Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose)

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Background: **Whereas thermal ablation of incompetent saphenous veins is highly effective, all heat-based ablation techniques require the use of perivenous subfascial tumescent anesthesia, involving multiple needle punctures along the course of the target vein. Preliminary evidence suggests that cyanoacrylate embolization (CAE) may be effective in the treatment of incompetent great saphenous veins (GSVs). We report herein early results of a randomized trial of CAE vs radiofrequency ablation (RFA) for the treatment of symptomatic incompetent GSVs.**

Methods: **Two hundred twenty-two subjects with symptomatic GSV incompetence were randomly assigned to receive either CAE (n = 108) with the VenaSeal Sapheon Closure System (Sapheon, Inc, Morrisville, NC) or RFA (n = 114) with the ClosureFast system (Covidien, Mansfield, Mass). After discharge, subjects returned to the clinic on day 3 and again at months 1 and 3. The study's primary end point was closure of the target vein at month 3 as assessed by duplex ultrasound and adjudicated by an independent vascular ultrasound core laboratory. Statistical testing focused on showing noninferiority with a 10% delta conditionally followed by superiority testing. No adjunctive procedures were allowed until after the month 3 visit, and missing month 3 data were imputed by various methods. Secondary end points included patient-reported pain during vein treatment and extent of ecchymosis at day 3. Additional assessments included general and disease-specific quality of life surveys and adverse event rates.**

Results: **All subjects received the assigned intervention. By use of the predictive method for imputing missing data, 3-month closure rates were 99% for CAE and 96% for RFA. All primary end point analyses, which used various methods to account for the missing data rate (14%), showed evidence to support the study's noninferiority hypothesis (all $P < .01$); some of these analyses supported a trend toward superiority ($P = .07$ in the predictive model). Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4 for CAE and RFA, respectively, on a 10-point scale; $P = .11$). At day 3, less ecchymosis in the treated region was present after CAE compared with RFA ($P < .01$). Other adverse events occurred at a similar rate between groups and were generally mild and well tolerated.**

Conclusions: **CAE was proven to be noninferior to RFA for the treatment of incompetent GSVs at month 3 after the procedure. Both treatment methods showed good safety profiles. CAE does not require tumescent anesthesia and is associated with less postprocedure ecchymosis. (J Vasc Surg 2015;61:985-94.)**

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Chronic venous disorders (CVDs) are progressive medical conditions that afflict approximately 30 million adults in the United States or approximately 35% of screened adults in the United States [1] and the United Kingdom.[2] In the most common manifestation of CVD, the valves in the great saphenous vein (GSV) and other superficial veins transporting blood from the legs toward the heart are dysfunctional, leading to venous dilation and stasis, causing symptoms and physical findings such as fatigue, swelling, pain, chronic skin changes, spontaneous hemorrhage, and leg ulcers. As CVD progresses, symptoms can be burdensome and profoundly affect quality of life. In the United States, time away from work due to CVD exceeds work time lost from peripheral artery disease.[3] Nonetheless, only a small fraction of those with CVD seek treatment.[4]

Treatment of CVD and saphenous insufficiency has undergone a substantial shift in the past decade. Previously, surgical treatment (ligation and stripping) was the primary treatment choice, in most cases requiring a general or regional anesthetic in an operating room. Complications from surgical treatments include hematoma,

paresthesia, disfigurement from scarring, and a high recurrence rate.[5-7]

Endovenous thermal ablation (EVTA) by radiofrequency ablation (RFA) or laser ablation has been shown to be a safe and effective treatment of CVD with high long-term target vein closure rates.[8] Both techniques have gained broad acceptance in many countries and by multiple specialties. One disadvantage of these techniques is the requirement for use of tumescent anesthesia (TA), which provides necessary local anesthesia, protects surrounding structures from potential thermal injury generated through the RF catheter and laser fibers, and reduces the caliber of the target vein to evacuate as much blood as possible to enhance vein wall thermal injury. TA not only requires additional time during a procedure but may also be associated with adverse events, such as pain, hematoma, and ecchymosis.[7-9] New treatments that circumvent the need for TA are desirable, provided treatment efficacy remains high.

Cyanoacrylate embolization (CAE) for varicose veins (VenaSeal; Sapheon, Inc, Morrisville, NC) has recently been approved for treatment of the incompetent GSV in the European Union, Hong Kong, and Canada. Cyanoacrylate adhesive (CA) has a long history of medical use, most notably in the embolic treatment of intracranial arteriovenous malformations.[10] Recently, a modified CA has been developed with the following desirable properties: (1) rapid polymerization on contact with blood and tissue, (2) flexibility sufficient to tolerate dynamic movement in the legs without generation of symptoms or being perceptible by the patient, and (3) high viscosity to eliminate the risk of embolization to the deep veins or pulmonary circulation.

Two prospective clinical trials provided early evidence of CAE's safety and effectiveness. In the first trial, 38 subjects at a single center with symptomatic GSV reflux treated with CAE had a 92% 12-month target vein closure rate.[11] In a second study (the European Sapheon Closure System Observational ProspectivE [eSCOPE]), 70 subjects treated at seven sites in Europe had a 93% 12-month closure rate.[12] In neither of these studies did subjects receive perivenous TA or require postprocedure compression stockings. Subjects in both studies demonstrated clinically and statistically significant improvements in symptoms and health-related quality of life.

