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# Mid-term results of cyanoacrylate closure for the treatment of incompetent great and small saphenous veins: Findings from a Japanese prospective consecutive multi-center registry: Mid-term results of cyanoacrylate closure

**Takahiro Imai[1], Makoto Mo[2], Masayuki Hirokawa[3], Nobuhisa Kurihara[3], Shintaro Shokoku[4], Satoru Sugiyama[5], Nozomu Shirasugi[6], Hitoshi Kusagawa[7], Yuji Hoshino[8], Takashi Yamamoto[9], Eiichi Hyodo[10], Keichi Furubayashi[11] and Tomohiro Ogawa[12]**

## Abstract

**Objectives:** We evaluated the efficacy and safety of cyanoacrylate closure (CAC) for endovascular treatment of varicose veins with cyanoacrylate adhesive (VenaSeal® closure system) in Japan.
**Methods:** A multicenter prospective consecutive registry study was conducted at 12 centers in Japan on 125 patients with primary varicose veins who underwent CAC. The patients were evaluated on target vein occlusion, postoperative complications, Visual Analogue Scale (VAS) for pain, revised Venous Clinical Severity Score (rVCSS), Aberdeen Varicose Vein Questionnaire (AVVQ), and EuroQol 5 dimensions 5-level (EQ-5D-5L) for 1-year after the surgery.
**Results:** The closure rate was 92.6% at 1 year postoperatively, and 95.0% and 90.2% for GSV and SSV respectively with little difference ($p$ = .491). The mean VAS in the immediate postoperative period was 18.9 ± 23.4. Postoperative complications were observed in 20 patients (16%). Hypersensitivity-type phlebitis occurred in 7 patients (5.6%). Infection of the treated vein resulted in resection of GSV. The rVCSS and AVVQ improved significantly after 90 days and 1 year postoperatively ($p$ < .001), while the EQ-5D-5L have not changed.
**Conclusion:** Cyanoacrylate Closure was considered generally a safe and minimally invasive treatment with good mid-term outcomes including SSV. However further study is required for some CAC specific complications.

## Keywords

Cyanoacrylate closure, varicose veins, small saphenous vein insufficiency, quality of life questionnaire, multicenter review

[1]Department of Vascular Surgery, Nishinokyo Hospital, Nara, Japan
[2]Department of Cardiovascular Surgery, Yokohama Minami Kyosai Hospital, Yokohama, Japan
[3]Ochanomizu Vascular and Vein Clinic, Tokyo, Japan
[4]Shokoku Shintaro Clinic, Okayama, Japan
[5]Department of Surgery, Hiroshima Teishin Hospital, Hiroshima, Japan
[6]Department of Vascular Surgery, Yokohama Asahi Chuo General Hospital, Yokohama, Japan
[7]Matsusaka Ohta Clinic, Matsusaka, Japan
[8]Department of Vascular Surgery, Fukuoka Sanno Hospital, Fukuoka, Japan
[9]Yamamoto Vein Clinic, Kobe, Japan
[10]Hyodo Internal Medicine and Eye Clinic, Amagasaki, Japan
[11]Umeda Vascular & Vein Clinic, Osaka, Japan
[12]Department of Vascular Surgery, Fukushima Daiichi Hospital, Fukushima, Japan

**Corresponding author:**
Takahiro Imai, Department of Vascular Surgery, Nishinokyo Hospital, 95-1, 7-Jo Machi, Nara-Shi, Nara 630-8051, Japan.
Email: my-fists@cello.ocn.ne.jp

## Introduction

In 2011, endovenous ablation was approved by national health insurance in Japan. Since then, endovascular treatment has become the standard treatment for varicose veins in Japan, instead of surgical treatment such as stripping. Cyanoacrylate closure (CAC) using VenaSeal® closure system, mainly composed of n-butyl-2-cyanoacrylate (NBCA), was approved by the United States FDA in 2015 and Japan in December of 2019. In 2020, Japanese guidelines for CAC treatment were published. We reported the results of physician-led clinical research and post-marketing surveillance on the efficacy and safety of CAC using VenaSeal® closure system at 12 centers in Japan.

