months after the procedure.
Follow up	**18 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The patient was followed up at 7 days and 18 months.

Study design issues: This case report described a case of allergic contact dermatitis caused by VenaSeal following surgical intervention for venous incompetence. The operator's training and experience of the procedure was not described.

Study population issues: The patient had a previous history of allergic rhinitis and pompholyx type eczema but reported no past history of contact hypersensitivity reactions to adhesives.

Key efficacy and safety findings

Safety
Number of patients analysed: **1** At 7-day follow up: - **Pruritic, tender, blotchy erythematous eruption** that extended and tracked upwards from the medial surface of the right knee towards the right hip. The localised cutaneous eruption resolved over the course of 7 days. Patch testing using IQ Ultra chambers with extended British standard series, plastic and glue series, an acrylate series (Chemotechnique Diagnostics, Vellinge, Sweden), and the VenaSeal adhesive tested "as is" at 18-month follow up: - **Strong positive reaction(++) to the VenaSeal adhesive** on day 4, with a crescendo course after day 2. - **Negative results with the acrylate series and all other tested contact allergens** at day 4. Patch testing with undiluted Dermabond (containing 2-octyl cyanoacrylate), ethyl cyanoacrylate 10% pet, and Histoacryl (also containing n-butyl-2-cryanoacryalte) "as is": - **Positive reaction (+) to Histoacryl** at day 4. - **Negative results with Dermabond and ethyl cyanoacrylate** at day 4. The patient was diagnosed with **allergic contact dermatitis** caused by the VenaSeal adhesive (containing n-butyl-2-cyanoacrylate).

Study 13 Çalik ES (2019)

Details

Study type	**Randomised controlled trial**
Country	Turkey (single centre)
Recruitment period	2014 to 2016
Study population and number	n=**400 (200 CAC versus 200 EVLA; 412 procedure [208 CAC procedures versus 204 EVLA procedure])** Patients with symptomatic GSV incompetence
Age and sex	CAC: mean 38.6 years; 57% (114/200) female EVLA: mean 38.4 years; 55% (109/200) female
Patient selection criteria	Inclusion criteria: patients were between 18 years and 75 years with symptomatic varicose veins; CEAP classification between C2 to C5; GSV insufficiency 0.5 sec determined by CDUS; could come to follow up examinations; and were mentally healthy to approve the operation. Exclusion criteria: saphenous vein duplication or accessory saphenous vein with venous insufficiency; advanced tortuous GSV; saphenous vein under 3 mm and over 15 mm diameter; history of deep venous thrombosis; active thrombophlebitis in deep or superficial veins; arterial insufficiency history or ankle-brachial index under 0.9; significant femoral or popliteal vein insufficiency; history of saphenous vein intervention (surgical, thermal or chemical ablation); hypersensitivity to the cyanoacrylate glue or reaction history with the past surgeries; cancer; and life expectancy under 2 years.
Technique	GSV embolisation was done with Turkish Glue Kit (TGK). The tip of the 4F delivery catheter was confirmed to be 3 cm distal to the SFJ by ultrasonography. The delivery system injected 0.3 cc CA in 5 seconds for 10 cm of vein, and a pulling back rate of 2 cm per second related to 0.03 cc of CA applied to each cm of the vein. If necessary, other concomitant procedures such as microphlebectomy, perforator ablation or foam sclerotherapy were done at 3-month follow up.
Follow up	**Mean 14 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up at days 1 and 7, and then months 1, 3, 6 and 12.

Study design issues: This prospective randomised controlled trial assessed the safety and efficacy of the cyanoacrylate glue ablation therapy of the GSV insufficiency in comparison to laser ablation. Consecutive treatment methods were blindly assigned as cyanoacrylate ablation or EVLA by using block randomisation with sealed envelopes. The patients were assessed and had treatment and followed by the same investigators.

The clinical findings were assessed based on CEAP, and the quality of life assessment, including general pain and associated physical, social and psychological parameters, was done using the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ), version 2. The Wong-Baker FACES pain scale was used for pain scoring. Intention-to-treat analysis was not applied.

Study population issues: Of 400 patients with GSV insufficiency, 412 procedures were successfully done. There were 8 bilateral procedures in the CAC group and 4 in the EVLA group. In terms of baseline features (age, gender, GSV diameter, CEAP classification, VCSS and QoL scores), there were no statistically significant differences between the groups. Leg pain, heaviness in the legs, cramps, itching and oedema were dominating symptoms. Risk factors for CVI, symptoms and signs were similar in both groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **400 (200 CAC versus 200 EVLA; 412 procedure [208 CAC procedures versus 204 EVLA procedure])**

Procedure characteristics

Characteristics	CAC	EVLA	P
Length of treated GSV, cm (mean±SD)	30.4±5.3	31.2±6.1	0.263
Procedure duration, minutes (mean±SD)	13±3.4	31.7±8.8	**<0.001**
Tumescent anaesthesia amount, mL	-	272 (150 to 650)	
CA delivered, mL	1.2 (0.8 to 2)	-	
Length of the stump, mm (day 1, mean±SD)	21.2±9.4	16.4±6.7	0.086

GSV closure rates and its diameter at follow up

Time	CAC (n=208)		EVLA (n=204)		P	
	Occlusion, % (n)	GSV diameter, mm	Occlusion, % (n)	GSV diameter, mm	Occlusion	GSV diameter
Day 1	100 (208)	4.56±1.54	100 (204)	4.48±1.49	0.984	0.586
Day 7	100 (208)	4.45±1.51	100 (204)	4.25±1.37	0.984	0.675
Month 1	100 (208)	3.85±1.39	99.5 (203)	3.72±1.18	0.865	0.596
Month 3	98.6 (205)	3.22±1.25	97.4 (199)	3.38±1.04	0.578	0.765
Month 6	97.1 (202)	3.08±1.14	95.6 (195)	3.15±0.95	0.535	0.745
Month 12	96.6 (201)	2.96±1.04	94.1 (192)	2.91±0.87	0.348	0.856

