A prospective safety and effectiveness study using endovenous laser ablation with a 400-μm optical fiber for the treatment of pathologic perforator veins in patients with advanced venous disease (SeCure trial)

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ABSTRACT

Background: Treatment of pathologic perforator veins (PPVs) can shorten time to healing and reduce recurrence of ulcers in patients with advanced venous disease. Because of limited clinical evidence and device options, widespread adoption of PPV treatment is controversial. The objective of this study was to evaluate the safety and efficacy of endovenous laser therapy using a 400-μm optical fiber to treat PPVs.

Methods: This study was a single-arm, prospective, seven-center, nonblinded clinical study examining patients with advanced skin changes or healed or active ulceration (Clinical, Etiology, Anatomy, and Pathophysiology clinical class C4b, C5, and C6). Patients received treatment with a 1470-nm laser. Procedural technical success and 10-day primary closure were evaluated. All device-related adverse events were reported. Follow-up of patients was continued for 12 months after initial ablation.

Results: The primary PPV closure (at 10-day visit) rate was 76.9% (95% confidence interval, 70.3%-82.4%). Successful primary closure rates of 75.7%, 70.3%, 62.1%, 68.8%, and 71.3% of PPVs were achieved at 1 month, 3 months, 6 months, 9 months, and 12 months, respectively. Statistically significant improvements ($P < .05$) were seen in patients' quality of life at 1 month, 3 months, 6 months, 9 months, and 12 months compared with screening. The percentage of patients with ulcers (22.9% at screening, 14.1% at 1 month, 13.7% at 3 months, 10.1% at 6 months, 12.3% at 9 months, and 11.1% at 12 months) displayed improvement during the course of the study. Tibial deep venous thrombosis and procedural pain were the only device-related adverse events observed.

Conclusions: Endovenous laser therapy for PPV using the 400-μm optical fiber with the 1470-nm laser yielded safe and effective outcomes with no major adverse sequelae. (J Vasc Surg: Venous and Lym Dis 2020;■:1-9.)

Keywords: Perforators; Endovenous laser; Venous insufficiency; QOL; Venous ulcer

Lower extremity venous insufficiency affects up to 25% of women and 15% of men in the United States, causing significant health care expenditures.[1-3] Up to 50% of patients with significant superficial venous insufficiency will eventually progress to chronic venous insufficiency (CVI) characterized by lower extremity swelling, and up to 30% will develop skin changes that may lead to ulceration.[4,5]

The suspected importance of incompetent perforator veins (IPVs) in the pathogenesis of CVI was first described by Homans[6] and later by Linton.[7] These investigators highlighted the importance of interrupting IPVs to reduce superficial venous hypertension in the treatment of venous ulcerations. Their work led to an open surgical approach to ligate IPVs through a subfascial medial calf incision. Following this open surgical method, a less

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invasive procedure of subfascial endoscopic perforator surgery (SEPS) was developed. Currently, the less invasive treatment option of percutaneous ablation of perforators (PAPs) has emerged. These techniques have improved recovery and decreased the morbidity associated with open surgery.[8-11]

Current practice guidelines of the Society for Vascular Surgery and American Venous Forum define pathologic perforator veins (PPVs) as those near or adjacent to a healed ulcer demonstrating >0.5 second of reflux and measuring ≥3.5 mm in diameter. These guidelines suggest treating PPVs in patients with Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) clinical class of C5 or C6 with methods that may include percutaneous thermal ablation, sclerotherapy, or endoscopic ligation apart from the open surgical approach.[12]

Studies of endovenous techniques have focused on successful PPV ablation as a primary outcome measure. Closure rates, although important, are a surrogate marker that may have less value to the patient than quality of life (QOL) measures. In this study, we describe the results from the SeCure trial, focusing on the safety and efficacy of perforator ablation as well as QOL measures using the 400-μm optical fiber with a 1470-nm laser.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, prospective, nonrandomized cohort study
- **Key Findings:** Primary pathologic perforator vein (PPV) closure rate at 10 days after treatment with a 1470-nm laser was 76.9%. Successful primary closure rates of 75.7%, 70.3%, 62.1%, 68.8%, and 71.3 % of PPVs were achieved at 1 month, 3 months, 6 months, 9 months, and 12 months, respectively. Statistically significant improvements ($P < .05$) were seen in patients' quality of life at 1 month, 3 months, 6 months, 9 months, and 12 months compared with screening. Ulcer healing displayed improvement during the course of the study.
- **Take Home Message:** Endovenous ablation of perforator veins with laser ablation using a 400-μm fiber is a safe and effective treatment of PPVs.