## Methods

### Study design

When a new treatment is approved in Japan, a post-marketing surveillance is required to confirm the initial results of induction based on safety measures. Therefore, we had aimed to clarify the efficacy and safety of CAC in patients with varicose veins in a prospective, consecutive case-registration, single-arm clinical trial in Japan. The study was a multicenter study (12 centers) conducted by experienced physicians and well-equipped medical institutions regarding treatment of varicose veins. All doctors at the 12 facilities have more than 10 years of experience in varicose vein operation and have treated hundreds of cases with endovenous treatment (EVT). The target number of patients was 60 consecutive patients with great saphenous vein (GSV) treatment and 65 patients with small saphenous vein (SSV) treatment. The target number of patients was calculated considering the accurate evaluation of safety endpoints and the dropout rate during the study period. Since SSV cases were not included in the previous clinical trials at the time of CAC approval, the Pharmaceuticals and Medical Devices Agency (PMDA) decided to enroll the same number of SSV cases as GSV cases in this study in order to evaluate the results of CAC for SSV.

### Patients

Consecutive patients who underwent CAC with the VenaSeal® closure system at 12 centers in Japan between December 2019 and June 2020 with a diagnosis of primary varicose veins were included. The patient inclusion and exclusion criteria are based on Japanese guidelines for CAC based on previous liturtitures.[1,2] Patients were selected of those over 40 years of age with CEAP classification C2 to C5. This treatment was performed for the first time in Japan, and the long-term outcomes of the treatment were unknown. Therefore, we decided that the subjects of our study would be patients aged 40 years or older. Diagnosis of the primary varicose veins were based on ultrasonography with reflux time of the GSV or SSV for more than 0.5 s. The maximum diameter of the treated vessel was 12 mm or less. Patients with saphenous veins close to the body surface were excluded. Patients who met the guideline exclusion criteria such as allergic conditions were excluded (Table 1).

### Procedure

Cyanoacrylate Closure was performed using the VenaSeal® closure system and in accordance with the instruction for use. Anesthesia was administered locally with 1% Lidocaine. In some cases, a combination of local anesthesia and intravenous sedation such as with propofol were used in some centers. Under ultrasound guidance, the tip of the catheter filled with cyanoacrylates (CA) was placed 5 cm from the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ). For CA injection, the ultrasound probe was placed 2–3 cm proximal to the catheter tip. While the target vein was compressed with probe, 0.10 mL of CA was injected with holding the trigger of the gun for 3 s. After the first injection, the catheter was quickly pulled back 1 cm and 0.10 mL of CA was additionally injected. The catheter was quickly pulled back 3 cm and pressure was applied on the whole injected segment of the vein by finger for 3 min. After the first compression, repeat procedure of 0.10 mL of CA injection, the catheter pullback by 3 cm, and compression for 30 s were performed. After the last compression, the introducer sheath was pushed forward from the puncture site and the delivery catheter was placed into the introducer sheath. Then introducer and delivery catheter were removed together to prevent adhesive residue in the subcutaneous tissue at the puncture site. Basically, no phlebectomy nor postoperative compression with elastic stockings were not used. Non-steroidal anti-inflammatory drugs (NSAIDs) were routinely prescribed for 7 days postoperatively. Prior to this study, all primary physicians at each facility attended the precise lecture on CAC including hands-on training. Then they visited experienced overseas facilities for onsite training. The first case was performed under the supervision of the experienced proctor.

### Data collection and postprocedural follow-up

The data collection was performed before operation, at the day of surgery, 7 days, 30 days, 90 days and 1 year after the operation. The total observation period of the study was 1 year. Saphenous vein closure rate, postoperative pain, clinical sign, symptoms, quality of life (QoL), and post-operative complications were recorded. The closure rate was evaluated by ultrasonography. Target vein occlusion was defined as the closure of the treated vein segment without an opening more than 3 cm in the middle segment or 5 cm in proximal segments from sapheno-femoral junction

