

# Current practice of cyanoacrylate endovenous ablation: American vein and lymphatic society position statement

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## Abstract

**Background:** Cyanoacrylate endovenous ablation and closure of incompetent saphenous veins have become increasingly utilized since its approval for use in the United States in 2015. This increase in usage necessitates a societal update to guide treatment and ensure optimal and consistent patient outcomes.

**Method:** The American Vein and Lymphatic Society convened an expert panel to write an updated Position Statement with explanations and recommendations for the appropriate use of cyanoacrylate endovenous ablation for patients with venous insufficiency.

**Result:** A Position Statement was produced by the expert panel with recommendations for appropriate use, treatment technique, outcomes review, and potential adverse events. Their recommendations were reviewed, edited, and approved by the Guidelines Committee of the Society.

**Conclusion:** This societal Position Statement provides a useful document for reference for physicians and venous specialists to assist in the appropriate use of cyanoacrylate endovenous ablation in the treatment of patients with venous insufficiency.

## Keywords

Catheter-based interventions, endovascular treatment, pharmacologic agents, saphenous vein, venous reflux

## Background

Cyanoacrylate adhesives, popularly referred to as “super glue,” were invented in 1942. They are liquid monomers that polymerize rapidly in the presence of anions, including the hydroxyl moiety of water. N-butyl cyanoacrylate (n-BCA) is the most common adhesive used in medicine. The VenaSeal<sup>TM</sup> cyanoacrylate formulation for closure of incompetent saphenous veins received a CE Mark for use in 2011 followed by Australia and the United States in 2012 and 2015, respectively. It has also received approval for use in Canada. VenaSeal<sup>TM</sup> is a non-tumescent, non-thermal treatment for patients suffering with symptomatic superficial venous reflux disease and is the only approved cyanoacrylate for such use in the United States. VariClose (Biolas; Ankara, Turkey), Venex (Vesta Medical; Ankara, Turkey), VenaBlock and Veinoff (Invamed; Ankara, Turkey) employ proprietary forms of the liquid adhesive and claim unique physico-chemical properties that can influence the clinical application but are not available in the United States and Canada although they have entered the

international market. VariClose is CE marked for use in the European Union, but this does not necessarily mean that it is approved by all European countries. Because of the more limited approval and published data on the other cyanoacrylate formulations, this position statement will focus specifically on the VenaSeal<sup>TM</sup> product. The increased nationwide utilization of cyanoacrylate for superficial endovenous ablation and relative lack of familiarity with its appropriateness, particularly among regional payers,

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suggested a need for a published societal position statement on its applicable use and clinical indications.

The Research Committee of the AVLS recommended an expert panel of authors to develop a position statement on cyanoacrylate endovenous ablation. These recommended panel members were reviewed and approved by the Executive Committee of the AVLS. The draft statement was revised and approved by the Guidelines Committee of the AVLS and represents societal endorsement of its recommendations.

## Appropriate use

Saphenous vein ablation to treat axial reflux in symptomatic patients with CEAP Clinical classes 2–6 is supported by clinical evidence and multiple published clinical guidelines.<sup>1–3</sup> Both thermal and non-thermal ablation technologies are recommended for saphenous vein treatment depending on the available expertise of the treating physician and the preference of the patient. Endovenous cyanoacrylate closure (CAC) has been proven to be an effective and safe treatment option for incompetent saphenous veins. As a non-thermal ablation treatment, it offers several advantages compared to thermal ablation techniques. CAC does not require tumescent anesthesia to protect surrounding tissues and superficial nerves. Without the need for the multiple needle injections for tumescence, it lessens intra-procedural patient discomfort as well as the risk of hematoma formation, especially in patients who are obese or on anticoagulation therapy. CAC can also be safely performed in the below knee great saphenous vein and the small saphenous vein, without the risk of nerve injury associated with thermal techniques, allowing for more distal vein treatment. Cyanoacrylate closure does not require the use of a compression garment after the procedure for vessel wall coaptation which is a benefit for patients who have difficulty tolerating compression garments.<sup>4,5</sup> However, post procedure compression has utility in patients who also have multiple tributary varicosities, incompetent perforator veins, and lymphedema.