METHODS

Trial design and participants. The SeCure trial is a single-arm, prospective, multicenter, nonblinded clinical trial conducted at seven centers in the United States. The study protocol and informed consent at each site were approved by either a site-specific or central Institutional Review Board. Patients diagnosed with PPVs and meeting all inclusion criteria and none of the exclusion criteria were eligible for this study. Informed consent was obtained for each patient before enrollment. All patients treated had symptomatic CVI with CEAP clinical class of C4b, C5, or C6. In order to not confound the study results, any pathologic saphenous truncal reflux, if present, had to have been treated at least 30 days before PPV treatment. Significant proximal suprainguinal iliac or inferior vena cava disease was either absent or previously treated. The efficacy population (83 patients and 125 PPVs) in which vein access was attempted and energy was delivered was used to evaluate the primary effectiveness end points, secondary technical success end point, and other clinical outcome data; 93 patients and 145 PPVs were used for the adverse event analysis. The adverse event population (safety population) included lead-in patients. According to the study protocol, lead-in patients were not included in the efficacy population. Diagnosis and definition of perforating vein insufficiency were consistent with the Society for Vascular Surgery and American Venous Forum clinical practice guidelines.[11] A perforator is considered to be pathologic when outward flow is >0.5 second in duration immediately after release of manual compression, measures ≥3.5 mm (measured at the level of the fascia), is located superior to the foot and distal ankle, and is located near the area of disease (ulcer, healed ulcer, or skin changes). Veins meeting these criteria were eligible for treatment. Only one limb per patient was treated in this study, although multiple PPVs within the study limb were allowed to be treated. Fig 1 presents a schematic representation of the trial design with all the inclusion and exclusion criteria for the study.

Devices and procedure. The VenaCure endovenous laser therapy 400-μm perforator and accessory vein ablation kit (PVAK; AngioDynamics, Latham, NY) contains a 400-μm optical fiber with site mark and compression clamp, 21-gauge venous access needle, 10-cm × 4F introducer sheath, and 0.018-inch guidewire as shown in Fig 2. The study procedure was conducted according to the instructions for use included with the VenaCure endovenous laser therapy 400-μm PVAK. Briefly, the 1470-nm laser and the 400-μm fiber were directly inserted into the PPV through a 21-gauge needle or 4F introducer sheath using ultrasound guidance. The laser was positioned to be 1 cm from the deep vein and at or near the fascia. Anesthetic was administered around the perforator vein. The generator was set at 5 to 7 W, and the vein was then treated using a continuous energy delivery setting for 10 to 15 seconds. This equated to approximately 50 to 70 J given to each level of the perforator that was treated. Most treatments were "spot welding" of two or three levels of a perforator—just below the fascia, at the fascia, and just above the fascia if possible. A true pullback treatment most of the time was not possible because perforating veins tend to be tortuous.

Procedural follow-up. After the study procedure, all patients were seen at 10 (±3) days for primary effectiveness end point (ablation success rate as determined by