**Table 1.** Study eligibility criteria.

| | |
|---|---|
| Inclusion criteria | Patients with symptomatic primary saphenous vein insufficiency. |
| | Age ≧ 40 years and ≦90 years. |
| | Maximum diameter of the target vein does not exceed 12 mm. |
| Exclusion criteria | CEAP classification of C6. |
| | Saphenous vein outside the compartment or near the surface of the skin. |
| | MRSA infection. |
| | Previous or suspected deep vein thrombosis or pulmonary embolism. |
| | Previous or suspected collagen disease. |
| | Previous or suspected granuloma. |
| | Daily use of antihistamine drugs. |
| | Multiple allergies. |
| | Known sensitivity to CA adhesives. |
| | Known sensitivity to formaldehyde. |
| | Allergy to eyelash extensions and nail polish. |
| | Eyelash and nail technicians. |
| | Other patients with contraindications according to Japanese ETA guidelines[2]. |

CEAP: clinical-etiology-anatomy-pathophysiology; MRSA: methicillin-resistant *staphylococcus aureus*; CA: cyanoacrylate.

or sapheno-popliteal junction.[3–6] Postoperative pain was evaluated using the Visual Analogue Scale (VAS). Symptoms and sign of chronic venous insufficiency was assessed using the revised Venous Clinical Severity Score (rVCSS). QoL was assessed by using The Aberdeen Varicose Vein Questionnaire (AVVQ) and the Euro QoL 5-dimensions 5-levels (EQ-5D-5L).[7–9] The physicians at each institution recorded postoperative complications and reported the occurrence of each incident to an independent event review committee organized by three of the authors (HM, OT, and MM). The committee analyzed each reported complication and categorized them according to each definition. Briefly superficial thrombophlebitis is a condition in which localized induration is the main symptom and thrombus is found in the same area on ultrasound imaging. The patients with pain as the main symptom without thrombus were classified as "foreign body reaction." Hypersensitive reactions were classified into the so-called Type I Immediate hypersensitivity, in which symptoms such as anaphylactic shock occur immediately after treatment, and Type IV delayed hypersensitivity, which appears within a few days to a few weeks with symptoms of itching sensation. Type IV delayed hypersensitivity was further classified into allergic contact dermatitis and hypersensitivity-type phlebitis. Each complication was prospectively investigated in a multicenter setting. Each survey was conducted by the physician or nurse in charge of the examination.

### *Statistical analysis*

Fisher's exact test was applied to compare the closure rate between the GSV and SSV groups. The Mann-Whitney U test was used to compare the VAS between the group. The results of rVCSS, AVVQ, and EQ-5D-5L were analyzed using a linear mixed model. The significance level of statistical tests is set at $p < .05$. Statistical analyses were performed using the statistical software IBM SPSS Statistics 24.0 for Windows/IBM Corporation (Chicago, IL, USA).

## Results

### *Patient and follow-up*

The subjects were 125 patients with 143 legs, aged between 39 and 88 years (68.8 ± 13.2 years), 39 males and 86 females. Seven patients (29.2%) had history of mild allergies. Preoperative CEAP classification was C2: 71 legs, C3: 47 legs, C4a: 16 legs, C4b: 8 legs, and C6: 1 leg. Targeted vessels were 72 great saphenous veins (GSV) and 71 small saphenous veins (SSV). Follow-up of 125 treated patients was 121 (96.8%) at 1 week, 123 (98.4%) at 1 month, 116 (92.8%) at 3 months, and 103 (82.4%) at 1 year.

### *Procedural details*

The mean length of the target vessel was 21.4 ± 11.7 cm overall, 33.3 ± 9.9 cm for GSV patients, and 14.8 ± 5.4 cm for SSV patients. Only few numbers of phlebectomy were performed (Table 2).

### *Anatomical outcomes*

All 143 legs of 125 patients treated were followed up by ultrasonography. 9 patients (6.3%) had more than 5 cm of patency at the proximal treated site at 1 year postoperatively. By treated vein, 3 patients (5.0%) had for GSV and 6 patients (9.8%) for SSV. The overall closure rate of the treated vein was 92.6% at 1 year postoperatively. By treated vein, GSV was 95.0% and SSV 90.2%, with no significant difference between the two groups (Table 3).