We report initial results of VeClose in a prospective, multicenter randomized clinical trial comparing CAE with RFA for the treatment of the incompetent GSV. Because RFA with ClosureFast has been shown to cause less ecchymosis and pain in the postoperative follow-up period compared with laser ablation,[13] we chose RFA as the comparator for this pivotal trial of the effectiveness and safety of CAE. The goal of the study was to show statistical noninferiority of CAE efficacy compared with RFA.

METHODS

Study design. VeClose is a multicenter, prospective randomized controlled trial conducted under investigational device exemption from the U.S. Food and Drug Administration at 10 participating sites in the United States. The goal of the study was to show statistical noninferiority of CAE efficacy compared with RFA. Subjects were enrolled between March and September 2013. All sites obtained central Institutional Review Board approval before enrollment. The study underwent rigorous remote and on-site monitoring as well as 100% source verification.

Study subjects. The study enrolled adults aged 21 to 70 years with symptomatic moderate to severe varicosities (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical classification of symptomatic C2-C4b) and incompetence of the GSV, with reflux time of at least 0.5 second assessed in the standing position. Subjects were excluded if they had hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, prior treatment of the target GSV, symptomatic peripheral arterial disease, a history of deep venous thrombosis or pulmonary embolism, or aneurysm of the target GSV >12 mm in diameter (additional eligibility criteria are shown in Table I).

After eligibility was confirmed and informed consent was obtained, subjects underwent baseline examination, including a brief, focused physical examination, completion of CEAP and Venous Clinical Severity Score (VCSS) assessments,[14] and duplex ultrasound of both legs. In addition, subjects completed the EQ-5D quality of life survey[15] and the Aberdeen Varicose Vein Questionnaire (AVVQ).[16] Subjects were then randomized (1:1) to CAE performed with VenaSeal Sapheon Closure System (VSCS; Sapheon, Inc, Morrisville, NC) or RFA performed with ClosureFast (Covidien, Mansfield, Mass). Randomization was stratified by study site and used random block sizes of 4 or 6; assignments were obtained with an interactive voice response system linked to a web-based database. The first two subjects at each site were not randomized but rather treated with CAE (ie, roll-in cases) to ensure familiarity with the CAE procedure. All operators were experienced with EVTA procedures and were currently using RFA. Because study outcomes in roll-in subjects (n = 20) did not differ from the randomized cohort (n = 222), this report excludes discussion of roll-in cases.

Devices and procedures. VSCS consists of a delivery system and proprietary CA. Endovenous embolization of the GSV with VSCS was performed as previously described.[11] Briefly, with high-resolution ultrasound guidance, a 5F introducer sheath/catheter was advanced to the saphenofemoral junction (SFJ) and positioned 5.0 cm caudal to the SFJ. With proximal GSV compression by the ultrasound probe, two injections of approximately 0.10 mL CA were given 1 cm apart at this location, followed by a 3-minute period of local compression, and then repeated injections and 30-second ultrasound probe and hand compression sequences until the entire length of the target vein segment was treated. The sheath/catheter was removed and compression applied to the catheter entry site until hemostasis was achieved. A single small bandage was applied, and venous occlusion was confirmed by duplex ultrasound.

RFA of the target vein was performed with ClosureFast according to the manufacturer's instructions for use.

Table I. Study eligibility criteria

Inclusion criteria
1. Age ≥21 years and ≤70 years at the time of screening
2. Reflux in the GSV >0.5 second
3. One or more of the following symptoms related to the target vein: aching, throbbing, heaviness, fatigue, pruritus, night cramps, restlessness, generalized pain or discomfort, swelling
4. GSV diameter while standing of 3-12 mm throughout the target vein as measured by duplex ultrasound
5. CEAP classification of C2 (if symptomatic)-C4b
6. Ability to walk unassisted
7. Ability to attend follow-up visits
8. Ability to understand the requirements of the study and to provide informed consent
Exclusion criteria
1. Life expectancy <1 year
2. Active treatment for malignant disease other than nonmelanoma skin cancer
3. Symptomatic peripheral arterial disease with ABI <0.89
4. Daily use of narcotic or nonsteroidal anti-inflammatory pain medications to control pain associated with GSV reflux
5. Current, regular use of systemic anticoagulation (eg, warfarin, heparin)
6. Previous or suspected deep venous thrombosis or pulmonary embolus
7. Previous superficial thrombophlebitis in the target GSV
8. Previous treatment of venous disease in target limb, other than spider vein treatment
9. Known hypercoagulable disorder
10. Conditions that prevent vein treatment with either RFA or VSCS
11. Immobilization or inability to ambulate
12. Pregnant before enrollment
13. Tortuous GSV, which, in the opinion of the investigator, will limit catheter placement or require more than one primary access site
14. Aneurysm of the target vein with local vein diameter >12 mm
15. Significant, incompetent, ipsilateral small saphenous veins, intersaphenous veins, or anterior accessory GSVs
16. Known sensitivity to cyanoacrylate adhesives
17. Current participation in another clinical study involving an investigational agent or treatment or within the 30 days before enrollment
18. Patients who require bilateral treatment during the next 3 months
19. Patients who require additional ipsilateral treatments on the same leg within 3 months following treatment

ABI, Ankle-brachial index; *CEAP*, clinical, etiology, anatomy, and pathophysiology classification; *GSV*, great saphenous vein; *RFA*, radiofrequency ablation; *VSCS*, VenaSeal Sapheon Closure System.

