Three-year follow-up results of the prospective European Multicenter Cohort Study on Cyanoacrylate Embolization for treatment of refluxing great saphenous veins

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ABSTRACT

Objective: Cyanoacrylate closure of refluxing saphenous veins has demonstrated excellent safety and effectiveness results in feasibility and pivotal studies. This article provides the 36-month follow-up results of a prospective, multicenter, nonrandomized cohort study.

Methods: A total of 70 patients were enrolled in a prospective, multicenter study conducted at seven centers in four European countries and underwent treatment of a solitary refluxing great saphenous vein with endovenous cyanoacrylate embolization without the use of tumescent anesthesia or postprocedure compression stockings. The primary effectiveness end point was freedom from recanalization (closure rate) of the great saphenous vein at 6 months. Safety was assessed by occurrence of adverse events after the procedure and during the 6-month follow-up period. Quality of life and clinical improvement parameters were measured before and after the procedure and through a 12-month follow-up period. Anatomic success and clinical improvement were assessed through 36 months after the procedure.

Results: Of 70 treated patients, 64 (91%) were available for the 3-year follow-up. The closure rates by Kaplan-Meier life table methods at 6-, 12-, 24-, and 36-month time points were 91.4%, 90.0%, 88.5%, and 88.5%, respectively. Through 36 months, the improvement in change of the mean venous clinical severity score over time was statistically significant by dropping from 4.3 at baseline to 0.9 at the 36-month follow-up ($P < .001$).

Conclusions: The 3-year follow-up results of the prospective, multicenter eSCOPE study demonstrated the continued anatomic and clinical effectiveness of cyanoacrylate embolization over an extended follow-up period. (J Vasc Surg: Venous and Lym Dis 2021;9:329-34.)

Keywords: Cyanoacrylate; Endovenous laser; Saphenous vein; Varicose vein; Radiofrequency

Over the years, thermal ablation techniques have replaced traditional surgery for the treatment of venous insufficiency. However, these techniques require tumescent anesthesia and carry the risks of thermal injury beyond the treated vessel and surrounding tissue. These limitations led to the development of nonthermal nontumescent techniques for the abolition of reflux of saphenous veins. One of these techniques involves the use of polidocanol endovenous microfoam, which is made of carbon dioxide and oxygen combined with a very low concentration of nitrogen.[1] Another technique, mechanochemical ablation combines mechanical damage to the endothelium by a rotating wire with simultaneous catheter-guided infusion of a liquid sclerosant.[2,3] Although both microfoam and mechanochemical ablation have demonstrated the ability to close veins, they have the disadvantage of dose limits, which precludes the treatment of more than one saphenous vein in one session. Moreover, post-treatment care requires patients to wear medical compression stockings after all these treatment modalities.

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood and have been used successfully in the treatment of conditions such as arteriovenous malformation, pelvic congestion syndrome, and now chronic venous insufficiency.[4,5] Once

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The original sponsor of the European Sapheon Closure System Observational ProspectivE (eSCOPE) trial was Sapheon. Sapheon was acquired by Covidien Ltd, which was then acquired by Medtronic, Inc. (Santa Rosa, Calif).

This trial (NCT01570101) was registered on clinicaltrials.gov.

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implanted, cyanoacrylates elicit a foreign body reaction in the vein wall, leading to subsequent fibrotic ingrowth. In addition, cyanoacrylates do not have a dose limit, which means that multiple saphenous veins could be treated in one session if clinically indicated.[6] The closure system used in this study was the first device developed to use cyanoacrylates to treat refluxing saphenous veins. When administered endovenously, cyanoacrylate embolizes the vein to treat venous reflux. The cyanoacrylate closure (CAC) system has undergone extensive clinical trials, was CE marked in September 2011 and received premarket approval from the US Food and Drug Administration in February 2015.