Recanalisation rates at follow up, %(n)

	CAC	EVLA
Partial recanalisation		
1 month	0	0.5 (1)
3 months	1.4 (3)	2 (4)
6 months	1.4 (3)	2 (4)
12 months	0.5 (1)	1.5 (3)
Total recanalisation		
6 months		(1)
12 months	(1)	(2)

Change in symptoms after treatment at 12 months

Safety

Postoperative complication rates at first week and 3 months

Variable	CAC (n=200)	EVLA (n=200)	P
1 week			
Pain score	2.8±3.1	5.4±3.7	**<0.001**
Induration	4.2±2.3	9.2±4.6	**<0.001**
Pigmentation	3.5% (7)	5.5% (11)	0.554
Ecchymosis	12% (24)	26% (52)	**<0.001**
Paraesthesia	3% (6)	11% (28)	**<0.001**
Phlebitis	3.5% (7)	7% (14)	0.328
DVT	0	1% (2)	0.123
Time to return to daily activity, day	1.5±0.6	2.9±1.8	**<0.001**
3 months			
Pain score	0.6±0.4	0.7±0.5	0.458
Induration	0.3±0.2	0.4±0.3	0.523
Pigmentation	0.5% (1)	1.6% (3)	0.087
Ecchymosis	0	0	0
Paraesthesia	1.1% (2)	7% (13)	**<0.001**
Phlebitis	0	0	0
DVT	0	1.1% (2)	0.633
Time to return to daily activity, day	-	-	-

Symptoms	Preprocedural, % (n)		Free of symptoms, % (n)		No difference, % (n)		Worsening, % (n)	
	CAC	EVLA	CAC	EVLA	CAC	EVLA	CAC	EVLA
Leg pain	86 (172)	89 (178)	97.7 (168)	97.2 (173)	1.7 (3)	1.7 (3)	0.6 (1)	1.1 (2)
Heaviness in the legs	67 (134)	63 (126)	98.5 (132)	99.2 (125)	1.5 (2)	0.8 (1)	0	0
Cramp	41 (82)	39 (78)	96.3 (79)	98.7 (77)	3.6 (3)	1.3 (1)	0	0
Itching	31.5 (63)	39 (78)	98.4 (62)	97.4 (76)	1.6 (1)	2.6 (2)	0	0
Oedema	27 (54)	29 (58)	94.4 (51)	94.8 (55)	3.7 (2)	3.4 (2)	1.8 (1)	1.7 (1)
Pigmentation	4 (8)	2.5 (5)	25 (2)	20 (1)	62.5 (5)	80 (4)	12.5 (1)	0

Clinical assessments at follow up

	CAC (n=200)	EVLA (n=200)	P
VCSS, mean±SD (n)			0.875
Preprocedural	5.7±2.1 (200)	5.8±1.9 (200)	
Month 1	2.7±1.6 (196)	2.9±1.8 (195)	
Month 3	2.4±1.4 (188)	2.6±1.5 (186)	
Month 6	2.2±1.3 (184)	2.3±1.3 (182)	
Month 12	1.2±0.8 (181)	1.3±0.9 (174)	
CIVIQ, mean±SD (n)			0.928
Preprocedural	40.6±17.8 (200)	41.4±18.3 (200)	
Month 1	23.4±6.7 (196)	24.1±6.7 (195)	
Month 3	20.2±4.8 (188)	20.9±4.7 (186)	
Month 6	16.7±3.6 (184)	17.2±3.8 (182)	
Month 12	12.3±2.5 (181)	12.8±2.6 (174)	

At the 1-year follow up, VCSSs statistically significantly declined from 5.7±2.1 to 1.2±0.8 ($p<0.001$) for CAC and from 5.8±1.9 to 1.3±0.9 ($p<0.001$) for EVLA.

The mean CIVIQ scores showed statistically meaningful improvement for each group during the follow up, $p<0.001$. In the total CIVIQ scores, there were no statistically significant difference between CAC and EVLA groups.

Additional treatments at follow up, % (n)

	CAC	EVLA	P
3 months			
Foam sclerotherapy	2.1 (4)	2.7 (5)	0.586
Mini phlebectomy	1 (2)	0	-
6 months			
Foam sclerotherapy	4.9 (9)	4.9 (9)	0.128

Mini phlebectomy	3.8 (7)	4.4 (8)	0.487		
12 months					
Foam sclerotherapy	21 (38)	24.7 (43)	0.678		
2nd sclerotherapy	(4)	(5)	-		
Mini phlebectomy	2.8 (5)	2.3 (4)	0.389		

Abbreviations used: CA, cyanoacrylate glue; CAC, cyanoacrylate closure; CIVIQ, chronic venous insufficiency quality of life questionnaire; EVLA, endovenous laser ablation; GSV, great saphenous vein; SD, standard deviation; VCSS, venous clinical severity score.

Study 14 Almeida JI (2019)

Details

Study type	**Case report**
Country	Not reported
Recruitment period	Not reported
Study population and number	n=**1** Patients with incompetent GSVs
Age and sex	65 years; male
Patient selection criteria	The patient had incompetent GSVs (clinical, aetiology, anatomy and pathophysiology class C4s in the left leg, C3 in the right leg).
Technique	The procedure was done using VenaSeal (Medtronic, Minneapolis, Minn).
Follow up	**5.5 years**
Conflict of interest/source of funding	This study was funded by an investigator-initiated study grant, which was provided by Medtronic.