Cyanoacrylate closure has been used off label as a non-thermal approach to close pathologic perforator veins with good efficacy and safety profile. Although designed and approved for use as a catheter-directed procedure only, expert clinicians have used CAC by direct percutaneous injection. However, more evidence is needed to support this approach.<sup>6</sup>

## Treatment technique

The manual and procedure guide for use of the VenaSeal™ Closure System provides details for doing the procedure and is available online.<sup>7</sup> This section will include some current usage options. It should be emphasized that CAC should only be performed by a trained physician with experience in the diagnosis and treatment of venous reflux disease with endovenous techniques.

An informed discussion with the patient should take place regarding the risks and complications of all treatment options, and possible remedial actions in the event of adverse outcomes, before the procedure. Unlike other venous ablation techniques, cyanoacrylate is a permanent implant that can be associated with its own unique complications and allergic reactions. As such, CAC is contraindicated in patients with autoimmune diseases, granulomatous disease, hypersensitivity and other systemic inflammatory disorders including vasculitis, mastocytosis, sarcoidosis, systemic lupus erythematosus, atopy, or active infection.

Detailed ultrasound mapping of the targeted vein should be performed and documented to include the diameter, location of the epifascial segments, and status of large tributaries and perforator veins.<sup>5</sup>

Beginning the procedure, venous access is attained at the lowest point of reflux with the “starred” catheter tip position verified and positioned using ultrasound in both the longitudinal and transverse planes. The catheter tip should be at least 5 cm distal to the saphenofemoral (SFJ) or saphenopopliteal (SPJ) junction to decrease the chance of adhesive extension into the deep venous system.<sup>5,8</sup> Prior to the first delivery of adhesive, specific and uninterrupted compression of the great saphenous vein (GSV) must be applied using the ultrasound probe in a transverse position 2–3 cm above the catheter tip near the SFJ. Each aliquot delivers 0.10 mL of adhesive into the target vein by pulling the trigger of the dispenser gun once and holding the trigger for 3 s. After delivery of the first aliquot of adhesive while pulling back the delivery catheter for 1 cm, and delivering a 2nd aliquot while withdrawing the catheter for 3 cm, ultrasound probe compression should be held continuously for 3 min to allow full adhesive polymerization. During this time, additional but compassionate hand compression is applied caudal to the transducer over the injected target vein. At the conclusion of the procedure, ultrasound visualization of the relevant saphenofemoral or saphenopopliteal junction is made to confirm and document continued patency.

Recommendations for delivery of additional adhesive and longer compression times along the length of the target vein have allowed for some modifications according to physician discretion and experience. In the manufacturer’s Instructions for Use, it allows for modifications to be made for segmental treatment of the target vein with any combination of 3 cm, 6 cm, or 9 cm lengths. While compression is always maintained just above the catheter tip with the ultrasound probe, 1 aliquot is typically dispensed for each 3 cm segment while the catheter is withdrawn over a 3-sec interval. Allowances are also possible for additional aliquots of adhesive in the areas of larger diameter, tributaries and perforator veins. Additionally, cyanoacrylate delivery into large tributaries may have a positive therapeutic effect similar to that of concomitant procedures.<sup>9</sup> Longer hand compression time along treated segments achieves more even distribution of the adhesive and more complete evacuation of blood from the vessel. Additional



“drops” of adhesive did not increase the development of occurrence of endovenous glue-induced thrombosis (EGIT).<sup>8</sup>

To minimize exposure of adhesive to subcutaneous tissue and decrease exit site complications, modifications for the removal of the delivery catheter have been suggested. After the 30 sec of compression associated with the final injection within the target vein, unlock the spin-lock mechanism of the white delivery catheter from the blue introducer. Maintain the introducer position within the target vessel. While holding the blue introducer stationary, retract the white catheter into the introducer until the catheter’s proximal laser mark is visible 1–5 cm outside of the introducer hub. Remove the introducer and catheter together and apply hand pressure as long as necessary to achieve hemostasis at the access site.