The first human feasibility study was initiated to assess the safety and effectiveness of CAC for great saphenous vein (GSV) treatment. The 12-month results of that single-center study reported that the technology was safe and effective, and these outcomes were maintained through the 3-year follow-up.[7-10] However, a 21.1% initial rate of thread-like glue extensions at the saphenofemoral junction subsequently lead to a change in the standard instructions for use, recommending an increased distance of 5 cm of the tip of the glue deploying catheter to the junction already for the present study. After the study reported herein was initiated, a pivotal clinical study was performed, randomizing CAC vs radiofrequency segmental ablation for incompetent GSVs, to submit for US Food and Drug Administration approval in the United States. Both randomization groups reported high GSV closure rates and a very favorable safety profile at all follow-ups through 36 months.[11] Subsequently, there has been an extended 60-month follow-up of the study patients under a separate protocol to further assess long-term safety and efficacy. This extended 60-month follow-up demonstrated durable closure and sustained improvements in symptoms and quality of life measures, with a high degree of patient satisfaction with either procedure.[12] Furthermore, there were several prospective and retrospective studies, all of which reported this technology to be safe and effective.[13-18] However, these studies do not cover our long-term data from a cohort of patients in Europe.

The present study was initiated shortly after completion of the feasibility study and CE marking with the objective of obtaining anatomic and clinical data from four countries in Europe. The 12-month results of this study published earlier have reported excellent closure rates, significant improvement in quality of life scores, and minimal adverse events as assessed through 6 months.[6] This article describes the 3-year results of this study, confirming sustained efficacy of a CAC system in the treatment of symptomatic refluxing saphenous veins.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, prospective, nonrandomized cohort study
- **Key Findings:** Of 70 patients treated by cyanoacrylate embolization of refluxing great saphenous veins, 64 were available through 36 months of follow-up. The occlusion rate obtained by life table analysis was 88.5%. Sustained improvement of the venous clinical severity score was observed at 36 months of follow-up with a value of 0.9, decreasing from 4.3 at baseline.
- **Take Home Message:** Cyanoacrylate embolization of refluxing great saphenous veins shows sustained anatomic and clinical efficacy during a 3-year follow-up.

METHODS

The European Sapheon Closure System Observational ProspectivE (eSCOPE) study was an international, prospective, single-arm, observational, postmarket cohort study carried out in seven centers that specialize in the diagnosis and treatment of peripheral venous diseases in four European countries. Each site obtained local ethics committee approval before initiation, and all participants signed an ethics committee-approved, study-specific informed consent form before participation.

Patient selection, procedural technique, and statistical analysis have been described in detail elsewhere.[6] A brief synopsis is presented here.

The study allowed enrollment of males or nonpregnant females between 18 and 70 years of age with symptomatic GSV incompetence (Clinical, Etiologic, Anatomic, and Pathologic classification [CEAP] of C2, C3, or C4) with or without varicosities as confirmed by duplex ultrasound examination. Patients with a life expectancy of less than 1 year, who were on regular pain medications or anticoagulants, or with prior deep vein thrombosis (DVT)/superficial thrombophlebitis in the GSV were excluded from the study. The proprietary VenaSeal (Medtronic Inc, Santa Rosa, Calif) adhesive was delivered 5 cm caudal from the saphenofemoral junction, followed by repeated injections and compression sequences, working distally until the entire targeted vein segment was treated. Compression stockings were not used after VenaSeal closure system treatment, and patients were allowed to ambulate immediately after the procedure.

The pretreatment evaluation and the 24- to 72-hour and 1-, 3-, and 6-month follow-up visits included an evaluation of the access site, a physical examination, completion of the venous clinical severity scores (VCSS) questionnaire, documenting new adverse events, a duplex ultrasound examination of the affected leg to assess GSV patency and the occurrence of any DVT. Adjunctive vein treatments for potentially remaining tributaries at the study limb were not allowed until after the 3-month visit was complete.

Although the primary end point was evaluated at 6 months after the procedure, patients were asked to continue with yearly follow-ups through 3 years after the procedure. The yearly visits included a duplex ultrasound examination of the treated leg to assess GSV patency and the occurrence of any DVT.