Analysis

Study design issues: This case report described the findings from the histopathologic analysis of a great saphenous vein segment that was excised 5.5 years after cyanoacrylate implantation. The patient had a segment of the left GSV, previously treated with 1.4 mL of cyanoacrylate, excised for histopathologic analysis. The treated GSV segment was 6.0 cm long with a diameter of 0.4 cm, thickened wall (0.1 to 0.2 cm), obliterated lumen, and adventitia with patches of haemorrhage. This was divided into two separate 3-cm segments. A segment of untreated GSV was collected as a control from the midcalf region by a second incision. The control GSV segment was a 1.5-cm-long, small-calibre vessel with a diameter of 0.2 cm, patent lumen, and minimal adventitial haemorrhage.

Key efficacy and safety findings

Safety
Number of patients analysed: **1** At 5.5-year follow up, histopathologic analysis of the treated GSV segment showed that the vessel wall was intact with alternating areas of thickening and thinning. - **Foreign body reaction with granulomatous inflammation**: the vessel was occluded with collagenised mature fibrous tissue interspersed with foreign material, presumed to be polymer remnants. Multinucleated giant cells encapsulated the foreign material, and focal areas of granulomatous inflammation were present in the medial layer extending to the adventitia.

Validity and generalisability of the studies

- Evidence came from 2 systematic reviews, 3 randomised controlled trials (1 RCT was not blinded and per-protocol analysis was applied for most outcomes in 3 RCTs), 3 non-randomised comparative studies, 4 case series and 2 single case reports.
- Studies 3 and 11 were conducted in the US, studies 2, 4 to 9, and 13 in Turkey, study 10 in Korea, study 12 in the UK, and studies 1 and 14 did not report a country.
- Two systematic reviews included studies 4 to 6, but the total sample of 4,432 patients derived from removing duplications.
- Three different devices (VenaSeal Closure System, VariClose Vein Sealing System and VenaBlock Venous Closure System) and ablation techniques were used across the studies. The variation in applied technique was especially concerned with the first segment distal to the sapheno-femoral junction and the dosage of cyanoacrylate delivered.
- There was a variation in the samples among the studies. Nine studies focused on patients with incompetent GSVs[1, 3, 5-9, 13, 14], 2 studies[2, 10] emphasised patients with incompetent GSVs and SSVs, and 2 studies[4, 11] assessed patients with incompetent GSVs, SSVs and perforator veins or accessory saphenous veins. Study 12 investigated 1 patient with deep vein thrombosis-induced venous incompetence.
- The mean age was ≥38 years among the studies and the longest follow up was 5.5 years in study 14, followed by 36 months in study 3. Most of the remaining studies had a follow up of 1 year to 2 years[1, 2, 4-9, 12, 13].
- Losses to follow -up were high (more than 10%) in 5 studies[1, 3, 7-9].
- The operator's training and experiences of the procedures was only discussed in studies 1, 5 and 11 even though a relatively short learning period was needed.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Endovenous mechanochemical ablation for varicose veins. NICE interventional procedures guidance 557 (2016). Available from https://www.nice.org.uk/guidance/ipg557
- Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedures guidance 440 (2013). Available from https://www.nice.org.uk/guidance/ipg440
- Endovenous laser treatment of the long saphenous vein. NICE interventional procedures guidance 52 (2004). Available from https://www.nice.org.uk/guidance/ipg52
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedures guidance 37 (2004). Available from https://www.nice.org.uk/guidance/ipg37
- Cyanoacrylate instillation for occlusion of parotid sinuses. NICE interventional procedures guidance 42 (2004). Available from https://www.nice.org.uk/guidance/ipg42
- Radiofrequency ablation of varicose veins. NICE interventional procedures guidance 8 (2003). Available from https://www.nice.org.uk/guidance/ipg8

NICE guideline

- Varicose veins: diagnosis and management. NICE clinical guideline 168 (2013). Available from https://www.nice.org.uk/guidance/cg168

Additional information considered by IPAC

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. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four specialist advisor questionnaires (including 1 incomplete questionnaire) for cyanoacrylate glue occlusion for varicose veins were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE received 3 completed questionnaires. The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- Cyanoacrylate Closure Versus Surgical Stripping for Incompetent Saphenous Veins (CASS); NCT03835559; RCT; Korea; n=146; Estimated Study Completion Date: February 2021
- Mechanochemical Ablation Compared to Cyanoacrylate Adhesive; NCT03392753; RCT; UK; Estimated Study Completion Date: December 2020
- VeClose Five Year Follow-Up Extension Study; NCT03455699; Prospective cohort study; US; Estimated Study Completion Date: April 2019

References

1. Vos CG, Ünlü Ç, Bosma J et al. (2017) A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. Journal of vascular surgery, 5(6): 880-896
2. Bissacco D, Stegher S, Calliari FM et al. (2019) Saphenous vein ablation with a new cyanoacrylate glue device: a systematic review on 1000 cases. Minimally invasive therapy & allied technologies, 28(1): 6-14
3. Morrison N, Kolluri R, Vasquez M et al. (2019) Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36-month outcomes of the VeClsoe randomised controlled trial. Phlebology, 34(6): 380-390

   Morrison N, Gibson K, Vasquez M et al. (2017) VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. Journal of Vascular Surgery, 5(3): 321-330

   Morrison N, Gibson K, McEnroe S et al. (2015) Randomised trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). Journal of Vascular Surgery, 61(4): 985-994

   Gibson K, Morrison N, Kolluri R et al. (2018) Twenty-four month results from a randomised trial of cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. Journal of Vascular Surgery, 6(5): 606-613
4. Eroglu E and Yasim A (2018) A randomised clinical trial comparing n-butyl cyanoacrylate, radiofrequency ablation and endovenous laser ablation for the treatment of superficial venous incompetence: two year follow up results. European journal of vascular and endovascular surgery, 56: 553-560
5. Koramaz I, Kiliç HE, Gökalp F et al (2016) Ablation of the great saphenous vein with nontumescent n-butyl cyanoacrylate versus endovenous laser therapy. Journal of vascular surgery, 5(2): 210-215
6. Bozkurt AK and Yilmaz MF (2016) A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. Phlebology, 31(1S): 106-113
7. Ovali C and Sevin MB (2019) Twelve-month efficacy and complications of cyanoacrylate embolization compared with radiofrequency ablation for incompetent great saphenous veins. Journal of vascular surgery, 7(2): 210-216