**Table 2.** Baseline characteristics.

| | Total number of patients, $n$ = 125 | GSV, $n$ = 60 | SSV, $n$ = 65 |
|---|---|---|---|
| Patients' characteristics | Mean ± SD (range) or number (frequency) | | |
| Age (years) | 68.8 ± 13.2 (39–88) | 70.3 ± 10.5 (39–87) | 67.6 ± 11.2 (45–88) |
| Gender (%) | | | |
| Female | 86 (68.9%) | 38 (63.3%) | 48 (73.8%) |
| Male | 39 (31.1%) | 22 (36.7%) | 17 (26.2%) |
| BMI (kg/m$^2$) | 24.5 ± 4.5 (17.8–34.4) | 25.2 ± 3.5 (19.1–32.0) | 23.8 ± 4.1 (17.8–34.4) |
| Treated veins (legs) | Total number of veins (legs), 143 | GSV, 72 | SSV, 71 |
| Mean largest diameter of target vein (mm) | 8.3 ± 2.3 (2.7–13.7) | 8.3 ± 2.3 (4.7–13.7) | 6.5 ± 2.4 (2.7–10.6) |
| CEAP clinical class | | | |
| C2 | 70 (49.0%) | 29 (40.3%) | 41 (57.7%) |
| C3 | 47 (32.9%) | 29 (40.3%) | 18 (25.4%) |
| C4a/b/c | 25 (17.5%) | 14 (19.4%) | 11 (15.5%) |
| C6 | 1 (0.6%) | 0 (0.0%) | 1 (1.4%) |
| Operative details | | | |
| Length (cm) | 21.4 ± 11.7 (8.5–49) | 33.3 ± 9.9 (13–49) | 14.8 ± 5.4 (8.5–25) |
| Injection numbers | 8.4 ± 3.9 (2–19) | 10.6 ± 3.6 (3–19) | 5.5 ± 1.6 (2–9) |
| Total volume of CA (cc) | 2.8 ± 0.4 (0.2–1.9) | 1.1 ± 0.4 (0.3–1.9) | 0.6 ± 0.2 (0.2–0.9) |
| Concomitant phlebectomy | 4 (2.8%) | 2 (2.8%) | 2 (2.8%) |

GSV: great saphenous vein; SSV: small saphenous vein; BMI: body mass index; CEAP: clinical-etiology-anatomy-pathophysiology; CA: cyanoacrylate.

**Table 3.** Closure rate at different time points as judged by duplex scan.

| | Closure rate | | | |
|---|---|---|---|---|
| Timepoints | Total, 143 | GSV, 72 | SSV, 71 | $p$ value |
| Day 7–10 | 100% (139/139) | 100% (68/68) | 100% (71/71) | NA |
| Month 1 | 99.3% (140/141) | 98.6% (70/71) | 100% (70/70) | 1.0 |
| Month 3 | 97.8% (131/134) | 96.9% (63/65) | 98.6% (68/69) | .95 |
| Month 12 | 92.6% (112/121) | 95.0% (57/60) | 90.2% (55/61) | .50 |

GSV: great saphenous vein; SSV: small saphenous vein.

## *Clinical outcomes*

The mean preoperative rVCSS was 3.9 ± 2.4. A linear mixed model analysis showed that the rVCSS was 1.1 ± 1.6 ($p < .001$) at 30 days postoperatively and 0.90 ± 1.6 ($p < .001$) at 90 days postoperatively, both of which were significantly improved (Figure 1). The mean preoperative AVVQ was 9.2 ± 7.6. The mean AVVQ was 2.8 ± 4.1 ($p < .001$) at 90 days postoperatively and 2.8 ± 5.2 ($p < .001$) at 1 year postoperatively, both of which were significantly improved. Postoperative pain was generally mild, with an immediate postoperative mean VAS of 18.9 ± 23.4, 12.4 ± 18.4 at 7 days, and 8.0 ± 17.1 at 30 days, indicating improvement over time. Regarding immediate postoperative pain, the GSV group showed significant improvement at 3 months ($p < .01$), while the SSV group showed significant improvement at 1 week ($p = .015$). The SSV group showed an earlier improvement in immediate postoperative pain than the GSV group ($p = .011$). Although there was no significant difference between the GSV and SSV groups in the mean VAS immediately after surgery ($p = .717$), the median value of the GSV group was 10.0 and that of the SSV group was 0 at 7 days after surgery, which was significantly higher in the GSV group than in the SSV group ($p = .011$). However, there was no significant difference between the GSV and SSV groups at 30 days postoperatively ($p = .831$) (Table 4). There was no significant difference in rVCSS and AVVQ between the GSV and SSV groups at the final evaluation. The mean preoperative Euro QOL of EQ-5D-5L was 83.9 ± 14.2. At 90 days postoperatively, the mean value was 86.4 ± 16.1 ($p = .365$), and at 1 year postoperatively, the mean value was 87.1 ± 12.4 ($p = .711$), showing no difference between the pre- and postoperative periods (Figure 1).