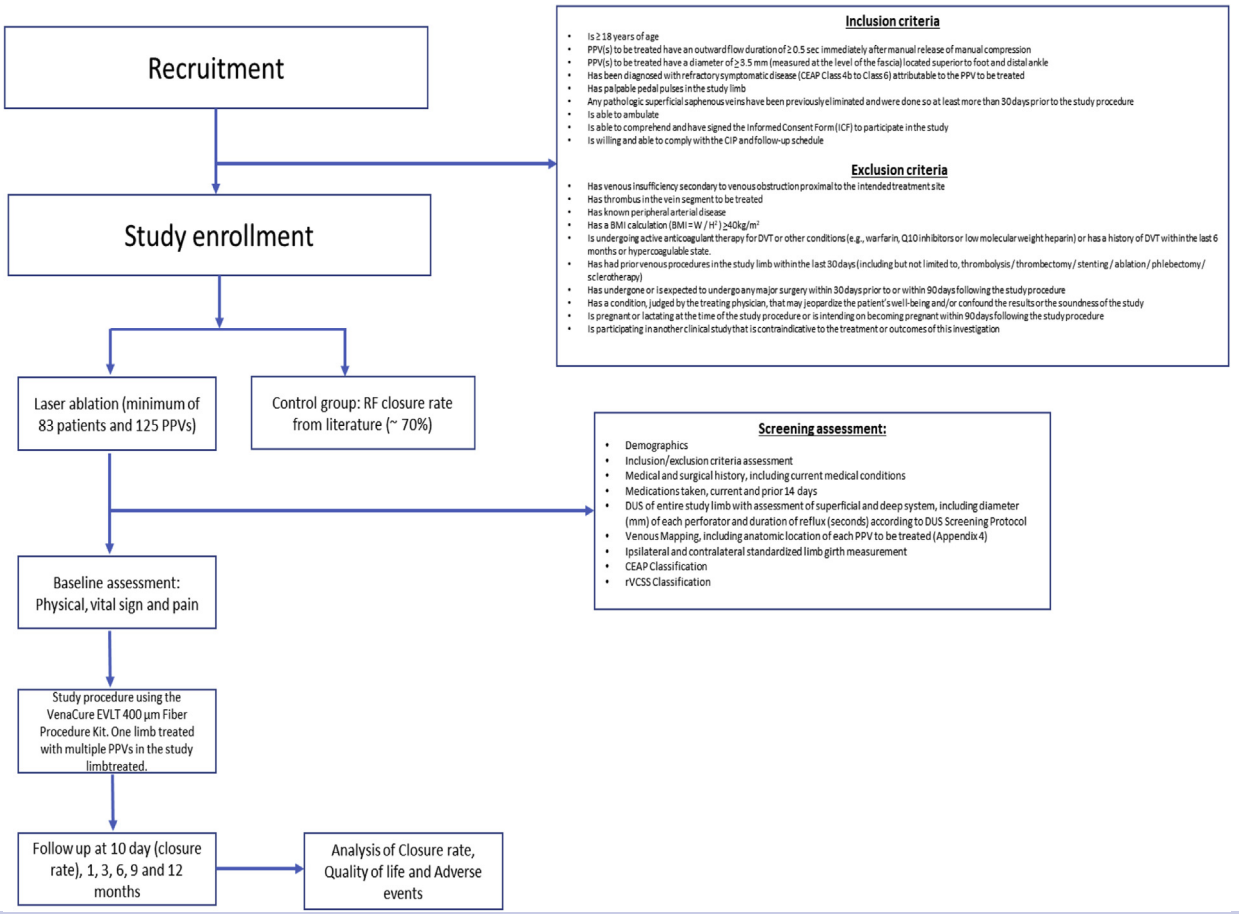

Fig 1. Schematic representation of the trial design with all the inclusion and exclusion criteria for the study. *BMI,* Body mass index; *CEAP,* Clinical, Etiology, Anatomy, and Pathophysiology; *CIP,* clinical investigational plan; *DUS,* duplex ultrasound; *DVT,* deep venous thrombosis; *EVLT,* endovenous laser therapy; *PPVs,* pathologic perforator veins; *RF,* radiofrequency; *rVCSS,* revised Venous Clinical Severity Score.

ultrasound). The 10-day (±3 days) acute primary ablation success rate associated with the optical fiber was compared with a PPV ablation success rate performance goal of 70% (based on published experience with endovascular radiofrequency ablation).[13-22] Patients were evaluated 1 month, 3 months, 6 months, 9 months, and 12 months after the procedure to collect longer term outcome data including closure rates, procedural technical success (successful access and entry into the PPV to be ablated and ability to deliver the intended laser energy), QOL, and ulcer healing data (percentage of patients with healed ulcer and ulcer surface area). Ulcer healing time was not included in the study protocol.