Perivenous TA was delivered to the saphenous compartment surrounding the vein, and the dosage was recorded. Use of reprocessed catheters was not allowed. Double cycles of RF were employed at the first treatment zone near the SFJ in all subjects.

All procedures took place in an outpatient setting at the investigator's clinic with use of standard sterile technique. Immediately after venous access, subjects rated their pain on venous access on a numeric rating scale of 0 to 10 (0, no pain; 10, worst imaginable pain). When the procedure was completed, subjects used the same scale to rate intraoperative pain experienced during the procedure itself, including during TA but excluding pain felt during venous access. Subjects were discharged from the clinic on completion of the procedure. Consistent with the ClosureFast instructions for use, postprocedure compression stockings were used in both groups for 3 days continuously and an additional 4 days during waking hours. Subjects were instructed to avoid strenuous activities for 1 to 2 days.

Postoperative study visits. Subjects returned to the clinic at day 3 for a brief clinical assessment, including the subject's reporting of pain medications taken within 24 hours, the subject's rating of pain experienced in the index leg, and the investigator's assessment of the presence of ecchymosis, rated on a previously used 0- to 5-point graded scale (0, none; 1, involving <25% of the treatment area; 2, 25%-50%; 3, 50%-75%; 4, 75%-100%; 5, extension above or below the treatment segment).[13] Subjects also returned at month 1 and month 3 for clinical assessment (including CEAP score [month 3 only] and VCSS), quality of life evaluation (AVVQ and EQ-5D), and duplex ultrasound examination of the treated limb. The allowed 3-month window was ±4 weeks. No subject underwent ipsilateral adjunctive varicose vein treatments until the 3-month visit was complete to evaluate index device/procedure efficacy without the potential for confounding by additional therapies. Trial follow-up continues to 36 months after index treatment.

Adverse events were monitored at each study visit by querying subjects using a list of expected adverse events with RFA and CAE procedures. Investigators rated event severity as well as the relationship of the adverse events to the device and the procedure. Safety was reviewed by an independent data safety and monitoring board.

End points and statistical methods. The study's primary end point was complete closure of the target GSV, defined as Doppler ultrasound examination (including color flow, compression, and pulsed Doppler) showing closure along the entire treated target vein segment with no discrete segments of patency exceeding 5 cm at the month 3 visit. Closure was confirmed by an independent vascular ultrasound core laboratory (VasCore, Boston, Mass). Incomplete closure seen with any of these methods counted against the primary end point. The primary end

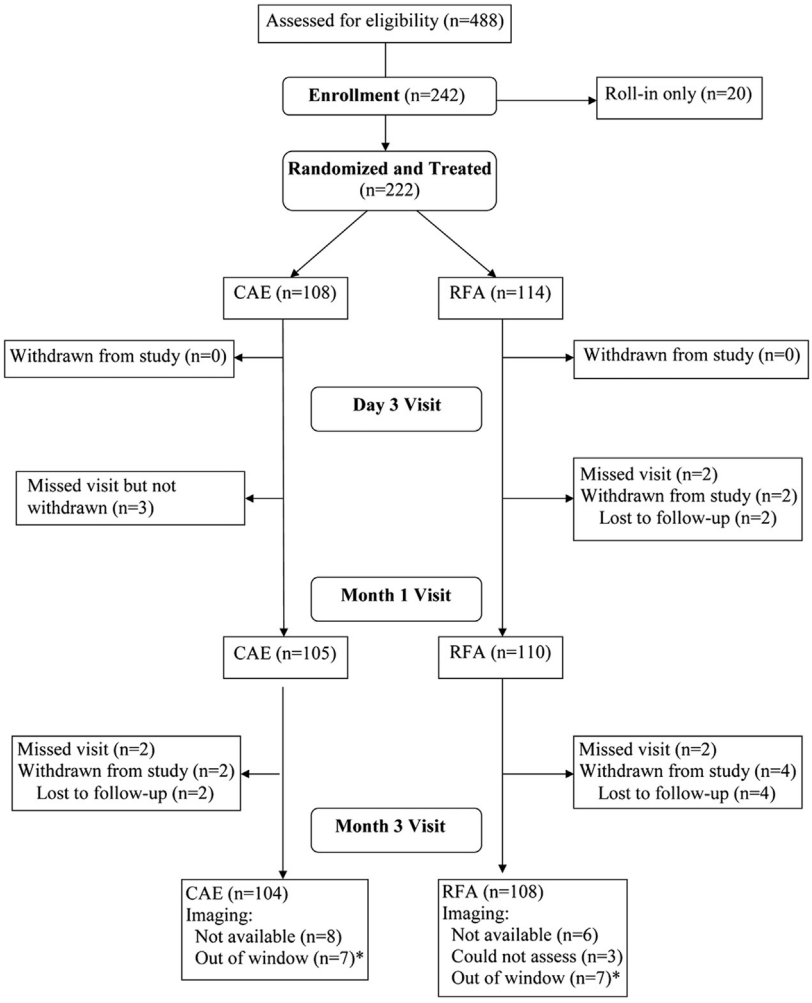

Fig 1. Study disposition. *CAE*, Cyanoacrylate embolization; *RFA*, radiofrequency ablation. *All out-of-window scans showed complete occlusion of the target vein.