The primary end point was duplex ultrasound examination-proven GSV closure with a lack of pathologic reflux at 6 months and further assessed at planned intervals. Complete occlusion was defined as no segments of patency exceeding 10 cm. Additionally, the proportion of patients with freedom from more than 10 cm of recanalization was estimated using Kaplan-Meier methods.

The secondary end point was safety, reflected by the rate of occurrence of all adverse events (procedure related and not procedure related; serious and not serious) occurring immediately after the procedure and during a 6-month follow-up period. Other exploratory outcome measures were quality of life up to 12 months and patient reported pain at all follow-up intervals. Pain was assessed via subject-reported clinical symptoms using a graded scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Changes from baseline in VCSS, Aberdeen Varicose Vein Questionnaire (AVVQ), and the general quality of life tool EuroQol questionnaire (EQ-5D) were evaluated by repeated measures and analysis of variance. Mean values were used because the numerical variation of the obtained results covers only a limited range of numbers and outliers that would affect the mean more than the median are not present in this study. A *P* value of less than .05 was considered statistically significant.

RESULTS

Baseline demographics. Between December 2011 and July 2012, 70 patients (55 women and 15 men) with a mean age of 48.4 years (range, 22-72 years) and mean body mass index of 25.7 (range, 18.9-43.3) were enrolled. Each patient had one solitary refluxing GSV; no deep vein reflux was observed in the study leg.

Risk factors included a family history of venous disease (30%, n = 21) and obesity (5.71%, n = 4). Other vascular risk factors included cigarette smoking (12.8%, n = 9), hypertension (7.14%, n = 5), abnormal blood lipids (5.71%, n = 4), and diabetes mellitus (4.29%, n = 3).

Of the 70 patients, each with one solitary refluxing GSV, procedural success was achieved in 69 patients (98.6%). A single case still showed flow in the proximal 20 cm of the GSV, as it was fed through a large tributary entering at the distal point of flow. To achieve full occlusion, foam sclerotherapy was injected during the index procedure, which was a major protocol deviation. This case was ultimately considered a treatment failure.

The mean GSV diameter in the study at the saphenofemoral junction was 7.8 ± 2.1 mm (range, 0.7-14.0 mm), whereas the mean procedure time from skin puncture to catheter out was 18.6 minutes (range, 8-74 minutes).

Closure of the GSV. A total of 64 patients were available for the 36-month follow-up. A total of eight cases of recanalization were detected through the 36-month follow-up period. The freedom from recanalization rates at 6-, 12-, 24-, and 36-month follow-ups were 91.4%, 90.0%, 88.5%, and 88.5%, respectively; 95% confidence intervals are listed in Table I. The previously published article originally reported the 6-month closure rate to be 92.9% rather than 91.4%. However, this was before the decision was made to consider one patient as a case of treatment failure based on the protocol deviation as described. This patient had received adjunctive foam sclerotherapy treatment before month 3. Nevertheless, the revised rate of 6-month closure rate still met the predefined success criteria, with a lower confidence limit of 83.5% or greater (Fig 1).

Adverse events. Adverse events that were related to the device and/or procedure were reported through the 6-month follow-up and were classified as light or moderate, and have been described elsewhere.[6] Briefly, within the first 3 weeks after the intervention, eight patients (11.4%) had a phlebitis-like reaction along the treated vein or its tributaries defined as reddening of the overlying skin and pain on palpation. Pain without phlebitis-like reaction was noticed in five patients (8.6%). Specific treatment of phlebitis-like reactions was under the discretion of the treating physician, but only two patients under this condition received nonsteroidal anti- inflammatory drugs for 2 and 15 days. No serious adverse event occurred; moreover, paresthesia was not observed. There were no DVTs at any follow-ups throughout the study.

Improvement in venous disease severity. Improvements of clinical scores and patient-reported outcome measures were observed after the procedure. The mean VCSS improved from 4.3 at baseline to 0.9 at the 36-month follow-up (Fig 2). Through 36 months, the improvement in change in VCSS score over time was statistically significant ($P < .001$). VCSS remained almost constant at a low level throughout follow-up from month 3 on, indicating that the observed recanalizations of the GSV did not translate into worsening of the VCSS.