## Outcomes

The clinical evidence supporting the safety and effectiveness of CAC is derived from a number of clinical studies. The VeClose trial was a prospective randomized, multicenter study in patients with venous reflux of the GSV who were treated with either CAC or radiofrequency ablation (RFA) therapy. This demonstrated continued noninferiority of CAC compared with RFA with closure rates at 5 years of 91% and 85%, respectively.<sup>10</sup> Clinical improvement was also noted with the Venous Clinical Severity Score (VCSS) enhanced by 75% and 72% from baseline in the CAC group and the RFA group ( $p < .0001$ ), respectively. Similarly, the Aberdeen Varicose Vein Questionnaire (AVVQ) and the EuroQol-5 (EQ-5D) scores were significantly improved by 55% and 67% ( $p < .0001$ ) and 15% and 12% ( $p < .0001$ ), respectively, in each group at 5 years. Additionally, the CAC group demonstrated significant improvement in pain, discomfort, and mobility from baseline which was maintained at 5 years after the procedure.

Similar long-term results were demonstrated at 3 years in the eSCOPE (European Saphenous Closure System Observational Prospective Study) with closure rates of 89% and significant improvement in the VCSS scores from 4.3 to 0.9.<sup>5</sup>

Hwang et al. demonstrated that covering the entry points of varicosities and being able to access the saphenous vein lower down the leg was associated with more complete regression of varicose veins.<sup>9</sup> The ability with CAC to access and treat the target vein as distal as the ankle may also provide an advantage in ulcer healing. O’Banion et al. demonstrated a shorter time to wound healing in CEAP 6 patients after successful vein closure with CAC as compared to RFA with a lower ulcer recurrence rate.<sup>4</sup> Widespread international clinical experience with CAC has shown it to be an effective treatment modality for superficial venous insufficiency with a favorable safety profile.

## Adverse events

The most significant published adverse events are superficial phlebitis and DVT, hypersensitivity reaction (HSR),

endovenous glue-induced thrombosis (EGIT)/ablation-related thrombus extension (ARTE), and foreign body granuloma.<sup>11,12</sup> A recent publication of adverse events submitted to regulatory bodies in the United States, United Kingdom, and Australia documents deaths and strokes not previously reported in the medical literature although definitive causal relationships with cyanoacrylate adhesive could not be determined.<sup>13</sup>

## Superficial phlebitis and DVT

Phlebitis is the most common adverse event after CAC with a higher occurrence rate than after endothermal ablation techniques.<sup>11</sup> The reported rate varies from 0.8% to 12% after endothermal ablation techniques compared to 1.2%–25% after CAC.<sup>11</sup> However, there is no clear consensus on the signs and symptoms to define phlebitis and as such it can be difficult clinically to distinguish from a hypersensitivity reaction.<sup>11</sup> Superficial phlebitis, induration, and hyperpigmentation may be more likely when cyanoacrylate is used in very superficial veins compared to other techniques, and thus CAC should be used with caution in epifascial saphenous veins. The odds of occurrence of DVT are reported to be the lowest among all superficial venous interventions.<sup>12</sup>

## Hypersensitivity reaction

Hypersensitivity reaction (HSR) is an exaggerated immune system response to a foreign substance and is a unique adverse event specific for this type of endovenous ablation (Figure 1) associated with the fact that CAC is a permanent bioimplant.<sup>11</sup> Type IV hypersensitivity is a delayed (1–3 days) cell-mediated inflammatory reaction directed against the cyanoacrylate along the course of the treated vein. This is more frequently reported than type I hypersensitivity which is an immediate reaction and involves immunoglobulin E (IgE) release of antibodies against a foreign allergen invoked by a previous exposure. Parsi et al. have postulated CAC HSR is a combined type I and type IV response as can be seen in latex exposure.<sup>1</sup>

HSR has been reported in 6% of patients manifested as an erythematous rash along the course of the treated vein.<sup>6</sup> It was of mild severity in 4.2%, moderate in 1.3%, and severe in 0.3%. The symptom onset began 1–23 days after the procedure with a duration of 3–28 days and necessitated one explant. We are unaware of any reports of anaphylaxis. Such hypersensitivity reactions appear to be more likely if extravascular tissues are exposed to the uncured CAC monomer. Patients with prior and repeated exposure to cyanoacrylate products, and those with autoimmune conditions, atopic dermatitis, recurrent infections, granulomatous disease, and multiple sensitivities or mast cell disorders are at higher risk for this complication.