## *Postoperative complications*

Among 125 patients, 20 (16%) adverse events occurred during the 1-year postoperative observation period. They

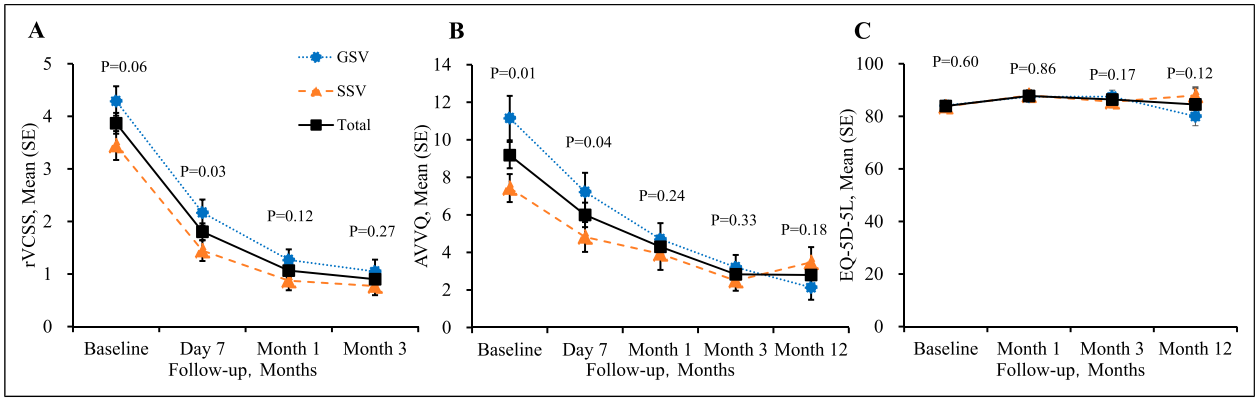


**Figure 1.** QOL scores at baseline and follow-up. Change in revised venous clinical severity score (rVCSS) (A), aberdeen varicose vein questionnaire (AVVQ) score (B) and EuroQol 5-Dimensions 5-Levels (EQ-5D-5 L) severity score (C) in the treatment groups over 3 and 12 months. *p* values are comparisons between the GSV and SSV groups using the Mann-Whitney test.

**Table 4.** Changes in visual analogue scale of pain.

| | Total | GSV | SSV | *p* value |
|---|---|---|---|---|
| After operation | 18.9 ± 23.4 (0–90) | 19.9 ± 24.8 (0–90) | 18.1 ± 22.5 (0–80) | .71 |
| Day 7–10 | 12.4 ± 18.4 (0–90) | 17.1 ± 21.5 (0–90) | 8.6 ± 14.5 (0–80) | .01 |
| Month 1 | 8.0 ± 17.1 (0–100) | 7.9 ± 17.5 (0–100) | 7.0 ± 15.3 (0–95) | .83 |

GSV: great saphenous vein; SSV: small saphenous vein.

**Table 5.** Adverse events.

| | | Total | GSV | SSV | *p* value |
|---|---|---|---|---|---|
| Reported adverse events | | 20 | 11 | 9 | .81 |
| Superficial venous thrombosis | | 5 (4.1%) | 4 | 1 | .36 |
| Type I: immediate hypersensitivity | | 1 (0.8%) | 1 | 0 | 1.0 |
| Type IV: delayed hypersensitivity | Allergic contact dermatitis | 1 (0.8%) | 1 | 0 | 1.0 |
| | Hypersensitivity-type phlebitis | 7 (5.6%) | 3 | 4 | .71 |
| Foreign body reaction | | 2 (1.6%) | 1 | 1 | 1.0 |
| Infection | | 1 (0.8%) | 1 | 0 | 1.0 |
| EGIT | | 1 (0.8%) | 0 | 1 | .49 |
| Others[a] | | 2 (1.6%) | 0 | 2 | .24 |