8. Sarac A (2019) Two-year follow-up of a n-butyl-2-cyanoacrylate glue ablation for the treatment of saphenous vein insufficiency with a novel application catheter with guiding light. Vascular, 0(0): 1-7
9. Yavuz T, Acar AN, Aydin H et al. (2018) A retrospective study of a new n-butyl-a-cyanoacrylate glue ablation catheter incorporated with application guiding light for the treatment of venous insufficiency: twelve-month results. Vascular, 26(5): 547-555
10. Park I, Jeong MH, Park CJ et al. (2019) Clinical features and management of “phlebitis-like abnormal reaction” after cyanoacrylate closure for the treatment of incompetent saphenous veins. Annals of vascular surgery, 55: 239-245
11. Gibson K and Ferris B (2017) Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: Initial outcomes of a post-market evaluation of the VenaSeal system (the WAVES study). SAGE, 25(2): 149-156
12. Watts TJ, Thursfield D and Haque R (2019) Allergic contact dermatitis caused by VenaSeal tissue adhesive. Contact dermatitis, 80(6): 393-395
13. Çalik ES, Arslan Ü and Erkut B (2019) Ablation therapy with cyanoacrylate glue and laser for refluxing great saphenous veins – a prospective randomised study. Vasa 48: 405-412
14. Almeida JI, Murray SP and Romero ME (2019) Saphenous vein histopathology 5.5 years after cyanoacrylate closure. Journal of vascular surgery: venous and lymphatic disorders

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	15/10/19	Issue 10 of 12, October 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	15/10/19	Issue 10 of 12, October 2019
HTA database (CRD website)	15/10/19	-
MEDLINE (Ovid)	15/10/19	1946 to October 14, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	15/10/19	1946 to October 14, 2019
EMBASE (Ovid)	15/10/19	1974 to 2019 Week 41

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- 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/ (4779)

2 Cyanoacrylat*.tw. (3894)

3 Tissue Adhesives/ (6453)

4 Acetates/ (39090)

5 Acetat*.tw. (128623)

6 Acrylates/ (8030)

7 Acrylat*.tw. (4240)

8 Tumescentless.tw. (7)

9 ((CA or cyanoacry* or Medic* or Tissu*) adj4 (adhes* or superglue* or glue* or gum* or resin*)).tw. (8686)

10 ((CA or cyanoacry*) adj4 (endoven* or ablat*)).tw. (457)

11 ((adhes* or superglue* or glue* or gum* or resin*) adj4 (occlus* or clos* or block)).tw. (2523)

12 or/1-11 (182478)

13 exp Venous Insufficiency/ (7403)

14 telangiectasis/ (3823)

15 ((venous or vein*) adj4 (incomp* or insuffic*)).tw. (6360)

16 ((venous or vein*) adj4 ulcer*).tw. (4406)

17 telangiect*.tw. (12725)

18 ((reticular or thread or spider) adj4 (vein* or venous)).tw. (230)

19 (varix or varices or microvaricosity or phlebarteriectasia or phlebectas* or prevaricos* or vein ectasia or venectasia).tw. (13713)

20 or/13-19 (41079)

21 exp lower extremity/ (161784)

22 (lower limb* or lower extremit* or leg* or calf or valves or thigh* or membrum inferius).tw. (407066)

23 21 or 22 (506506)

24 20 and 23 (8277)

25 exp varicose veins/ (17715)

26 (varicos* adj4 vein*).tw. (6701)

27 Saphenous Vein/ (15148)

28 ((saphenous or perforator) adj4 (vein* or vena or incomp* or insuffic*)).tw. (13955)

29 GSV.tw. (776)

30 or/24-29 (40380)

31 12 and 30 (254)

32 Venaseal.tw. (7)

33 Sapheon.tw. (6)

34 32 or 33 (10)

35 31 or 34 (255)

36 animals/ not humans/ (4595018)

37 35 not 36 (239)

38 limit 37 to ed=20190331-20191031 (16)

Appendix

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
Almeida JI, Javier JJ, Mackay EG et al (2015) Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology, 30(6), 397-404.	Case series 38 patients (median 51 years; 76% [29/38] female) Follow up: 24 months Loss to follow up: n=2	Complete occlusion of the treated GSV was confirmed by duplex ultrasound in all patients except for 1 complete and 2 partial recanalisations seen at, 1, 3 and 6 months of follow up, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92.0% (95% CI 0.836–1.0) at 24 months follow up. VCSS improved in all patients from a mean of 6.1±2.7 at baseline to 1.3_1.1, 1.5±1.4 and 2.7±2.5 at 6, 12 and 24 months, respectively (p<.0001). Oedema improved in 89% of legs (n=34) at 48 hours follow up. At baseline, only 13% were free from pain. At 6, 12 and 24 months, 84%, 78% and 64% were free from leg pain, respectively.	This study includes a small sample.
Almeida JI, Javier JJ, Mackay E et al. (2013) First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Journal of Vascular Surgery, 1(2):174-180	Case series 38 patients (median 51 years; 76% [29/38] female) Follow up: 12 months	Kaplan-Meier analysis yielded an occlusion rate of 92% at 12 months of follow up. Side effects were generally mild and self-limited, most frequently, phlebitis in six patients (15.8%). Eight patients (21.1%) showed thread-like thrombus extensions into the common femoral vein of a mean length of 12.6 mm (range, 3.5 mm to 35 mm), which resolved spontaneously without anticoagulation. VCSS improved in all patients from a mean of 6.1±2.7 at baseline to 1.5±1.4 at 12 months (p< 0.0001). Edema improved in 34 legs (89%) at the 48-hour follow up.	This study includes a small sample.
Almeida JI, Julian JJ, Mackay EG et al. (2017) Thirty-sixth-month follow-up of first-in-human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Journal of vascular surgery, 5(5), 658-666	Case series 38 patients (median 51 years; 76% [29/38] female) Follow up: 36 months Loss to follow up: n=7	At 36 months after treatment of 38 patients with a cyanoacrylate-based adhesive, 27 of the 29 patients available for follow up had occluded GSV (94.7%; 95% CI, 87.9% to 100%). The mean VCSS improved (p,0.0001), and adverse events were mild or moderate and self-limited.	This study includes a small sample.
Anwar MA, Lane TR Franklin IJ et al. (2014) Cyanoacrylate for the	Case report	The procedure was completed with immediate technical success. There were no procedure related	This is a single case report.