point was analyzed by an intent-to-treat approach with the following prespecified methods to impute missing data: last observation carry forward, pessimistic and optimistic models, and Bayesian predictive models. Predictive models, used for missing RFA observations only, took into account the following in-study factors predictive of incomplete occlusion: male gender, decreased body mass index, and number of tributaries >3 mm in diameter. The study was interpreted as a primary end point success if the proportion of subjects with complete closure with CAE was statistically noninferior to that with RFA, with a 10% noninferiority margin. Proportions were compared by χ^2 tests for two independent binomial event rates, and confidence limits were calculated by the method of Miettinen and Nurminen.[17] Noninferiority was concluded when the P value was $< .05$ and the lower confidence interval for the difference in success rates exceeded -10%. If noninferiority was demonstrated, superiority was then tested by similar methods.

The study's two secondary end points were subject-rated pain experienced during the procedure (ie, pain experienced after vein access but before all treatment/access catheters were removed) and investigator-rated ecchymosis at day 3. Treatment differences for the former were compared by a two-tailed t-test, the latter by a Wilcoxon test. Changes from baseline in VCSS, AVVQ, and EQ-5D were compared between groups by repeated-measures analysis of variance and a Wilcoxon test for CEAP category at month 3. The rates of adverse events were compared by Fisher exact test. All analyses were performed with R, an open-source statistical package.[18]

RESULTS

Subject characteristics and disposition. Of 488 patients screened at 10 sites between March and September 2013, 242 met enrollment criteria and were enrolled (Fig 1). The first two subjects at each site (20 total) were treated with CAE in the roll-in phase; 222 subjects were

Table II. Demographic and baseline characteristics of VeClose study subjects

Characteristic	*VSCS (n = 108)*	*RFA (n = 114)*	P *value*
Female[a]	83 (77)	93 (82)	.48
Hispanic[a]	4 (4)	8 (7)	.43
Nonwhite[a]	6 (6)	8 (7)	.32
Target leg[a]			
Right	47 (44)	56 (49)	.48
Left	51 (57)	58 (51)	
Age, mean (range)[b]	49.0 (26.6-70.6)	50.5 (25.6-70.1)	.34
Body mass index, mean (range)[b]	27.0 (17.4-44.5)	27.0 (17.0-46.7)	.95
Primary symptom[a]			
Pain	33 (31)	24 (21)	.65
Aching	32 (30)	39 (34)	
Swelling	17 (16)	18 (16)	
Heaviness	14 (13)	16 (14)	
Burning	5 (5)	3 (3)	
Itching	2 (2)	5 (4)	
Other	4 (4)	7 (6)	
Smoking[a]			
Current	16 (15)	5 (4)	.02
Former	25 (23)	35 (31)	
Never	66 (61)	74 (65)	
GSV diameter, mean (range), mm[b]			
Mid GSV	4.9 (0-9)	5.1 (2.4-11)	.28
Proximal GSV	6.3 (3-12)	6.6 (2.8-12)	.15
CEAP category[a]			
C2 (varicose veins)	61 (57)	64 (56)	.96
C3 (edema)	32 (30)	36 (32)	
C4a (pigmentation/eczema)	13 (12)	12 (11)	
C4b (lipodermatosclerosis and atrophie blanche)	2 (2)	2 (2)	
VCSS, mean (SD)[b]	5.5 (2.6)	5.6 (2.6)	.99
AVVQ, mean (SD)[b]	18.9 (9.0)	19.4 (9.9)	.72
EQ-5D TTO, mean (SD)[b]	0.935 (0.113)	0.918 (0.116)	.29

AVVQ, Aberdeen Varicose Vein Questionnaire; *CEAP,* clinical, etiology, anatomy, and pathophysiology classification; *GSV,* great saphenous vein; *RFA,* radiofrequency ablation; *SD,* standard deviation; *TTO,* time trade-off; *VCSS,* Venous Clinical Severity Score; *VSCS,* VenaSeal Sapheon Closure System.
Data are presented as number (%) unless otherwise indicated.
[a]Binary or ordinal outcomes tested by χ^2 tests.
[b]Continuous outcomes tested by unpaired *t*-tests.