EGIT: endovenous glue-induced thrombosis; GSV: great saphenous vein; SSV: small saphenous vein.
[a]Adverse events not related to varicose veins or the treatment area.

occurred at a mean time of 19.4 ± 22.2 days (0–77). Hypersensitivity-type phlebitis was the most frequent adverse event in 7 patients (5.6%), followed by superficial venous thrombosis in 5 patients (4.1%). Allergic contact dermatitis was occurred in one patient. No patients need systemic administration of steroids. In addition, there was one case (0.8%) of class 3 endovenous glue-induced thrombosis (EGIT) and one case (0.8%) of stripping due to suspected infection from the CA used (Table 5). There was no significant difference between the GSV and SSV groups in terms of complications by treatment vein: 15.2% in the GSV group and 12.6% in the SSV group ($p$ = .81).

## Discussion

Regarding the background of varicose vein treatment in Japan, endovenous ablation was covered by national public insurance in 2011 in Japan. Since then, endovascular treatment has become the standard treatment for varicose veins instead of surgical treatment such as stripping. According to the National Database (NDB) Open Data of

Ministry of Health, Labor and Welfare of Japan, database on public medical insurance receipts, the percentage of endovascular treatment for saphenous varicose veins in 2014 was 55.9%, but it had increased to 88% by 2020.[10]

It was approved for insurance coverage in Japan in December 2019, because CAC is minimally invasive, and international reports have shown good outcomes.[3–5,11–16] Japanese guidelines for CAC were also published in Japan in 2020. According to the NDB open data in 2021, the percentage of saphenous varicose veins treated with CAC is 4.6% of all endovascular treatment of the varicose veins in Japan.[10] We report the results of a post-marketing survey and a physician-led clinical study conducted at 12 centers in Japan from December 2019 to June 2020 to evaluate the efficacy and safety of CAC.

Regarding anatomical outcomes, the closure rate of the treated vein was 92.6% at 1 year postoperatively, showing mid-term results (Table 3). Previous literature reports a 5-years closure rate of 92–96% in patients treated with GSV, and the closure rate is reported to be comparable to that of radiofrequency ablation (RFA).[3–5] We speculated that the factor behind the SSV result was high venous pressure being applied to the SPJ due to anatomical reasons, resulting in a higher rate of recanalization after the operation than GSV. An additional possibility is that the anatomical shape of the SPJ forced us to place the catheter tip more than 5 cm away from the SPJ. However, sufficient data on SSV have not been reported, yet. Two retrospective studies of SSV have been reported so far, and the postoperative closure rate of SSV was 96.3% and 93.8% at 1 year postoperatively, as good as that of GSV.[17,18]

Regarding clinical outcomes, the VAS seemed to have low values throughout the observation period (Table 4). In term of the clinical efficacy of CAC, all patients showed a clinical improvement in VCSS at 3 months and AVVQ at 1 year postoperatively compared to preoperative values (Figure 1).

Regarding postoperative complications, hypersensitivity-type phlebitis, which was the most frequent complication, occurred at an average of 12.4 ± 7.2 days, but all cases resolved within 22 days without use of systemic steroid. The incidence of hypersensitivity-type phlebitis among adverse events has been reported at 4–20% of all treated patients, occurring 1–3 weeks after surgery and characterized by skin redness, pain, and itchiness localized to the treated vessel and its surrounding branches.[3,11,12,14,15,19–21] Acetaminophen and nonsteroidal anti-inflammatory drugs are used for the treatment, and the symptoms improve rapidly within a week or so, and recurrence of fever is reported to be rare.[11] Superficial venous thrombosis occurred at an average of 18.6 ± 32.7 days, but all cases were quickly relieved by conservative treatment with NSAIDs and other drugs. The mean 1-month postoperative VAS was 6.7 ± 14.3 and 12.7 ± 24.6 in the groups with no complications and those with complications, respectively. The Mann-Whitney U test was used to compare the 1-month postoperative VAS between the group with complications, mainly hypersensitivity-type phlebitis and superficial venous thrombosis, and the group with no complications. There was no difference between the two groups ($p$ = .158), suggesting that these pains were mild. In conclusion, although the incidence of hypersensitivity-type phlebitis and superficial venous thrombosis is high, no case of serious condition was observed, suggesting that CAC is a safe and effective treatment.