treatment of small saphenous vein venous incompetence. Cureus, 6(10): e221.	1 patient	complications. Follow up at 6 weeks and 4 months showed improvement in symptoms and complete occlusion of SSV with no evidence of DVT	
Bademci MS, Tayfur K, Ocakoglu G et al. (2018) A new percutaneous technique: N-butyl cyanoacrylate adhesive for the treatment of giant saphenous vein insufficiency. Vascular, 26(2), 194-197.	Retrospective case series 50 patients (mean 46.4 years; 60% [30/50] female) Follow up: 12 months	full closure was seen in giant saphenous vein in 94% (47/50) of patients in the 12th month control duplex ultrasound. The median VCSS scores in the 1st, 6th and 12th months were 3, 2 and 1, respectively (p<0.001); the median AVVQ scores in the 1st, 6th and 12th months were 7, 5 and 4, respectively (p<0.001). In the access site, 2 patients developed phlebitis and 1 developed ecchymosis.	Studies with a larger sample are included in table 2.
Bellam Premnath KP, Joy B, Raghavendra VA et al. (2018) Cyanoacrylate adhesive embolization and sclerotherapy for primary varicose veins. Phlebology, 33(8), 547-557.	Case series 124 patients (145 limbs; Follow up: 1 year	Technical success rate was 100%. Saphenous vein closure rate was 96.5% at 1 year. There was no femoral venous extension of cyanoacrylate in any of the patients. Posterior tibial vein extension of cyanoacrylate was seen in 3 patients (2.6%) without untoward clinical effect. Significant improvement was found in VCSS from a baseline mean of 7.98±4.42 to 4.74±3, 1.36±1.65 and 0.79±1.19 at 1, 6 and 12 months follow up. Ulcer healing rate was 100%.	Studies with a larger sample are included in table 2.
Bootun R, Lane TRA and Davies AH (2016) A comparison of thermal and nonthermal ablation. Reviews in vascular medicine, 4, 1-8.	Review	The nonthermal methods are viable alternatives to thermal ablation and will be able to offer additional benefits to patients.	The only cited RCT is included in table 2, with other mainly cited papers are covered in the appendix.
Çalik ES, Arslan Ü, Ayaz F et al. (2016) N-butyle cyanoacrylate in the treatment of venous insufficiency – the effect of embolization with ablative polymerisation. Vasa 45(3), 241-246.	Case series 181 patients (mean 37.6 years; 61% [110/181] female) Follow up: mean 7.5 months Loss to follow up: n=18	The procedural occlusion rate was 100%. Postoperative pain was seen in 11 patients (6.1%) and thrombophlebitis was seen in 1 patient. No total recanalisation was seen. Five (2.7%) partial recanalisation were seen at the 6-month follow up. The 6-month total occlusion rate was 97.2%.	Studies with a larger sample are included in table 2.
Chan YC, Law Y, Cheung GC et al. (2017) Predictors of recanalization for incompetent great saphenous veins treated with cyanoacrylate glue.	Case series 55 patients (median 65 years; 62% [34/55] female)	Of 108 legs, 2 had minimal extension of thrombus to deep vein, and 4 had superficial thrombophlebitis. Kaplan-Meier analysis showed GSV closure rates were 97.2%, 92.3%, 98.2% and 75.7% at 1 week, 1 month, 6 months and 12 months after the procedure. With a median follow-up period of 5	This study includes a small sample.