Table III. Procedure characteristics

Characteristic	*VSCS (n = 108)*	*RFA (n = 114)*	P *value*[a]
Treatment zone maximum diameter, mm	5.9 (2-12)	6.2 (1.5-11)	.19
GSV treatment length, cm	32.8 (8-61)	35.1 (6.5-84.5)	.17
Tumescent anesthesia amount, mL	—	272 (50-550)	—
Stump length, cm	22.5 (0-83)	18.9 (0-330)	.38
CA delivered, mL	1.2 (0.4-2.3)	—	—
Procedure duration, minutes	24 (11-40)	19 (5-46)	<.01
Volume lidocaine, mL	1.6 (0.2-6)	2.7 (0.2-10)	.1

CA, Cyanoacrylate adhesive; *GSV,* great saphenous vein; *RFA,* radiofrequency ablation; *VSCS,* VenaSeal Sapheon Closure System.
Data are presented as mean (range).
[a]*P* values derived from unpaired *t*-test or Wilcoxon test.

randomly assigned to either CAE or RFA. All subjects returned for the day 3 visit, and subsequently a small and similar number of subjects in each group were lost to follow-up or voluntarily withdrew. The majority of subjects were women (79%) and white (94%) (Table II). Most (87%) subjects had CEAP clinical class 2 and 3 venous disease. There was a slight predominance of current and former smokers in the CAE groups ($P = .02$). The predominant symptoms were leg pain and aching. Risk factors for varicose veins were common and similar between groups. VCSS and AVVQ scores were consistent with mild to moderate venous reflux disease. Baseline characteristics were similar between treatment groups.

Procedure characteristics. All subjects received the assigned intervention. The average maximum diameter of the GSV in the treatment zone was 6 mm (Table III).

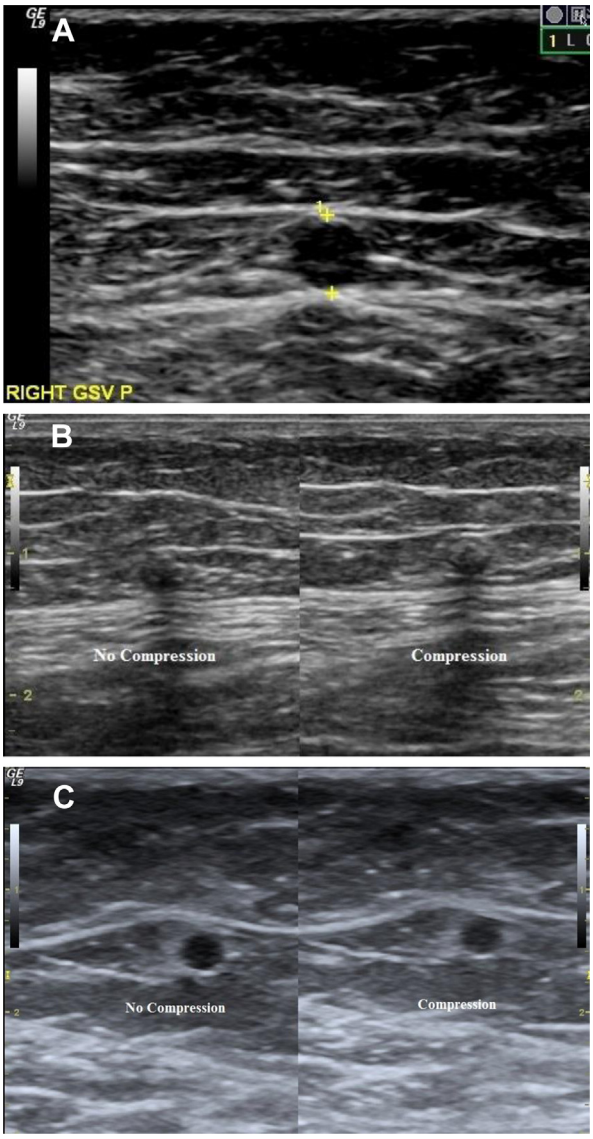

Fig 2. Ultrasound images of incompetent great saphenous vein (*GSV*) **(A)** before treatment and **(B)** after treatment with cyanoacrylate embolization (CAE) and **(C)** after treatment with radiofrequency ablation (RFA).

The treatment zone had a mean (range) of 1.4 (0-12) tributaries >3 mm in diameter. Mean procedure time was 5 minutes longer for CAE vs RFA (24 vs 19 minutes; $P <$ .01). At the end of the procedure, one subject each in the CAE and RFA groups had residual flow along the treated segment. Five (4%) technical deviations occurred during RFA treatment, requiring use of an additional separate hydrophilic guidewire (Cook HiWire, Bloomington, Ind) in four cases to assist in proximal positioning of the RFA catheter. No technical deviations occurred during CAE treatment. Fig 2 shows an ultrasound image of the GSV before (*A*) and after (*B* and *C*) the CAE and RFA procedure.

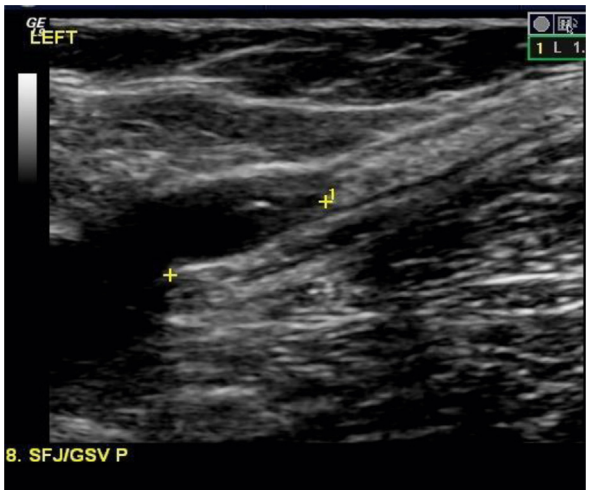

Fig 3. Complete closure of cyanoacrylate embolization (CAE)-treated incompetent great saphenous vein (*GSV*) with stump length calipers.