Statistical analysis. Standard statistical methods were employed to analyze all data. All data collected in this study were documented using summary tables and patient data listings. Continuous variables were summarized using descriptive statistics, including counts, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by frequencies and percentages.

The proportion of PPVs in the treatment group having achieved the primary effectiveness end point (calculated using a generalized estimating equation model) was

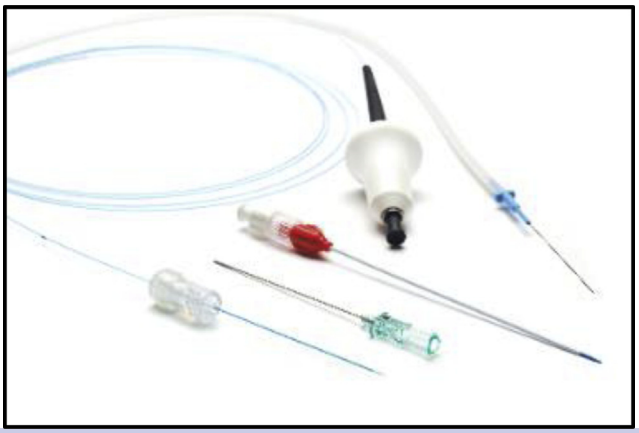

Fig 2. VenaCure endovenous laser therapy 400-µm perforator and accessory vein ablation kit (PVAK) components. (Courtesy AngioDynamics, Latham, NY.)

Table I. Demographics

Parameter	
Sex	
Female	45.8 (38/83)
Male	54.2 (45/83)
Age, years	63.7 (12.2) 67 (37-90)
Race	
American Indian or Alaska Native	1.2 (1/83)
Asian	2.4 (2/83)
Black or African American	8.4 (7/83)
White	88 (73/83)
Ethnicity	
Hispanic or Latino	6 (5/83)
Not Hispanic or Latino	89.2 (74/83)
Unknown	4.8 (4/83)
Body mass index, kg/m^2	30.2 (5) 29.8 (18.7-39.8)
CEAP clinical class	
C4b	43.4 (36/83)
C5	33.7 (28/83)
C6	22.9 (19/83)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology.
Categorical variables are presented as percentage (n/N). Continuous variables are presented as mean (standard deviation) and median (minimum-maximum).

compared with the performance goal of 70% using a one-sample proportion test with a significance level of .05. The cumulative success rate observed (from literature) for radiofrequency ablation was between 70.6% and 80.5% (95% confidence interval). Actuarial methods were not used for closure follow-up because reinterventions occurred to maintain closure over time. Hence, time at risk was not directly measurable. The closure rate reported in this study was the cross-sectional proportion of patients with ablated PPVs who were evaluated at each visit. Based on the lower 95% confidence interval, a performance goal of 70% was used for hypothesis testing. A signed rank test was performed for the revised Venous Clinical Severity Score (rVCSS), visual analog scale (VAS) pain score, and QOL score to evaluate the change from baseline values at each time point to check whether they were significantly different from their respective baseline values. For ulcer healing, patients were summarized by percentages. The trial design was submitted to the Food and Drug Administration before recruitment of patients.

RESULTS

Demographics and disease class. Patients' demographic and CEAP clinical classes are shown in Table I. Female patients composed 45.8% of the population and 54.2% were male, with a mean age of 63.7 (±12.2; range, 37-90) years. The majority of patients were white (88%) and not Hispanic or Latino (89.2%). The mean body mass index was 30.2 kg/m^2. Healed or active ulcers were present in 56.6% of patients; the remainder had skin damage (CEAP clinical class C4b).

Ultrasound screening. PPVs had reflux present at screening, with a mean duration of reflux of 2.8 seconds (±2 seconds). The mean distance of the vein from the instep was 20.1 cm; the mean distance from the tibial crest was 7.3 cm. The mean diameter of the PPVs was 4.6 mm (±1 mm).