Journal of vascular and interventional radiology, 28(5), 665-671	Follow up: median 5 months (range 0 to 18 months).	months (range 0 to 18 months), 4 legs had clinical recurrence. Mean GSV diameter ≥6.6 mm was the only statistically significant predictor for recanalisation (hazard ratio 12.1; 95% CI, 1.6 to 92.7; p=0.016).	
Eroglu E, Yasim A, Ari M et al. (2017) Mid-term results in the treatment of varicose veins with n-butyl cyanoacrylate. Phlebology, 32(10), 665-669.	Case series 167 patients (mean 47.7 years: 53% [89/168] female) Follow up: 30 months	Full ablation was achieved in all patients following the procedure. No complications were encountered. Patients were monitored for 30 months. Ablation rates were 100% at the 3rd month, 98.3% at the 6th month, 96.6% at 1 year, and 94.1% at 30 months. Mean VCSS score was 10.2 before procedures, decreasing to 3.9 at 3 months, 4.2 at 6 months, 2.9 at 12 months, and 2.7 at 30 months (p=0.000).	Studies with a larger sample are included in table 2.
Gibson K, Minjarez R, Gunderson K et al. (2019) Need for adjunctive procedures following cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of postprocedure compression: three-month data from a postmarket evaluation of the VenaSeal System (the WAVES study). Phlebology, 34(4), 231-237.	Case series 50 patients (mean 49.5 years; 70% [35/50] female) Follow up: 3 months	Complete closure at 3 months was achieved in 70 (99%) of the treated veins (48 GSVs, 14 accessory saphenous veins, 8 SSVs). Revised venous clinical severity score improved from 6.4±2.2 to 1.8±1.5 (p<0.001) and AVVQ from 17.3±7.9 to 6.5±7.2 (P<0.0001). Sixty-six percent of patients had tributary treatment at 3 months. The percentage of patients who needed adjunctive treatments at three months was lower than had been predicted by the treating physicians (65% versus 96%, p=0.0002).	Studies with a larger sample and longer follow up are included in table 2.
Hirsch T (2017a) Varicose vein therapy and nerve lesions. Vasa, 46(2), 96-100.	Review	Acrylate adhesion to close insufficient saphenous veins is effective with minimum invasiveness, which is comparable with thermal methods. The advantage of the nonthermal methods over open surgery, EVLA, and RFA appears to be the much lower risk of peripheral neurological complications.	The only cited RCT for cyanoacrylate treatment was included in table 2, with other mainly cited papers being covered in the appendix.
Hirsch T (2017b) Nonthermal endovenous treatment: acrylate adhesion of varicose saphenous veins. Phlebology, 46(3), 143-149.	Review	Acrylate adhesion of varicose saphenous veins is minimally invasive and produces comparable results to those achieved with thermal methods. The procedure is safe and easy to learn and has few side effects. The risk of nerve damage in particular is lower than with thermal methods as tumescent anaesthesia is not needed. A safety distance of 5 cm from the	The only cited RCT and a comparative study for cyanoacrylate treatment were included in table 2, with other mainly cited papers being covered

		saphenofemoral and saphenopopliteal junctions is recommended.	in the appendix.
Hwang JH, Park SW, Kim KH et al. (2018) Regression of varicose veins after cyanoacrylate closure of incompetent great saphenous veins without a localised concomitant procedure. Journal of Vascular Surgery, 375-381	Case series 48 patients (mean 49.5 years; 62.5% (30/48) female) Follow up: 12 months Loss to follow up: n=2 (3 limbs)	In 60 of 63 limbs available for follow up, all treated GSVs showed complete closure during the follow-up period (8.4±3.0 months). VCSS scores at the time of all follow-up visits were statistically significantly lower ($p<0.001$) than those before CAC. Complete resolution of varicose veins was noted in 38 limbs (71.7%) after 3-month follow up. The proportion of limbs showing more than 50% varicose vein regression reached 90.6%. The more that varicosity entry was covered ($p=0.002$) and the farther down the leg the access site was located ($p=0.024$), the more complete resolution of varicose veins was seen. Phlebitis occurred in 10 limbs (16.7%), and hyperpigmentation occurred in 8 limbs (13.3%).	Studies with a larger sample and longer follow up are included in table 2.
Kolluri R (2016) Interventions for varicose veins: beyond ablation. Current Treatment Options in Cardiovascular Medicine, 18(7), 1-14.	Review	CAC is a simple procedure, with consistent procedural steps. TA is not needed during the procedure as are not compression socks after the procedure. CAC could potentially be considered for patients who lead active lifestyles and do not intend to have any downtime after the procedure and desire immediate return to activities. Adjunctive therapies such as foam sclerotherapy and phlebectomy may still be needed in addition to the CAC for the tributary vein treatment.	The cited RCT for cyanoacrylate treatment is included in table 2, with other mainly cited papers being covered in the appendix.
Kolluri R, Gibson K, Cher D et al. (2016) Roll-in phase analysis of clinical study of cyanoacrylate closure for incompetent great saphenous veins. Journal of vascular surgery, 4(4), 407-415	Comparative study (roll-in phase analysis) 20 patients (mean 53.1 years, 85% [17/20] female) Follow up: 12 months	The results from the VeClose study roll-in group show that despite the physician's lack of previous experience, initial treatment with CAC leads to comparable efficacy and safety results to RFA and is associated with a relatively short learning period.	Roll-in phase of an RCT included in table 2.
Korkmaz Ö, Göksel S, Gül M et al. (2018) Does the use of N-butyl-2 cyanoacrylate in the treatment of lower extremity superficial varicose veins cause acute systemic inflammation and allergic reactions? Cardiovascular journal	Retrospective case series 102 patients (mean 51.16 years; 70.6% [72/102] female) Follow up: 2 hours	Cyanoacrylate has been used in the endovenous medical ablation of varicose veins and superficial venous insufficiency over the last few years without the use of thermal energy and tumescent anaesthesia, which represents the greatest advantage of this method. In addition, since it causes no systemic allergic or acute inflammatory reaction, it appears to be safe to use.	Studies with a larger sample and a longer follow-up period are included in table 2.