Venous closure. On day 3, 100% of GSVs were closed in both groups (Fig 3). At month 1, patency of the treated vein segment on duplex ultrasound was identified in 15 GSVs treated with RFA and 0 GSVs treated with CAE, with closure rates of 86% and 100%, respectively ($P <$ .01 for both noninferiority and superiority). Of the 222 randomized subjects, a 3-month visit was done in 212 (96%), of which 7 (3%) were out of window. Month 3 Doppler ultrasound images, used for the core laboratory's assessments, were available in 194 of 222 subjects. Ultrasound images were missing or uninterpretable in 15 CAE and 16 RFA cases (total missing rate of 14%; Fisher exact, $P =$ 1.0). Missing images were due to early withdrawal (n = 8 and 6 in the CAE and RFA groups, respectively), uninterpretable images (3 RFA cases), and images beyond the allowed 3-month study window (n = 7 and 7 in the CAE and RFA groups). All out-of-window images showed complete occlusion. For available images, there was 100% agreement between site investigator and core laboratory readings of target vein closure.

Among available images, the GSV was patent in five RFA-treated subjects and one CAE-treated subject. Taking into account the 31 missing images using several prespecified imputation methods (Table IV), statistical noninferiority was demonstrated with P values $<$ .01 in all models. In three of the five missing data imputation methods, there was a trend toward statistical superiority for CAE ($P =$ .06, .06, and .07). With use of the predictive model for missing data interpretation, closure rates were 99% and 96% in the CAE and RFA groups, respectively.

Pain and ecchymosis. Mean pain ratings during venous access were similar between the two groups (1.6 for CAE vs 2.0 for RFA; $P =$ .13); mean intraprocedural pain ratings were also low and similar in both groups (2.2 vs 2.4; $P =$ .11). There was no difference between treatment groups in pain experienced in the 24 hours

Table IV. Primary end point analyses under various models for imputing missing data

Model	*Description*	*Closure rate*				
		VSCS (n = 108)	*RFA (n = 114)*	*Rate difference (95% CI)*	P *NI*	P *Sup*
Last observation carry forward	Most recent ultrasound observation used to impute missing value	107 (99%)	109 (96%)	3.5% (−0.7% to 8%)	<.01	.06
Optimistic	Assume missing values are successes	107 (99%)	109 (96%)	3.5% (−0.7% to 8%)	<.01	.06
Pessimistic	Assume missing values are failures	92 (85%)	93 (82%)	3.6 (−6.2 to 13)	<.01	.24
Alternative pessimistic	Assume missing values are failures but late month 3 evaluations are successes	99 (92%)	100 (88%)	3.9 (−4.0 to 12)	<.01	.17
Predictive	Estimate distribution of successes taking into account gender, body mass index, and number of tributaries ≥3 mm	99%[a]	96%	4%	<.01	.07

CI, Confidence interval; P_{NI}, *P* value for noninferiority; P_{Sup}, *P* value for superiority; *RFA,* radiofrequency ablation; *VSCS,* VenaSeal Sapheon Closure System.
[a]Number not reported as predictive values are distributions, not fixed values.

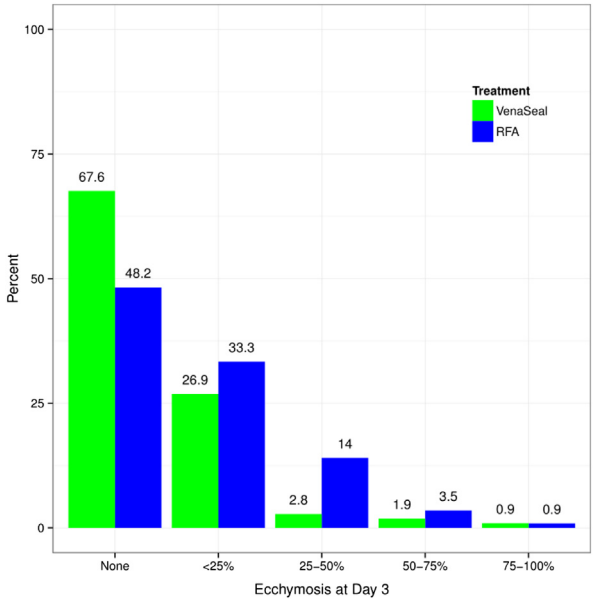

Fig 4. Ecchymosis assessed by investigators with a 5-point scale on day 3 by treatment group. Subjects treated with cyanoacrylate embolization (CAE) had less ecchymosis at day 3 compared with radiofrequency ablation (*RFA*) ($P < .01$, Wilcoxon test).

before the day 3 visit (0.93 in each group; $P = .36$). Ecchymosis severity at day 3 was lower in the CAE group ($P < .01$; Fig 4), and ecchymosis at day 3 was absent in significantly more subjects after CAE than after RFA (68% of CAE subjects vs 48% of RFA subjects; $P < .01$).

