



## Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER435
Topic:	Cyanoacrylate glue occlusion for varicose veins
Summary of findings:	<p>Health Technology Wales researchers searched for evidence on cyanoacrylate glue occlusion to treat varicose veins. This topic was identified from National Institute for Health and Care Excellence (NICE) interventional procedures guidance, which is used as the basis of this report.</p> <p>In addition to the NICE IPG670, we identified a health technology assessment from Ontario Health. Both products included the same two randomised controlled trials (RCTs), alongside other non-randomised comparative evidence. In addition, we also identified more recent systematic reviews, one of which included a network meta-analysis, as well as RCTs published after the secondary evidence. Overall, most evidence suggests that vein occlusion, recurrence and improved quality of life outcomes are similar between cyanoacrylate glue occlusion and other treatment options for varicose veins. Cyanoacrylate glue occlusion may have result in less pain (during and directly after treatment), although this is uncertain due to variation in the evidence. It may also have a shorter intervention time compared to other treatments.</p> <p>We identified multiple economic studies comparing cyanoacrylate glue occlusion against various other options for varicose vein treatment. This included two studies from the same authors, based in the UK. The economic evidence suggests that, when comparing various treatment options for varicose veins, cyanoacrylate glue occlusion is more costly than most other options with similar effectiveness. The economic evidence therefore suggests that it was not a cost-effective option.</p>

## Introduction and aims

Varicose veins are swollen and enlarged veins that usually occur on the legs and feet when small valves inside the veins stop working properly. The most commonly affected veins are the saphenous veins. Most people with varicose veins have no symptoms, but it may cause aching, heaviness, swelling, throbbing, cramping and itching. In more chronic cases, it can lead to skin discolouration, inflammatory dermatitis and ulceration.

Initial approaches to managing varicose veins include compression stockings, exercise and elevating the affected area. In more serious cases, such as those experiencing truncal reflux (backflow of blood through main superficial vein), people may be offered endothermal ablation, ultrasound-guided sclerotherapy or surgery.

Cyanoacrylate glue occlusion is a treatment that aims to close the varicose veins. The procedure is done under local anaesthetic using an ultrasound-guided catheter. The vein is compressed and the catheter is used to deliver medical glue to seal the vein.

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## Evidence overview

### Guidance and guidelines

The National Institute for Health and Care Excellence (NICE) published clinical guidelines on the diagnosis and management of varicose veins in 2013. The guideline includes recommendation on referral, assessment and treatment in a vascular service. The guideline does not refer to cyanoacrylate glue occlusion.

In 2020, NICE published interventional procedures guidance (IPG670), which recommended that evidence on safety and efficacy of cyanoacrylate glue occlusion for varicose veins was adequate to support its use under standard arrangements for clinical governance, consent and audit. It also stated that cyanoacrylate glue occlusion should only be performed by clinicians who are trained in the procedure and have experience in venous ultrasound. For this guidance, NICE did a rapid review of published efficacy and safety evidence up to October 2019. They identified two systematic reviews, three randomised controlled trials (RCTs), three non-randomised comparative studies, four case series and two case reports. The systematic reviews and RCTs are discussed in more detail below.

The first systematic review and meta-analysis (Vos et al. 2017) reported on 1,645 participants who received either cyanoacrylate glue occlusion or mechanochemical endovenous ablation of the great saphenous vein; the aim of the review was to evaluate efficacy of both interventions rather than comparative effectiveness between the two. Fifteen studies were included, two of which were RCTs. For both interventions, the review reported significant reduction in disease severity after treatment. All studies reported on complications, but type and rate varied.

The second systematic review (Bissacco 2019) reported on 918 participants with superficial vein insufficiency (either of great or small saphenous veins) who received the cyanoacrylate glue occlusion (specifically the Variclose system). Seven studies were included, none of which were RCTs. Based on two retrospective studies, Bissacco et al. (2019) reported that cyanoacrylate glue

occlusion had fewer complications compared with endovenous laser ablation, and a shorter procedure time (mean 15 minutes versus 33 minutes).

A US RCT included 222 participants with great saphenous vein insufficiency who received either cyanoacrylate glue occlusion or radiofrequency ablation, and reported up to 36 months follow up. Likelihood of recanalisation was lower in the cyanoacrylate glue occlusion group throughout the 36 month follow-up, although this was not statistically significant. Both groups showed and maintained improved quality of life (EQ-5D scores) and severity (VCSS and AVVQ scores) throughout the study period, but there was no significant difference between the two groups. Safety outcomes were also similar between the two groups, with the exception of ecchymosis (bruising) at day 3. Procedure duration was significantly shorter with radiofrequency ablation (mean 24 versus 19 minutes, respectively).

The final RCT, based in Turkey, recruited 456 participants with either great or small saphenous vein insufficiency to receive either cyanoacrylate glue occlusion, radiofrequency ablation or endovenous laser ablation. Occlusion rates were similar across all three groups at 6 months, 1 year and 2 year follow up. Procedure duration was significantly lower in the cyanoacrylate glue occlusion group (mean 15 minutes versus 27 minutes for radiofrequency ablation and 35 minutes for endovenous laser ablation).