Procedure details. Procedural details are listed in Table II. The mean duration of the procedure was 14.7 minutes (±15 minutes). The mean duration of energy delivery was 28.5 (±39) seconds. In terms of PPVs intended to treat, the majority of patients (57.8%) had only one PPV, 32.5% had two, 7.2 % had three, and 2.4% had four.

Primary efficacy. The primary effectiveness end point was defined as the complete lack of flow or PPV disappearance in the entire treated segment. Technical success was measured by duplex ultrasound imaging performed 10 days (±3 days) after the procedure. Of 125 treated PPVs, 96 met the primary end point of acute primary ablation success at the 10-day visit for an initial successful closure rate of 76.9% (from the generalized estimating equation model [Table III]), which was statistically significant compared with the performance goal of 70% ($P < .05$).[11-20]

Procedural technical success rate. The secondary effectiveness end point was procedural technical success, defined as successful access and entry into the PPV to be ablated and the ability to deliver the intended laser energy. Most of the PAPs procedures did reach technical success (95.2%), significantly exceeding the performance goal of 75% ($P < .001$) as shown in Table III. A total of six IPVs were not treated because of initial technical failure, with the most common reasons for failure being inability to successfully access the IPV with the introducer needle or to place the fiber correctly.

Long-term primary ablation closure rates. Primary ablation was achieved in 75.7% of PPVs at 1 month, 70.3% at 3 months, 62.1% at 6 months, 68.8% 9 months, and 71.3% at 12 months (Table III). A single PPV that required secondary ablation at 3 months was not successfully ablated. Four of five requiring secondary ablation at 9 months and five of the eight requiring secondary ablation at 12 months achieved successful ablation. Fourteen perforators were treated secondarily with methods including direct ligation (n = 1), foam

Table II. Procedure details

Parameter	83 patients, 125 PPVs
Procedure duration, minutes (N = 83 patients)	14.7 (15)
Laser wavelength used, nm	1470
Laser setting, W (n = 124 PPVs)	6.9 (2)
Any concomitant procedures performed	6 (5/83)
Local anesthesia	89.2 (74/83)
Sedative used	36.1 (30/83)
Patient placed in reverse Trendelenburg position	85.5 (71/83)
Limb treated	
Left	56.6 (47/83)
Right	43.4 (36/83)
No. of PPVs for which treatment is intended	
1	57.8 (48/83)
2	32.5 (27/83)
3	7.2 (6/83)
4	2.4 (2/83)

PPVs, Pathologic perforator veins.
Categorical variables are presented as percentage (n/N). Continuous variables are presented as mean (standard deviation).

sclerotherapy (n = 1), and laser retreatment (n = 12). The successful retreatment accounts for the higher closure rates at 9 months and 12 months than at 6 months.

Changes in disease severity, QOL, and pain scores. The rVCSS, Venous Insufficiency Epidemiological and Economic Study on Quality of Life/Symptoms (VEINES-QOL/Sym) scores, and VAS pain score were measured at baseline and at each follow-up visit. An analysis of the change from baseline for all of these instruments at the 10-day, 1-month, 3-month, 6-month, 9-month, and 12-month follow-up visits is presented in Table IV. At each follow-up time point, the mean rVCSS was statistically significantly improved from baseline ($P < .001$). For the QOL instruments, the mean score at each follow-up visit was statistically significantly improved from baseline ($P < .001$). The mean VAS score was also statistically significantly improved from baseline ($P < .001$ at 1 month, 3 months, 6 months, and 9 months; $P = .002$ at 12 months).

Ulcer healing. During the course of the study, the number of patients who had open ulcers steadily decreased up to the 6-month time point (Table V; Fig 3). At screening, 23% of patients had an ulcer (n = 19); 14% had an ulcer at 1 month (n = 11), 13.7% had an ulcer at 3 months (n = 10), and 10.1 % had an ulcer at 6 months (n = 7). This proportion increased slightly at 9 months, with 12.3% of patients having ulcers (n = 8), and then decreased again with 11.1% at 12 months (n = 7). One patient progressed from clinical class C4b at study start to an open ulcer (C6) during the study. A similar trend was seen in the overall wound surface area (represented as both mean and median), with initial decrease to the 6-month point and then an increase in mean area afterward. As can be inferred by the differences in the mean and median ulcer size, much of this increase at 3 months and 12 months was driven by a single limb with recurrence of an ulcer with a large surface area.