Clinical measures. Additional measures of clinical severity of CVD showed marked, sustained, and equal reductions in both groups over time (Table V). By month 3, VCSS had improved approximately 3.5 points from baseline ($P < .01$), with no differences between treatment groups. Similarly, by month 3, AVVQ score improved by approximately 8 points ($P < .01$), and EQ-5D time trade-off utility index had improved by approximately 0.03 unit ($P = .01$), with no differences between treatment groups. At baseline, no subject was CEAP 0/1; by month 3, 26% and 33% of subjects in the CAE and RFA groups were CEAP 0/1. CEAP improved by approximately 0.5 point per group ($P < .01$), with no difference between groups.

Table V. Follow-up clinical assessments

	VenaSeal (n = 108)	*RFA (n = 114)*	P *value*[a]
VCSS			
Baseline	5.5 (2.6), 108	5.6 (2.6), 114	.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			
Baseline	18.9 (9.0), 107	19.4 (9.9), 111	.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			
Baseline	0.935 (0.113), 108	0.918 (0.116), 114	.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	

AVVQ, Aberdeen Varicose Vein Questionnaire; *RFA,* radiofrequency ablation; *TTO,* time trade-off; *VCSS,* Venous Clinical Severity Score.
Values are given as mean (standard deviation), number.
[a]*P* values are derived from repeated-measures analysis of variance.

Safety. No subject withdrew because of an adverse event and no subject developed deep venous thrombosis or pulmonary embolism. Four mild adverse events occurred during the RFA procedure and one occurred after the CAE procedure (RFA: lightheadedness [1], nausea [1], and vasovagal symptoms [2]; CAE: lightheadedness after the procedure). As of the month 3 visit, 78 adverse events had occurred in 63 subjects (34 CAE subjects and 29 RFA subjects; Table VI; $P = .37$ for difference in number of adverse events per subject between treatment groups). The type and rate of expected predefined adverse events were similar between treatments, except that post-treatment phlebitis (in the treated segment or nontreated tributary) was somewhat more common after CAE (20 vs 15 events; $P = .36$). Most cases of phlebitis in both groups were mild, transient, and

Table VI. Adverse events

	VenaSeal, No. (%)	*RFA, No. (%)*	P *value*[a]
No. of adverse events per subject			
0	74 (69)	85 (75)	.37
1	28 (26)	22 (19)	
2	6 (6)	6 (5)	
3	0 (0.0)	0 (0.0)	
4	0 (0.0)	1 (1)	
Event severity			
Mild	26 (24)	30 (26)	.35[c]
Moderate	12 (11)	7 (6)	
Severe	2 (2)	1 (1)	
Procedure-related adverse events[b]	27 (25)	31 (27)	.76
Device-related adverse events[b]	13 (12)	7 (6)	.16
Reported adverse events			
Phlebitis, any zone	22 (20)	16 (14)	.36
Phlebitis in treatment zone	11 (10)	10 (9)	.82
Phlebitis not in treatment zone	8 (7)	4 (4)	.24
Phlebitis in both treatment zone and nontreatment zone	1 (1)	1 (1)	1.0
Paresthesia in treatment zone	3 (3)	3 (3)	1.0
Stocking irritation	2 (2)	3 (3)	1.0
Access site infection	1 (1)	1 (1)	1.0
Superficial thrombophlebitis	4 (4)	3. (3)	.72
Access site burn	0 (0)	1 (1)	1.0
Paresthesia not in treatment zone	0 (0)	1 (1)	1.0
Other adverse events[d]	10 (9)	11 (10)	1.0

RFA, Radiofrequency ablation.
Percentages represent number of events divided by number treated.
[a]*P* values derived from χ^2 test, Wilcoxon test, or Fisher exact test.
[b]Judged by investigator to be probably or definitely related.
[c]Cochrane-Armitage trend test.
[d]Adverse events not related to varicose veins or the treatment area.

successfully treated with over-the-counter nonsteroidal anti-inflammatory medication (ibuprofen). Three adverse events were rated severe (one case each of breast cancer, kidney stones, and symptomatic orthostatic hypotension), none of which was deemed related to either the index device or procedure. No device- or procedure-related serious adverse events occurred in either group, and no postprocedural thrombus extensions into the common femoral vein were identified by duplex ultrasound in any patient.

In both treatment groups, the number of adverse events that investigators attributed to the study device was small (Table VI). Events rated as probably or definitely related to CAE devices included moderate access site infection (1), mild paresthesia in the treatment zone (1), moderate paresthesia in the treatment zone (1), mild phlebitis in the treatment zone (6), moderate phlebitis not in the treatment zone (1), and mild superficial vein thrombophlebitis (3). Events rated as probably or definitely related to RFA study devices included mild access site burn (1), mild paresthesia in the treatment zone (2), mild phlebitis in the treatment zone (2), moderate phlebitis in the treatment zone (1), and mild phlebitis not in the treatment zone (1).

DISCUSSION

Results from this study confirm that CAE is safe and highly effective for the treatment of CVD. The study showed that occlusion of the target vein at 3 months by CAE was at least as effective as RFA. Short-term (3-month) probability of complete closure of the target GSV with CAE in this study was high (99%) and similar to that observed in a prior single-arm CAE study (95% in a small feasibility study[19]) and in a prospective CAE multicenter European study (96%).[12] High long-term GSV closure rates with RFA (93% at 3 years) have been reported,[20] although a meta-analysis reported somewhat lower long-term success rates (84% at 3 years[8]). The reports in this meta-analysis included the use of an earlier generation RF system (VNUS Closure; VNUS Medical Technologies, San Jose, Calif), which may be the reason for lower success rates than are seen with newer RF equipment. In addition, methods to assess complete occlusion varied slightly across studies. Closure rate associated with RFA may have been lower in this study because of the critical ultrasound evaluation performed at each study center. Long-term follow-up from the current study may provide the best estimate of differences in venous closure rates between CAE and RFA.