**Figure 1.** Hypersensitivity inflammatory skin reaction (red ellipse) after cyanoacrylate closure of the thigh portion of the GSV.

Treatment of HSR is focused on alleviating the symptoms and is successful in the majority of patients. This may include the combined use of non-steroidal anti-inflammatory drugs (NSAID), oral or topical antihistamines, oral or topical steroids, and in more severe cases, longer steroid taper or IV steroids.<sup>1</sup> Some have advocated pretreatment CAC skin patch testing. However, the lack of a skin reaction does not exclude the possibility of HSR and may itself induce sensitization. Additionally, the Instructions for Use recommends against prior skin exposure to the adhesive. It has been strongly recommended that professionals using CAC avoid touching the product to prevent their own sensitization.<sup>1</sup>

### *Ablation-related thrombus extension*

Initial clinical experience with CAC reported an alarming 21% rate of thread-like glue extensions to the saphenofemoral junction of the GSV. It has been hypothesized that the mechanism is inadvertent proximal glue migration before complete polymerization, possibly aided by procedural compression.<sup>11</sup> This led to a change in the Instructions for Use, recommending an increased distance of 5 cm of the white catheter tip from the SFJ, resulting in fewer and less severe adverse events.<sup>11</sup> The extension of CAC and thrombus beyond the SFJ after treatment may assume different patterns of shapes and echogenicity. Cho et al. first described the term “endovenous glue-induced thrombosis,” or EGIT, and introduced a classification schema not dissimilar to that for endothermal heat induced thrombosis or EHIT,<sup>14</sup> with an incidence of < 2%.<sup>10,15</sup> A multi-specialty task force of the Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society,

however, has recommended the term ablation-related thrombus extension (ARTE) that would include EGIT and EHIT and thrombus developing following any type of venous ablation procedure.<sup>16</sup> ARTE after CAC may be like a thread or stick-like shape and is graded according to the glue/thrombus occupied area in the common femoral vein. The assessment of ARTE is done by transverse imaging at the junction level in a standing position (Figure 2). Grade I: vein <25% of the cross-sectional area. Grade II: 25%–49%. Grade III: 50%–74%. Grade IV: 75%–100%. Risk factors of advanced age, small GSV diameter of < 5 mm, and clotting history were reported in small retrospective studies but these findings have yet to be replicated by others.<sup>11,14</sup>

Most studies indicate that the majority of ARTE regressed or are not visualized in later follow-up periods while in a minority ARTE remains unchanged.<sup>15</sup> There has been one case report of a pulmonary embolism without DVT following VenaSeal™ treatment.<sup>11</sup> No criteria have been established for defining the ultrasound characteristics of cyanoacrylate extension from thrombus development. There are also no specific guidelines for the treatment of ARTE following CAC. However, analogous to the experience of the treatment of ARTE after endothermal venous ablations, anticoagulation therapy for symptomatic ARTE or asymptomatic class III or IV is recommended with a direct oral anticoagulant until the thrombus retracts, although the level of evidence is low.<sup>15,16</sup> The continuing presence of an intravascular foreign body in CAC, unlike other ablation modalities, may adversely affect the risk of thrombus formation and propagation.<sup>11</sup>