Unfortunately, by protocol, the AVVQ and EQ-5D scores were collected only through the 12-month follow-up and have been published elsewhere. All patients exhibited good overall health status at baseline. However, as previously reported, there was an improvement in their EQ-5D scores at the 30-day time point, which was sustained through the 12-month visit. A similar improvement in the AVVQ score was observed from baseline through

Table I. Closure of treated great saphenous vein (GSV)

Time point	No. recanalized/No. at risk	Freedom from recanalization calculated from KM method (95% CI)
Procedure	1/70	98.6% (95.8%-100.0%)
24-72 hours	2/69	95.7% (91.1%-100.0%)
Month 1	0/67	95.7% (91.1%-100.0%)
Month 3	2/67	92.9% (87.0%-99.1%)
Month 6	1/65	91.4% (85.1%-98.2%)
Month 12	1/64	90.0% (83.2%-97.3%)
Month 24	1/60	88.5% (81.3%-96.3%)
Month 36	0/56	88.5% (81.3%-96.3%)

CI, Confidence interval; *KM*, Kaplan-Meier.

the 12-month follow-up, with the greatest improvement observed at the 6-month time point.

Pain in the index leg was reported as a mean score of 0.73 at baseline and 0.71 at the 24- to 72-hour time point. Pain decreased at all visits through 12 months. Patient-reported index leg pain increased at the month 24 and month 36 visits in subjects available for evaluation (0.32 and 0.26, respectively; Table II). However, an increase in the mean pain score at 24 and 36 months follow-up was neither significant nor correlated with patients with observation of GSV recanalization.

Remarkably, the clinical CEAP stages improved substantially during 36 months of follow-up: at baseline, 37% of patients were clinical stage C2 (n = 26), 50% C3 (n = 35), and 13% C4 (n = 9), whereas at the 36-month follow-up, 59% of patients were classified as C0 or C1 (n = 38), 33% as C2 (n = 21), 5% as C3 (n = 3), and 3% as C4 (n = 2).

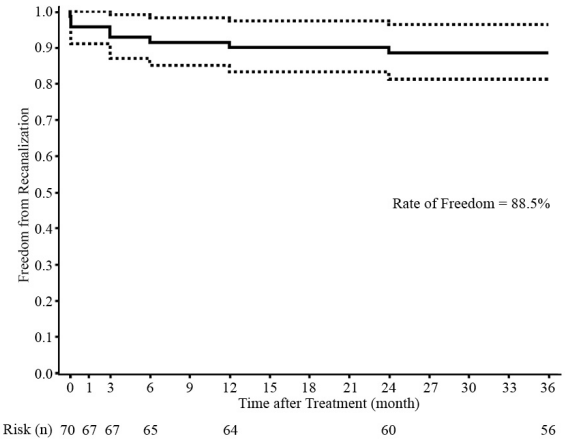

Fig 1. Life table analysis for freedom from recanalization after successful study treatment with a value of 88.5% at 36 months follow-up. Dashed lines represent corresponding 95% confidence interval. Bottom line provides numbers of great saphenous veins (GSV) at risk at given time intervals after study treatment.

DISCUSSION

The 3-year clinical follow-up of this eSCOPE study confirmed the continued efficacy of the studied CAC system.

Although 3-year occlusion rates are comparable with other nonthermal nontumescent technologies, when seen in context of more recent studies with this CAC system, this rate seems to be slightly lower, particularly if regarding the fact that recanalization was defined in the present study by a recanalized vein segment of at least 10 cm in length. The available clinical studies with 36 months of follow-up, such as the feasibility study, the pivotal randomized VeClose study, or another single-center study demonstrated closure rates of 94.7%, 94.4%, and 97.5% respectively.[9,11,18] In addition, the real-world evidence from the postmarket WAVES study reported a GSV closure rate of 98% at 12 months.[19] The comparatively low closure rate observed in the eSCOPE study may be attributed to the inherent limitations of this study, such as the small sample size that resulted in a high statistical impact of treatment failure in a single patient on GSV closure rates. Another noteworthy factor would be the fact that this device was being used by clinicians with no prior experience in cyanoacrylate occlusion, who were selected to participate in this study based on their experience in thermal ablation. Although the roll-in phase analysis of the VeClose trial suggested that the learning curve of the usage of the device is relatively short and its impact on clinical outcomes is negligible, it is essential to remember that the eSCOPE study was initiated much earlier than the VeClose trial and almost all clinicians involved in eSCOPE study had no prior experience with CAC technology.