In previous reports of CAE treatment of GSV, incomplete occlusion and recanalization appeared to be caused by continued flow of blood from GSV tributaries into the treated GSV, resulting in areas of failed closure. In the present study, high closure rates (especially in the CAE treatment group) were seen despite use of a stricter definition of vein closure (only 5 cm of patency allowed vs 10 cm used in some other studies[13]) and in the absence of adjunctive treatments at the time of index treatment.

Our findings suggest that adjunctive treatments may be withheld at the time of the index procedure when highly effective GSV closure methods are used, such as RFA or CAE, and delivered later, if required, as has been previously suggested.[21,22]

Both CAE and RFA were associated with low pain scores. Moreover, presumably because it does not require TA, CAE treatment resulted in less ecchymosis over the treated segment at day 3 compared with subjects treated with RFA. In addition, in controlled studies comparing RFA with ClosureFast to laser ablation, pain and ecchymosis measurements were also somewhat dissimilar to those in our studies.[13,23] In these studies, pain was not rated immediately after the procedure, as was done in our study. These differences make comparisons of some aspects of our study with previous studies difficult.

The severity and impact of venous disease on quality of life were measured with several end points in this study. Both CAE-treated and RFA-treated subjects improved significantly over time. VCSS scores of 1.5 points at 3 months, with significant improvements from baseline, are similar to those seen in previous CAE clinical trials.[12,19] Likewise, subjects' improvements in AVVQ and EQ-5D were similar to those previously reported with CAE treatment.[19] Although CEAP class improved significantly in both treatment groups, the importance of this finding is unclear.

Adverse events were similar between groups. No severe procedure- or device-related adverse events occurred in either group. Device-related adverse events with CAE were mostly cases of phlebitis of the treated GSV and, although not statistically significant, occurred somewhat more commonly than in RFA-treated subjects (20 vs 15 cases; $P = .36$). The difference might reflect the mechanism of action of the adhesive. Most cases of phlebitis in both groups were mild, transient, and successfully treated with over-the-counter nonsteroidal anti-inflammatory medication (ibuprofen). Slight technical deviations (use of additional guidewire), although minor, were experienced during only the RFA procedures.

The current study has several novel features compared with other clinical trials of treatments for CVD. A randomized active control group (RFA) allowed the observed closure rate for CAE to be compared in the same operator/investigator group. This study was tightly controlled, monitored, and 100% source verified, yielding high-quality data. The investigators' ultrasound results were confirmed by an independent vascular ultrasound core laboratory. The study's primary end point (occlusion of the target GSV) was objective and easily judged, with full agreement between investigator and core laboratory readings. Moreover, the study's primary ultrasonographic end point was more strictly defined than that used in some other studies of EVTA.[24] Given the high target vein occlusion rate in both groups, the observed improvements in CVD-associated symptoms (as assessed by VCSS and AVVQ) and general quality of life (as assessed with EQ-5D) were expected, with no significant difference between treatment groups found. Finally, the multicenter, multioperator performance of the study increases study validity by reporting the combined experience of multiple physician participants, removing the bias of a single-center/operator study. Study follow-up will continue to 3 years, allowing documentation of longer term index vein success rates as well as the likelihood of recanalization or CVD progression.

Although this study has some limitations, the results are significant even though data were missing in a small number of subjects. However, all methods used to impute missing data (including pessimistic models) provided strong evidence of noninferiority. The assessment of vein closure could not be blinded to treatment because the ultrasonographic appearance of the implanted cyanoacrylate is unique and different from that observed after RFA treatment. There was complete agreement, however, between site investigators and the core laboratory for all vein closure assessments. To reduce bias between groups, post-treatment stockings were worn by both CAE and RFA subjects because the RFA instructions for use require compression. Saphenous occlusion rates were high in prior studies of CAE without use of compression. Finally, adjunctive treatments were withheld until after the month 3 visit to prevent confounding variables in the primary occlusion analysis.

The advantages of CAE for the treatment of incompetent truncal veins are, first, because CAE does not require the use of TA, the patient avoids its associated burden; and second, CAE may also allow elimination of postprocedure compression stockings, for which compliance is known to be poor.[25,26]

CONCLUSIONS

In the current study, CAE was shown to be noninferior to RFA for the occlusion of symptomatic incompetent GSVs at 3 months. CAE does not require TA, which resulted in reduced side effects such as ecchymosis compared with RFA. The rate of postoperative phlebitis was slightly higher for CAE but not statistically significant compared with RFA.

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AUTHOR CONTRIBUTIONS

Conception and design: NM, DC
Analysis and interpretation: NM, DC, KG
Data collection: NM, DC, KG, SM, MG, TK, RW, AJ
Writing the article: NM, DC, KG
Critical revision of the article: NM, DC, KG
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