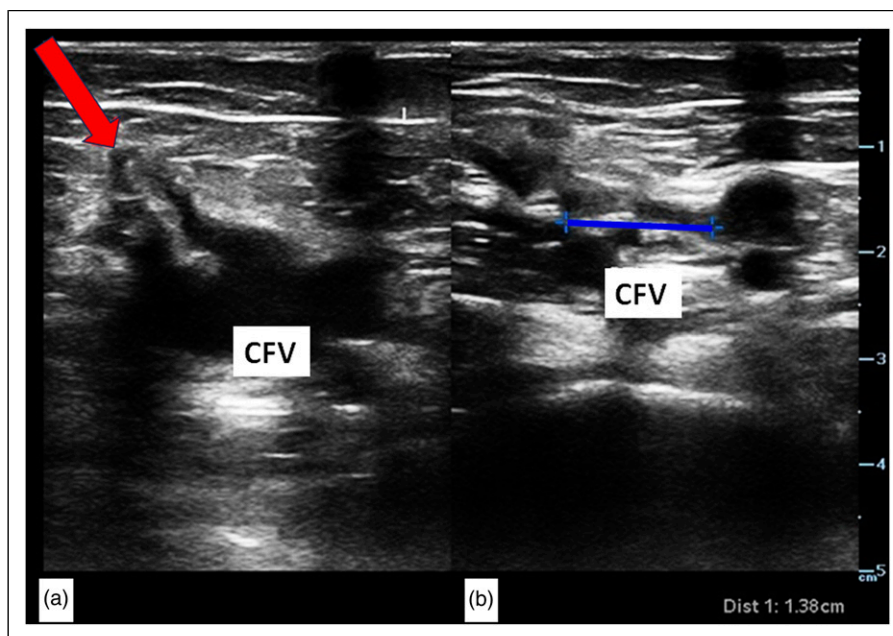
### *Foreign body granuloma/exit site complication*

The development of a foreign body granuloma with CAC is increasingly recognized but poorly understood. The histological presence of foreign body giant cells post CAC is thought to be a normal physiological response.<sup>1,11</sup> This innate reaction usually remains asymptomatic. However, progression to skin ulceration and foreign body granulomas along the course of the treated vein and at the skin entry site can occur. The risk factors and mechanism of action are unclear, but is likely due to CAC extrusion prior to polymerization into the peri-vascular space via tributaries or upon catheter removal. Retraction of the delivery catheter into the introducer prior to removal from target vein reduces exit site exposure. Treatment usually necessitates excision. There is the possibility of infection from bacteremic seeding or colonization after CAC due to its status as a bioimplant.<sup>11</sup>

### **Summary of recommendations**

1. Frank pre-procedure discussion with the patient regarding potential unique adverse events related to





**Figure 2.** Ablation-related thrombus extension (ARTE) Grade I after cyanoacrylate closure of the GSV. (a) Transverse ultrasound image of ARTE extending into the common femoral vein (CFV). (b) Longitudinal image measuring the ARTE extent of 1.38 cm.

CAC as a permanent foreign body and consideration of other treatment options.

2. Pre-procedure screening questionnaire for possible hypersensitivity reactivity.
3. Minimum 5 cm distance of delivery catheter tip from SFJ, possibly longer for smaller diameter veins <5 mm.
4. Uninterrupted compression for 3 min at SFJ following first delivery of CAC.
5. Minor technique modifications are allowed including additional adhesive and longer compression at areas of larger diameter, tributaries, and perforator veins based on the practitioner's experience, with documentation and outcome monitoring.
6. Delivery catheter retraction into introducer sheath prior to removal of device.
7. Direct oral anticoagulation for symptomatic post procedure DVT or asymptomatic ARTE Class III and Class IV.

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### Author contributions

Vasquez MV: Analysis and interpretation, data collection, writing the manuscript, critical revision, approval of the manuscript, and

agreement to be accountable; Di Iorio MD: Analysis and interpretation, data collection, critical revision, approval of the manuscript, and agreement to be accountable; Worthington-Kirsch RWK: Analysis and interpretation, data collection, critical revision, approval of the manuscript, and agreement to be accountable; Fakhoury EF: Analysis and interpretation, data collection, critical revision, approval of the manuscript, and agreement to be accountable; and Blebea JB: Conception and design, analysis and interpretation, data collection, writing the manuscript, critical revision, approval of the manuscript, and agreement to be accountable.

### Declaration of conflicting interests

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### Ethical statement

#### Ethical approval

Project approved by the Research Committee of the AVLS.

### Guarantor

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## Appendix

### Hypersensitivity Screening Questionnaire

Can be used for clinical assessment of potential hypersensitivity. The answer should be “NO” to all questions.

- Does the patient have a significant autoimmune disease or systemic inflammatory disorders such as psoriasis, rheumatoid arthritis, lupus, sarcoidosis, vasculitis, mastocytosis, or active infection?
- Does the patient have a history of atopic eczema?
- Does the patient have a known intolerance for CAC adhesives such as skin glue, acrylic nails, or glue for eyelash extensions?
- Does the patient have known multi-sensitivity to medications or foods?