The most common adverse event in eSCOPE was phlebitis, with eight patients (11.4%) showing a postprocedure phlebitic reaction along the treated vein or its tributaries; however, the precise location was not recorded. In the published literature on CAC, phlebitis is the most common adverse event with an incidence ranging from 4%

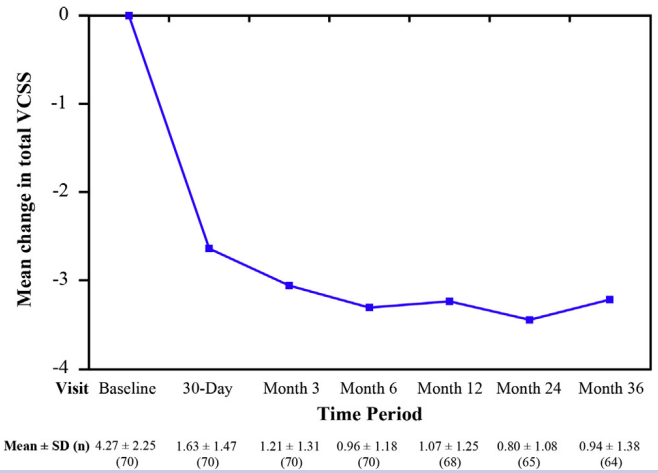

Fig 2. Time course of average Venous Clinical Severity Score (*VCSS*) during study follow-up. Bottom line provides numbers for mean VCSS ± standard deviation at given time intervals.

up to 20%.[7,19-22] In the randomized VeClose study, postoperative phlebitis was more common in the CAC group compared with the RFA group, although the difference was not statistically significant (20% vs 14%; $P = .36$).[23] None of the patients in the eSCOPE study developed paresthesia in the treatment zone, an adverse event associated with thermal ablation. Literature on other nontumescent techniques reported similar adverse events.[1-3]

Improvements in venous disease severity after VenaSeal closure system treatment were evident through statistically significant improvements from baseline in VCSS as seen during all follow-up visits of eSCOPE. This significant improvement of VCSS also corroborates similar results as seen in the VeClose, VeClose extension, and WAVES studies.

CONCLUSIONS

The 3-year follow-up results of the prospective, multicenter eSCOPE study demonstrated the continued efficacy of a CAC system over an extended follow-up period. The anatomic and clinical efficacy outcomes corroborate other long-term studies on the same CAC system. The study treatment is a valid option for treatment of refluxing saphenous veins without the use of tumescent local anesthesia and postinterventional use of medical compression stockings.

Table II. Pain in the index leg

Visit	Mean ± SD (n)
Baseline	0.73 ± 0.8 (70)
24-72 hours	0.71 ± 0.73 (70)
30 Days	0.10 ± 0.42 (70)
Month 3	0.04 ± 0.20 (70)
Month 6	0.07 ± 0.35 (70)
Month 12	0.07 ± 0.31 (68)
Month 24	0.32 ± 0.72 (28)
Month 36	0.26 ± 0.70 (35)

SD, Standard deviation.
Pain was assessed via subject-reported clinical symptoms using a graded scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

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AUTHOR CONTRIBUTIONS

Conception and design: TP, AD
Analysis and interpretation: TP, JA, SD, LR, MW, JL, AD
Data collection: TP, JA, SD, LR, MW, JL, AD
Writing the article: TP, JA, SD, LR, MW, JL, AD
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