of Africa, 29(4), 213-217.			
Lam YL, Maeseneer MD, Lawson J et al. (2017) Expert review on the VenaSeal system for endovenous cyano-acrylate adhesive ablation of incompetent saphenous trunks in patients with varicose veins. Expert review of medical devices, 14(10), 755-762.	Review	Cyanoacrylate adhesive embolisation of incompetent truncal veins suing the VenaSeal device is a safe and efficacious innovative technique. Further studies are needed to evaluate anatomical and clinical outcomes at long term.	The only cited RCT and a comparative study for cyanoacrylate treatment were included in table 2, with other mainly cited papers being covered in the appendix.
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, 1 (3): 298-300.	Case report 1 patient	Cyanoacrylate embolisation using the Sapheon Venaseal Closure System was tolerated well, and the treated vein showed complete early occlusion at 8 weeks; however, at 6 months extensive recanalisation was shown on duplex imaging.	This is a single case report.
Novotný K, Roček M, Pádr R et al. (2018) Treating great and small saphenous vein insufficiency with histoacryl in patients with symptomatic varicose veins and increased risk of surgery, Vasa, 47(5), 416-423	Case series 49 patients (56 limbs; mean 53.5 years; 59% [29/49] female) Follow up: 2 years Loss to follow up: n=3	The immediate success rate of the treatment was 98%. In follow-up intervals of 6 weeks, 6 months, 1 year, and 2 years, the anatomical success rates of embolisation (recanalisation of no more than 5 cm of the junction) were 98%, 96%, 94%, and 94%, respectively. At identical intervals the venous insufficiency was scored according to the AVVQ and the American VCSS. In both cases, improvement was shown over the 2-year follow up, with a 0.5% significance level. Specific clinical signs of venous insufficiency were also evaluated, such as pain, oedema, clearance of varicose veins, and healing of venous ulceration. One severe complication – a pulmonary embolism – was reported, without consequences.	This study includes a small sample and a modified technique was used as commercial kits were not available when the study was lunched.
Park I (2017) Initial outcomes of cyanoacrylate closure venaseal system for the treatment of the incompetent great and small saphenous veins. Vascular and Endovascular surgery, 51(8), 545-549.	Case series 34 patients (47 GSVs and 16 SSVs; mean 46.4 years; 79.2% [27/37] female) Follow up: 3 months	All treated veins had complete closure by duplex ultrasound during the follow-up period. Mean numerical pain rating scale of 6 hours after procedure was 2.7. The VCSS was improved during the follow-up period. Phlebitis-like “abnormal skin reaction” in the treatment area was occurred in 8 (23.5%) of 34 patients and recovered fully in 2 weeks.	This study includes a small sample.
Park SJ, Yim SB, Cha DW et al. (2019)	Case report	No adverse event occurred after CA. While assessments at 1 week, 1 month,	This is a single case report.

Diagnosis of recurrent reflux within the remnant non-treatment stump after bilateral cyanoacrylate ablation of the great saphenous veins, SAGE Open Medical Case Reports, 7, 1-4.	1 patient (54 years; female) Follow up: 9 months	and 3 months postoperatively showed complete occlusion and no reflux of the both SFJ, the assessment at 9 months showed complete occlusion of the treated GSVs but recanalisation with reflux in the both non-treated stumps.	
Parsi K, Roberts S, Kang M et al. (2019) Cyanoacrylate closure for peripheral veins: Consensus document of the Australiasian College of Phlebology, Phlebology, 0(0), 1-23.	Review	Cyanoacrylate adhesive closure appears to be an effective endovenous procedure, with short-term closure rates comparable to ETA and therefore greater efficacy than traditional surgery for treating superficial veins of the lower limbs. Ongoing data collection is needed to establish the long-term safety.	The mainly cited papers relating to safety issues were included in table 2, with other cited key papers being covered in the appendix.
Prasad K, Joy B, Toms A et al. (2018) Treatment of incompetent perforators in recurrent venous insufficiency with adhesive embolization and sclerotherapy, Phlebology, 33(4), 242-250.	Case series 69 patients (83 limbs; mean 48 years; 45% [31/69] female) Follow up: 6 months	Perforator and varicose veins occlusion rate was 100% (191/191). Deep venous extension of cyanoacrylate occurred in 4 (4.8%) patients, with no adverse clinical outcome. VCSS improved from a baseline of 8.18±3.60 to 4.30±2.48 on 3-month follow up and 2.42±1.52 on 6-month follow up (p<0.0001). All ulcers showed complete healing within 3 months. Significant prolonged thrombophlebitis occurred in 38.5% of limbs.	This study includes a small sample.
Premnath KPB, Joy B, Raghavendra VA et al. (2018) Cyanoacrylate adhesive embolization and sclerotherapy for primary varicose veins, Phlebology, 33(8), 547-557.	Case series 124 patients (145 limbs; mean 51.3 years) Follow up: 12 months	Technical success rate was 100%. Saphenous vein closure rate was 96.5% at one year. There was no femoral venous extension of cyanoacrylate, but posterior tibial vein extension of cyanoacrylate was seen in 2.6% without untoward clinical effect. Significant improvement was found in VCSS from a baseline mean of 7.98±4.42 to 4.74±3, 1.36±1.65 and 0.79±1.19 at 1, 6 and 12 months' follow up. Ulcer healing rate was 100%.	Studies with a larger sample and a longer follow up are included in table 2.
Proebstle TM, Alm J, Dimitri S et al. (2015) The European multicentre cohort study on cyanoacrylate emobilisation of refluxing great saphenous veins. Journal of Vascular Surgery.	Case series 70 patients (mean 48.4 years; 78.6% [55/70] female) Follow up: 12 months Loss to follow up: n=2	Cumulative 12-month survival free from recanalisation was 92.9% (95% CI, 87.0% to 99.1%). Mean (SD) VCSS improved from 4.3±2.3 at baseline to 1.1±1.3 at 12 months. AVVQ score showed an improvement from 16.3 at baseline to 6.7 at 12 months (p<0.0001). Side effects were generally mild; a phlebitis reaction occurred in 8 cases (11.4%) with a median duration of 6.5 days (range 2 days to 12 days). Pain without a phlebitis reaction was seen in 5 patients (8.6%) for a median duration of 1 day (range 0 to 12 days).	This study was included in the previous overview and is covered by a systematic review in table 2.