#### **Additional secondary evidence**

We identified a more recent, partially relevant health technology assessment from Ontario Health on nonthermal endovenous procedures, including cyanoacrylate glue occlusion and mechanochemical ablation, for symptomatic varicose veins. Studies up to January 2020 were included. The HTA included 11 studies on cyanoacrylate adhesive closure: two studies were the same RCTs included in NICE IPG670, and the remaining nine were nonrandomised comparative studies. Vein closure was reported to be similar between cyanoacrylate glue occlusion and radiofrequency ablation (based on one RCT and four nonrandomised studies), and between cyanoacrylate glue occlusion and endovenous laser ablation (based on three nonrandomised studies). Overall, the authors stated that there were comparable improvements in both venous disease symptoms and quality of life between cyanoacrylate glue occlusion and other alternative procedures.

We identified two further systematic reviews published after the NICE and Ontario Health. One included a network meta-analysis of various interventions for vein incompetence (Gasior et al. 2022), and did not include any new studies published after the Ontario Health search dates. The network meta-analysis showed that cyanoacrylate glue occlusion had reduced odds of procedural failure compared to other treatments. Cyanoacrylate glue occlusion also had reduced recurrence in the short-term (6 months) compared to other treatments, but longer term recurrence was less certain. The other was a systematic review and meta-analysis evaluating the efficacy and safety cyanoacrylate glue occlusion compared to endovenous laser ablation (Amshar et al. 2022). It included the two RCTs discussed above and three cohort studies, one of which was an additional retrospective study that was published after the Ontario Health review. Pooled results from the two RCTs (already identified above) showed no difference in venous closure rates at one year between cyanoacrylate glue occlusion and endovenous laser ablation. Pooled data from three cohort studies showed reduced peri-procedural pain scores, lower skin pigmentation rates and lower nerve damage rates with cyanoacrylate glue occlusion, as well as reduced procedural time.

#### **Additional primary evidence**

We searched for additional comparative primary evidence that was published after the systematic reviews. We identified seven studies in total, three of which reported randomised controlled trials

(Belramman et al. 2022, Joh et al. 2021, Morrison et al. 2020). The treatment that cyanoacrylate glue occlusion was compared against varied across studies, and included radiofrequency ablation, surgical stripping and mechanochemical ablation. Outcomes reported by the randomised controlled trials also varied, and included pain, quality of life, and target vein occlusion at various follow-up points.

Belramman et al. (2022) compared cyanoacrylate glue occlusion and mechanochemical ablation groups, and reported that short term pain directly after treatment did not differ between. Compared to surgical stripping, however. Joh et al. (2022) reported that cyanoacrylate glue occlusion resulted in significantly less pain post-treatment. Both studies reported no difference between treatment groups for quality of life (measured with generic EQ-5D score as well as disease-specific scores), disease severity or occlusion rates at up to 12-month follow up.

One study reported on a five-year extension study (report 26 to 60 month follow-up) following a randomised controlled trial comparing cyanoacrylate glue occlusion with radiofrequency ablation (Morrison et al. 2020). No additional recanalisation events were observed within the 36-60 month follow-up, and Kaplan-Meier estimates for 'freedom from recanalisation' showed that cyanoacrylate glue occlusion was non-inferior to radiofrequency ablation. As with previous studies, treatment groups showed similar results for quality of life and disease severity.

### **Economic evidence**

The health technology assessment from Ontario Health included an economic evidence review and evaluation. Their cost-utility analysis showed that differences in quality-adjusted life-years between cyanoacrylate glue occlusion, mechanochemical ablation, endovenous laser and radiofrequency ablation were small. In the reference case, surgical vein stripping was dominated by all other treatments, including cyanoacrylate glue occlusion. However, when comparing with endovenous laser ablation, cyanoacrylate glue occlusion had an ICER of CAD\$108,425. When applying a willingness-to-pay threshold of CAD\$50,000 per QALY gained, the probability of cyanoacrylate glue occlusion being cost effective was 18.8%. The most likely cost-effective option was endovenous laser ablation (55.6% probability of being cost effective).

The Ontario Health paper also reported on a cost-utility analysis from the UK (Epstein et al. 2018) comparing multiple options including cyanoacrylate glue occlusion. Epstein et al. (2018) reported that cyanoacrylate glue occlusion was more costly (£1,395 in 5 years), but no more effective, than other therapies. Cyanoacrylate glue occlusion was dominated by radiofrequency ablation, and authors concluded that it was not a cost-effective option (willingness-to-pay threshold £20,000).

We identified an additional two economic papers published after the Ontario Health report. The first was based in Spain and is not discussed further here, but is included in the reference list for completeness. The second, Epstein et al. (2022), was UK based and compared multiple treatment options. As with the 2018 study, authors concluded that cyanoacrylate glue occlusion had higher procedure costs (estimated at £640) but no evidence of greater benefits compared to other interventions, and was not a cost effective option.