In this study, we distinguished and classified so called "phlebitis" into superficial venous thrombosis, foreign body reaction and hypersensitivity type phlebitis based on superficial venous thrombosis based on presence of thrombus or foreign body, pain and itchiness. Hypersensitive reactions are classified into type I immediate hypersensitivity and type IV delayed hypersensitivity, which appears within a few days to 2–3 weeks. It has been speculated that this reaction may be caused by sensitization due to residual monomer from insufficient polymerization of cyanoacrylate, or that it may occur between exposed cyanoacrylate and subcutaneous tissue outside of blood vessels, and care should be taken to prevent leakage of cyanoacrylate outside of blood vessels during the procedure.[22] EGIT is a relatively rare complication, and its incidence is reported to be 0 to 2%.[3,11,15,23,24] It is reported that accurate positioning of the tip of the catheter for infusion during the procedure and firm central compression with a probe are important for prevention of this problem.[15] One patient was diagnosed with postoperative infection. The patient had office-based surgery performed at a private clinic. 0.5% chlorhexidine gluconate alcohol solution was used for preoperative antiseptic precautions. Clinically, it was unclear whether the inflammation of the skin of the treated medial thigh was caused by "phlebitis" or by infection, but the treated vessel was removed 4 days after the surgery because of exacerbation of symptoms. A small amount of Methicillin-susceptible *Staphylococcus aureus* (MSSA) was detected in culture of the specimen, and definitive diagnosis of postoperative infection was made. However, on pathological examination, it was difficult to distinguish infection from hypersensitivity or foreign body reaction. It is reported that postoperative CAC infection is usually limited to puncture site infection and surrounding cellulitis in 1–3% of cases. Although serious infection is considered to be a rare complication,[3,12,15,24–26] there have been cases of sepsis after CAC surgery, and therefore, adequate infection control measures should be taken during treatment.[27]

We reported comparable closure rate and clinical outcome with the initial experience of CAC in Japan, including SSV cases. The incidence of adverse events after CAC have been was reported overseas to be comparable to that of RFA.[3–5] Our study demonstrated reasonable clinical outcome with minimal invasive procedure. However, there was

some CAC specific complication were experienced as reported with caution, further study is required to find indication and definitive role of CAC in the varicose veins treatments.[28]

## Conclusion

We investigated the saphenous vein closure rate, postoperative pain, quality of life (QoL), and complications of CAC using the VenaSeal® closure system for saphenous vein insufficiency at 12 centers in Japan during the first year after surgery. CAC was considered to be generally a safe and minimally invasive treatment with mid-term outcomes. The results of CAC in SSV patients were similar to those of GSV patients. However, there is possibility that CAC specific complications might occur, Further study is required to clearly the role of CAC in varicose veins treatments.

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### Declaration of conflicting interests

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### Ethical statement

#### *Ethical approval*

At the time of treatment decision at each center, the patient's compliance with the enrollment criteria was confirmed and a written explanation and consent were obtained.

### Guarantor

MM

### Contributorship

There are no contributorship related to this Manuscript.

### Centers participating

Department of Vascular Surgery, Nishinokyo Hospital, Japan. Department of Cardiovascular Surgery, Yokohama Minami Kyosai Hospital, Japan. Ochanomizu Vascular and Vein Clinic, Japan. Shokoku Shintaro Clinic, Japan. Department of Surgery, Hiroshima Teishin Hospital, Japan. Department of Vascular Surgery, Yokohama Asahi Chuo General Hospital, Japan. Matsusaka Ohta Clinic, Japan. Department of Vascular Surgery, Fukuoka Sanno Hospital, Japan. Yamamoto Vein Clinic, Japan. Hyodo Internal Medicine and Eye Clinic, Japan. Umeda Vascular & Vein Clinic, Japan. Department of Vascular Surgery, Fukushima Daiichi Hospital, Japan.

### ORCID iDs

Takahiro Imai https://orcid.org/0000-0002-8284-5802
Makoto Mo https://orcid.org/0000-0003-3469-5181

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