Radak D, Djukic N and Neskovic M (2019) Cyanoacrylate embolisation: a novelty in the field of varicose veins surgery. Annals of vascular surgery, 2019, 55, 285-291.	Review	Evidence shows that CA ablation treatment is feasible, with high GSV occlusion rates and very few mild-to-moderate adverse events. Short procedure time and no need for tumescent anaesthesia or compressive stockings reduce patient's discomfort, and the CAC technique definitely seems to be a step forward in venous surgery.	The cited RCT and 2 comparative studies for cyanoacrylate treatment are included in table 2, with other mainly cited papers being covered in the appendix.
Tekin AI, Tuncer ON, Memetoglu ME et al. (2016) Nonthermal, nontumescent endovenous treatment of varicose veins. Elsevier, 36, 231-235	Case series 62 patients (mean 44.5 years; 38% [24/62] female) Follow up: 6 months	At 1 week and 1-month control, duplex scans showed total occlusion for all patients (100%), total occlusion for 58 patients (93.5%), and subtotal occlusion for 4 patients (6.5%) at 3rd month. At the end of 6 months, total occlusion 56 patients (90.3%) and subtotal occlusion for 2 patients (3.2%). For 4 (6.5%) patients, no occlusion was seen, and the diameter was >11 mm.	This study is included in a systematic review in table 2, and studies with a larger sample and longer follow up are also included in table 2.
Tang TY, Rathnaweera HP, Kam JW et al. (2019) Endovenous cyanoacrylate glue to treat varicose veins and chronic venous insufficiency – Experience gained from our first 100+ truncal venous ablations in a multi-ethnic Asian population using the Medtronic VenaSeal Closure System. Phlebology, 0(0), 1-9.	Case series 77 patients (93 legs; 103 procedures) Follow up: 1 year	There was 100% technical success. All procedures were well tolerated with a mean postoperative pain score of 3.0 (range 0 to 5). After 3 months, median patient satisfaction was 9.0 (interquartile range: 7.0 to 10.0) and SV was occluded in 51/53 (96.2%) veins and SSV completely closed in 5/5 (100%) veins. At 1 year, GSV and SSV occlusion rates were 54/59 (91.5%) and 5/8 (62.5%), respectively. There was one deep vein thrombosis. Transient superficial phlebitis was reported in 10/93 (10.8%) legs, which were all self-limiting. There were 9/103 (8.7%) anatomical recurrences, but no patients needed re-intervention as they were asymptomatic.	Studies with a larger sample are included in table 2.
Toonder IM, Lam YL, Lawson J et al. (2014) Cyanoacrylate adhesive perforator embolization of incompetent perforating veins of the leg, a feasibility study. Phlebology, 29(1S), 49-54.	Case series 23 patients (mean 52 years, 47.8% [11/23] female) Follow up: 3 months	On the follow-up DUS, occlusion without efflux was seen in 25 (76%) whereas 8 (24%) of the treated IPV had persistent efflux. 2 (9%) patients suffered from wound infections at the access point, 1 (4%) had a thrombophlebitis.	Studies with a larger sample and/or a longer follow up are included in table 2.
Varcoe RL, Thomas SD, Bourke V et al. (2017) Utility of adjunctive digital subtraction venography	Comparative study (ultrasound versus venography)	Technical success was 100%, and there were no contrast-related complications during the procedure, at discharge, or at the 30-day follow up.	Studies with a larger sample and longer follow-up are

for the treatment of saphenous vein insufficiency. Journal of endovascular therapy, 24(2), 290-296.	200 patients (87% had RFA and 13% had cyanoacrylate glue embolisation; meaning 60.9 years, 64% [128/200] female) Follow up: 30 days		included in table 2.
Whiteley MS (2015) Glue, steam and Clarivein – best practice techniques and evidence. Phlebology, 30(2S), 24-28.	Review	Having shown equivalence with endovenous thermoablation in the great saphenous vein, cyanoacrylate glue has now been reported in the treatment of an incompetent small saphenous vein and also to treat incompetent perforating veins.	Studies with a larger sample and/or a longer follow up are included in table 2 compared with the studies in this review.
Yasim A, Eroglu E, Bozoglan O et al. (2017) A new non-tumescent endovenous ablation method for varicose vein treatment: Early results of n-butyl cyanoacrylate (AvriClose). Phlebology, 32(3), 194-199.	Case series 180 patients (mean 47.7 years; 52% [94/180] female) Follow up: mean 5.5 months	Duplex examination immediately after the procedure showed closure of the treated vein in 100% of the treated segment. No complications were seen. The mean follow-up time was 5.5 months (range 3 months to 7 months). Recanalisation was not seen in any of the patients during follow up. The average VCSS was 10.2 before the procedure and decreased to 3.9 after 3 months ($p<0.001$).	Studies with a larger sample or a longer follow up are included in table 2.
Yang GK, Parapini M, Gagnon J et al. (2018) Comparison of cyanoacrylate embolization and radiofrequency ablation for the treatment of varicose veins. Phlebology, 0(0), 1-6.	Non-randomised comparative study 335 patients (mean 57 years; 78% female) Follow up: mean 58 days	Treatment success was 100% in CAC and 99% in RFA. Superficial phlebitis was the most common complication noted at mid-term follow up in 5% of CAC and 16% of RFA ($p<0.05$). One patient in each group had asymptomatic proximal thrombus extension treated with anticoagulation for 2 weeks to 3 weeks. Three superficial infections from glue clumps were noted in the CAC group requiring excision and drainage.	Studies with a larger sample or a longer follow up are included in table 2.
Zierau U (2018) 76 months long time experience with the VenaSeal-system in treatment of truncal varicose veins: A follow-up study conducted on 2091 truncal saphenous veins in 1128 cases. Scholarly journal of surgery, 1(2): 20-24	Prospective comparative study 1128 patients (2091 truncal varicose veins) Follow up: 72 months Patients lost to follow up was not reported	Of the 2091 treated veins, a closure rate of 97.61% was achieved within the 1st month post operation. 1380 saphenous veins (68.2%) were followed up over a 6-8 months' time period and 50 partial and 28 complete recanalisation's were found, resulting in an effectiveness of 96.23%. No further recanalisation's were found after 76 months. In terms of postoperative side effects, the VenaSeal procedure appeared to be superior in comparison	Studies with a better follow-up rate and better quality were included in table 2.

		with laser and radio frequency techniques.	