Adverse events. Three device-related adverse effects were observed in this study. One patient experienced moderate pain at the procedure site that resolved 7 months after the procedure. A second patient

Table III. Primary ablation success and technical success rate

	Performance goal		*P* value		
Initial technical success	75%[a]	95.2	<.001		
Follow up		**Closure rate, % (n/N)**	**95% Confidence interval, %**	**Lost to follow-up**	**Missed visit**
10 days	70%[a]	76.9[a] (96/125)	70.3-82.4	<.05	
1 month	N/A	75.7 (87/115)	66.8-83.2	6	4
3 months		70.3 (78/111)	60.9-78.6	13	1
6 months		62.1 (64/103)	52.0-71.5	18	4
9 months		68.8 (64/93)	58.4-78.0	28	4
12 months		71.3 (62/87)	60.6-80.5	38	

N/A, Not applicable.
[a]A generalized estimating equation model was used, resulting in an acute primary ablation success of 76.9% model success rate. This was compared with the performance goal of 70% using a one-sample proportion test with a significance level of .05. Performance goal and follow-up closure rates were taken from literature for endovascular radiofrequency ablation.[13-22]

Table IV. Venous clinical severity, pain, and quality of life (*QOL*) scores

	Screening /baseline	1-month follow-up	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow- up
rVCSS	12.4 (4) 13 (4-24)	9.9 (4) 10.5 (2-24)	9.2 (4) 9 (0-20)	8.8 (4) 8 (1-22)	8.8 (4) 8 (1-24)	8.6 (4) 9 (2-24)
VEINES-QOL	45.2 (10) 44.5 (18.1-62)	50.8 (9) 53.8 (24.8-62.2)	50.6 (10) 52.7 (21.9-62.7)	51.8 (9) 54.6 (24.2-62.6)	51.3 (10) 53.1 (22.1-62.8)	51.6 (10) 55.2 (22.2-63.1)
VEINES-Sym	44.8 (10) 46 (18.8-62.8)	50.5 (9) 52.8 (21.4-62.8)	50.7 (10) 52.3 (23.5-62.8)	51.5 (10) 55 (20.1-62.8)	51.4 (10) 54.3 (20.1-62.8)	52.1 (9) 54.2 (21.5-62.8)
VAS pain	23.4 (26) 11 (0-88)	14 (22) 3 (0-88)	14.5 (21) 5 (0-81)	12.7 (21) 2.5 (0-89)	12.4 (19) 3 (0-75)	14.2 (23) 2 (0-85)

rVCSS, Revised Venous Clinical Severity Score; *VAS*, visual analog scale; *VEINES-QOL/Sym*, Venous Insufficiency Epidemiological and Economic Study on Quality of Life/Symptoms.
Results are presented as mean (standard deviation) and median (minimum-maximum). All the follow-up scores were statistically significant from screening/baseline ($P < .001$).

experienced a short-segment posterior tibial deep venous thrombosis 1 week after the procedure as well as chronic venous obstruction as a result of this event beginning 3 months after the procedure. The patient was treated with aspirin prescribed for 3 months at that time. There was no progression of DVT in this patient. There was one death (serious adverse event) during the study period not associated with the treatment (sepsis after craniectomy for traumatic brain injury). There were no reported nerve injuries, arteriovenous fistulas, or pulmonary emboli.

DISCUSSION

Treatment of superficial venous reflux in patients with advanced venous disease is usually clinically indicated but may not be performed in many patients with skin damage or ulceration and PPVs. Current clinical practice guidelines[12] suggest treatment of perforating veins in patients with nearly healed or active venous ulcers (CEAP clinical class C5 or C6) or those with skin damage (CEAP clinical class C4b). More historic perforator treatments, such as open surgical ligation and SEPS, are now less frequently performed because of invasiveness and complication rates.