### **Areas of uncertainty**

The following would need to be considered should this topic proceed to appraisal:

- There are multiple options for treating varicose veins, and it is unclear at this stage which options are routine care in Wales. What is standard care in Wales will impact on the relevancy of the evidence identified.

- Varicose veins are normally located in the saphenous vein, and it appears in the majority of study participants it was located in the great saphenous vein. Consideration may be needed on the inclusion of other locations (if they exist) and how the synthesis should take location into account.
- More clarity is needed as to what point in the patient pathway a referral to cyanoacrylate glue occlusion or other endovenous ablation techniques would occur. Consideration would then be needed as to whether the evidence reflects this place in the pathway.
- It appears that the clinical, etiological, anatomic and pathophysiologic (CEAP) classification is commonly used to classify disease severity. It is unclear whether there are other classifications that may be used in the literature.
- How the following subgroups/subpopulations should be approached in fuller review:
  - great or small saphenous vein
  - with or without prior DVT
  - levels of disease severity (CEAP classifications or otherwise)
- At this stage it is unclear what costs and consequences were/were not considered in the identified cost effectiveness analyses and whether these would be appropriate for Wales.

## Literature search results

### Health technology assessments and guidance

NICE (2013). Varicose veins: diagnosis and management. Clinical guideline CG168. <https://www.nice.org.uk/guidance/cg168>

NICE (2020). Diagnosing and managing varicose veins in adults. Cyanoacrylate glue occlusion for varicose veins. Interventional procedures guidance [IPG670]. <https://www.nice.org.uk/guidance/ipg670>

Ontario Health. (2021). Nonthermal Endovenous Procedures for Varicose Veins: A Health Technology Assessment. Ont Health Technol Assess Ser. 21(8): 1-188.

### Evidence reviews and economic evaluations

Amshar M, Nugraha RA, Batubara EAD, et al. (2022). Cyanoacrylate embolization versus endovenous laser ablation in treating saphenous vein insufficiency: a systematic review and meta-analysis. *Ann Vasc Surg*. 80: 313-24.

Gasior SA, O'Donnell JPM, Aherne TM, et al. (2022). Outcomes of saphenous vein intervention in the management of superficial venous incompetence: a systematic review and network meta-analysis. *Ann Surg*. 275(2): e324-e33.

### Individual studies

Ay Y, Gunes E, Turkkolu ST, et al. (2021). Comparative efficacy and life quality effects of surgical stripping, radiofrequency ablation, and cyanoacrylate embolization in patients undergoing treatment for great saphenous vein insufficiency. *Phlebology*. 36(1): 54-62.

Belramman A, Bootun R, Tang TY, et al. (2022). Pain Outcomes Following Mechanochemical Ablation vs Cyanoacrylate Adhesive for the Treatment of Primary Truncal Saphenous Vein Incompetence: The MOCCA Randomized Clinical Trial. *JAMA Surgery*. 157(5): 395-404.

Daylan A, Islamoglu F. (2022). Comparative analysis of the results of cyanoacrylate ablation and radiofrequency ablation in the treatment of venous insufficiency. *Journal of Vascular Surgery*. 10(3): 661-8.e2.

El Kilic H, Bektas N, Bitargil M, et al. (2022). Long-term outcomes of endovenous laser ablation, n-butyl cyanoacrylate, and radiofrequency ablation for treatment of chronic venous insufficiency. *Journal of Vascular Surgery*. 10(4): 865-71.

Epstein D, Bootun R, Diop M, et al. (2022). Cost-effectiveness analysis of current varicose veins treatments. *Journal of Vascular Surgery*. 10(2): 504-13.e7.

Joh JH, Lee T, Byun SJ, et al. (2022). A multicenter randomized controlled trial of cyanoacrylate closure and surgical stripping for incompetent great saphenous veins. *Journal of Vascular Surgery*. 10(2): 353-9.

Morrison N, Gibson K, Vasquez M, et al. (2020). Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *Journal of Vascular Surgery*. 8(6): 978-89.

Vicente-Jimenez S, Lopez-Valcarcel B, Maynar M, et al. (2022). Clinical results and cost-effectiveness of radiofrequency and cyanoacrylate ablation compared with traditional surgical stripping for treating varicose veins. *Journal of Vascular Surgery*. 10(4): 846-54.e2.

**Date of search:**

December 2022

**Concepts used:**

Varicose veins, Cyanoacrylate glue occlusion, Cyanoacrylate adhesive closure

## Proposed research question and evidence selection criteria (if selected)

<b>Proposed research question</b>	<b>What is the clinical and cost effectiveness of cyanoacrylate glue occlusion to treat varicose veins, compared to standard care?</b>
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	<b>Included</b>	<b>Excluded</b>
<b>Population</b>	People with varicose veins	
<b>Intervention</b>	Cyanoacrylate glue occlusion	
<b>Comparison/ comparators</b>	Standard care	
<b>Outcomes</b>	(Saphenous) vein occlusion rate Re-canalisation Venous clinical severity score (VCSS) Symptom relief Quality of life Adverse events/Safety (hypersensitivity, granuloma formation, thromboembolism, nerve injury, paraesthesia)	
<b>Study design</b>		