Several authors have highlighted the efficacy of perforator vein closure and its contribution to improving venous ulcer healing and reducing ulcer recurrence.[2,23-25] Rueda et al[26] studied 64 CEAP clinical class C5 and C6 patients who underwent adjunctive PPV treatment. During a mean patient follow-up of 37 months, 41 patients treated with SEPS and 23 with radiofrequency ablation had ulcer healing in 88% and 100%, respectively. The authors concluded that they support an "aggressive approach to patients with C5/C6 disease," which would include treatment of incompetent perforating veins when appropriate. Of note, unlike in our study, the patients underwent concomitant great saphenous vein treatment, potentially confounding these results.[26] Other authors[27,28] have demonstrated that treatment of both superficial and perforating vein reflux resulted in rapid ulcer healing and low recurrence rates in patients with C5 and C6 disease. By requiring any incompetent saphenous vein treatment at least 30 days before PPV treatment, the SeCure trial decreases the confounding effect of truncal ablation and isolates the benefit of PPV ablation in terms of QOL and ulcer healing.

The currently available techniques and technologies for PAPs are less invasive than conventional surgery and can be performed in an in-office setting with decreased recovery times and morbidity. They have become the first line of treatment for managing venous insufficiency.[29] Whereas there is an extensive body of literature establishing the safety and effectiveness of thermal ablation techniques for saphenous ablation, more studies focusing on the utility of these techniques for treating PPVs are needed. Existing papers in the literature have focused on technical success rates for ablation of PPVs[30] as well as for ulcer healing,[31] but few have assessed impact on QOL.

Table V. Percentage of patients with ulcer present and total wound surface area

	Screening	1-month follow-up	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow-up
Ulcer present, %	22.9	14.1	13.7	10.1	12.3	11.1
Total wound surface, cm^2	7.8 (10) 3.8 (0.01-38.5)	4.1 (4) 3.4 (0.04-10.5)	10.9 (22) 2.9 (0-72)	4 (7) 1.5 (0.01-20)	7.1 (11) 1.5 (0.35-29.25)	16.7 (28) 2.3 (0.04-70)

Total wound surface area is presented as both mean (standard deviation) and median (minimum-maximum).

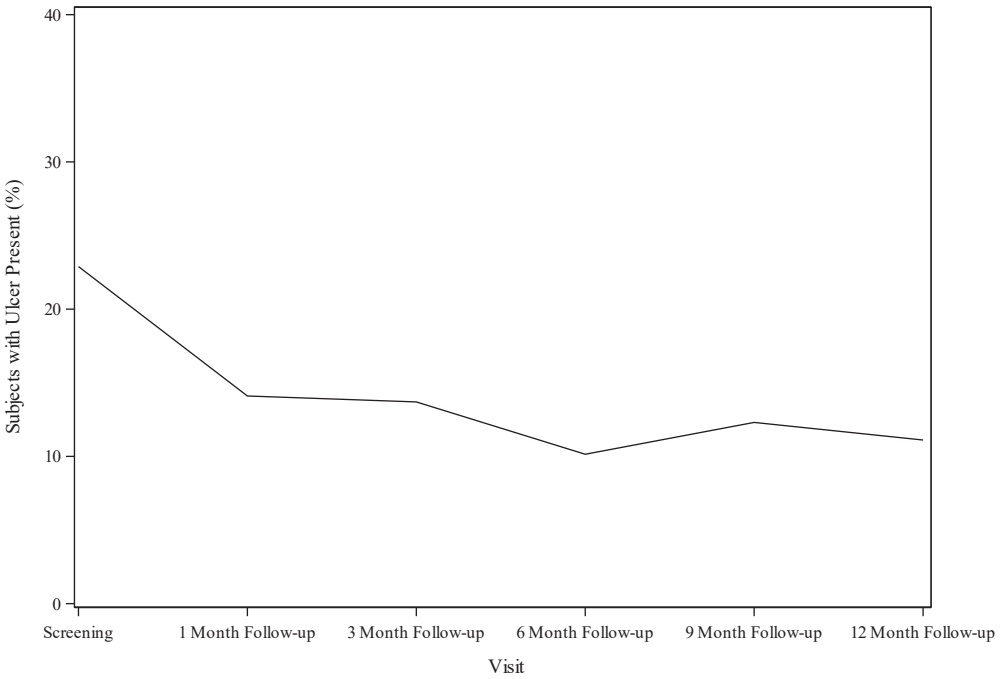

Fig 3. Percentage of patients with ulcer present at each follow-up time point.

The SeCure trial met its primary end point in terms of technical success at the 10-day visit but additionally assessed disease severity, QOL, and the presence of ulcers. The performance goal was established on the basis of the acute closure success rate associated with endovenous radiofrequency ablation published within the historical literature but also with input and concurrence of experienced endovascular interventionalists.[13-22] As shown previously by other authors, PPV ablation rates are lower than ablation rates achieved for truncal saphenous ablation. PPV ablation rates range between 60% and 80%.[23,24,32-35] Irrespective of the technique used, earlier studies and trials show that the overall long-term closure of a PPV is challenging compared with saphenous vein treatment. The reason for the difference in closure rates between PPVs and truncal veins may be due to technical difficulty in cannulation; patient factors, such as deep venous hypertension or obesity; and hemodynamic factors, such as a shorter length of closed vein. Overall, the success rate reported in this study is in congruence with the literature.[24]

Apart from the primary ablation success rate, this study also investigated several other clinically important outcomes, such as changes in QOL, percentage of limbs with ulcers, and improvement in rVCSS. At each time point, the mean rVCSS and VEINES-QoL, VEINES-Sym, and VAS scores were significantly improved from baseline. Among outcome assessments important to patients, the rVCSS and QOL instruments are important because they include patient responses to subjective questions.[36] Few studies have collectively considered specific clinical outcome assessments and QOL instruments in investigating treatment of PPVs,[37,38] making this trial unique.

In real-world situations, truncal ablation may be concomitantly performed with PPV treatment for patients with advanced venous disease, as shown by previous studies.[26,27] Concomitant truncal and perforator therapy is in fact suggested by the Society for Vascular Surgery and American Venous Forum clinical guidelines for ulcer patients.[12] Whereas concomitant therapy is appropriate, in clinical trials, separating the benefit of truncal ablation from PPV treatment is challenging. The SeCure trial is important in that it is the first study that isolates the effect of perforator vein treatment on patient QOL measures. By study protocol, any patient with clinically significant saphenous reflux had to have had saphenous vein treatment at least 30 days before entry into the SeCure trial.

Strengths of the study include its multicenter design, leading to a wider range of population groups and improving the overall generalizability and efficiency of the study. This study had several limitations, including absence of a comparator group and inability to blind participants. Another limitation is that the study did not mandate a standard protocol for compression stockings, bandaging, or wound care (left up to the study site discretion and standard of practice). This lack of uniformity between sites may have influenced patient outcomes. Like many multicenter trials, this study did observe large variability in the clinical outcomes, with the primary ablation success rate (after 10 days) ranging

from 29% to 100%. Also, the two exclusion criteria, namely, body mass index >40 kg/m^2 and active anticoagulation therapy, limited the rate of patient recruitment for a few centers and possibly applicability to all patients.

CONCLUSIONS

The 400-μm optical fiber with the 1470-nm laser is a safe and effective device for treating PPVs. Technical success rates were high, and closure rates were comparable to those of previous studies of PPV treatment. PPV treatment independent of truncal ablation improved patients' vein-specific QOL. The use of the 400-μm optical fiber with the 1470-nm laser is an effective tool in the management of advanced chronic venous disease associated with PPVs.

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AUTHOR CONTRIBUTIONS

Conception and design: MA, LK
Analysis and interpretation: KG, SE, MA, LK
Data collection: KG, SE, EH, DD, SV, PC, LK
Writing the article: KG
Critical revision of the article: KG, SE, MA, EH, DD, SV, PC, LK
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