Twenty-four month results from a randomized trial of cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins

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ABSTRACT

Objective: We previously reported 3-month and 12-month occlusion rates after treatment of clinically symptomatic saphenous vein reflux with either cyanoacrylate closure (CAC) using the VenaSeal Closure System (Medtronic, Dublin, Ireland) or radiofrequency ablation (RFA) in a randomized, multicenter, clinical trial, VenaSeal Sapheon Closure System vs Radiofrequency Ablation for Incompetent Great Saphenous Veins (VeClose). Herein we report the 24-month follow-up results of the VeClose trial.

Methods: There were 222 patients with symptomatic great saphenous vein (GSV) incompetence who were randomly assigned to receive either CAC (n = 108) or RFA (n = 114). Patients were not allowed to receive adjunctive treatment of tributary varicosities until after the 3-month visit. Duplex ultrasound of the target vein was performed at day 3 and months 1, 3, 6, 12, and 24 after treatment, and closure was assessed by ultrasound by the treating physician. Overall 24-month success rates were compared; in addition, time to first reopening of the target vein was evaluated using survival analysis. End points such as Venous Clinical Severity Score, EuroQoL-5 Dimension, and Aberdeen Varicose Vein Questionnaire were evaluated.

Results: Of 222 randomized patients, 171 completed the 24-month follow-up, which included 87 from the CAC group and 84 from the RFA group. The 24-month complete closure rate was 95.3% in the CAC group and 94.0% in the RFA group, demonstrating continued noninferiority of CAC compared with RFA ($P = .0034$). Symptoms and quality of life improved similarly in both groups. No clinically significant device- or procedure-related late adverse events occurred.

Conclusions: Both CAC and RFA were effective in closure of the target GSV, resulting in similar and significant improvements in the patient's quality of life through 24 months. These results suggest that CAC of the GSV is safe and durable out to 2 years. (J Vasc Surg: Venous and Lym Dis 2018;■:1-8.)

Keywords: Cyanoacrylate; Endovenous laser; Saphenous vein; Varicose vein; Radiofrequency ablation; Tumescent anesthesia; Nontumescent nonthermal

Chronic venous insufficiency is a common condition that affects between 10% and 35% of adults in the United States.[1] Chronic venous insufficiency may be a progressive and debilitating medical condition. Approximately 1% to 4% of the diseased population has a healed or active venous stasis ulceration (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical class 5 or 6).[2,3] Millions of patients with venous insufficiency have leg symptoms affecting their lifestyle, but in its most advanced phases, venous insufficiency exacts a considerable toll on quality of life (QoL) and is also associated with considerable health care costs.[3,4]

In the United States, traditional surgical therapy for saphenous insufficiency has largely been supplanted by endovenous thermal ablation techniques, namely, radiofrequency ablation (RFA) and endovenous laser ablation therapy.[5] These techniques have high closure rates as assessed by duplex ultrasound, with good safety profiles, and they are associated with minimal downtime compared with surgical stripping.[6] Whereas RFA and

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Author conflict of interest: The original sponsor of the VeClose trial was Sapheon, Inc. Sapheon was acquired by Covidien Ltd, which was then acquired by Medtronic, Inc. K.G., A.J., R.K., N.M., M.V., and R.W. were investigators in this trial and received payments to cover trial-related activities. In addition, K.G., A.J., R.K., N.M., and M.V. are consultants to Medtronic, Inc, but do not have individual stock or options in Medtronic, Inc. D.C. is also a consultant to Medtronic, Inc. M.M. was an investor and employee of Sapheon, Inc, and is now an employee of Medtronic, Inc. No clinical investigators in the VeClose trial were shareholders in Sapheon, Inc.

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endovenous laser ablation therapy can be performed in the office setting, they require the use of perivenous tumescent anesthesia, involving multiple needle sticks that can cause discomfort and ecchymosis. Moreover, there is a risk of thermal nerve damage that can result in paresthesia.[7,8]

More recently, nonthermal, nontumescent (NTNT) therapies for the treatment of saphenous insufficiency have become available. Mechanochemical ablation (ClariVein; Vascular Insights, Madison, Conn) and proprietary endovenous microfoam (Varithena; BTG, Conshohocken, Pa) are NTNT techniques that use a chemical sclerosant to achieve vein closure and require postprocedure compression stockings.[9,10] A third NTNT technology, cyanoacrylate closure (CAC) using VenaSeal Closure System (Medtronic, Dublin, Ireland), was approved by the Food and Drug Administration for commercial use in the United States in February 2015, following successful achievement of primary end points in the pivotal VenaSeal Sapheon Closure System vs Radiofrequency Ablation for Incompetent Great Saphenous Veins (VeClose) trial.[11] CAC is distinct from mechanochemical ablation and proprietary endovenous microfoam in that it requires neither sclerosant nor compression stockings to achieve acceptable closure rates.[12-14]

Previous prospective clinical trials, a first in human feasibility trial[12,15,16] and the European Sapheon Closure System Observational ProspectivE (eSCOPE) trial,[13] provided data on the safety and effectiveness of CAC. The first in human trial reported a 94.7% closure rate at 12 months that remained unchanged at 24 and 36 months.[12,15,16] In the eSCOPE trial, the closure rate at 12 months was 90%.[13] To gain insight into the relative utility of CAC, VeClose was designed as a prospective randomized trial comparing CAC with RFA for treatment of symptomatic great saphenous vein (GSV) incompetence.[11] At 3 months, using a last observation carried forward analysis and core laboratory adjudication, the target vein closure rate in VeClose was 99.0%, and at 12 months, the closure rate was 96.8% for CAC.[11,17] The 3- and 12-month results for RFA were 95.4% and 95.9%, respectively.[11,17] At both time points, CAC closure rates were noninferior compared with RFA. Significant and persistent improvements in target leg signs and symptoms (Venous Clinical Severity Score [VCSS]) and the patient's QoL were reported in both groups. Herein we describe 24-month results of the VeClose trial, focusing on durability of closure, symptom scores, and QoL measurements.

ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective randomized trial
- **Take Home Message:** Of the 222 patients randomized for incompetent great saphenous vein (GSV) treatment to either cyanoacrylate closure (CAC) using VenaSeal Closure System or to radiofrequency ablation using ClosureFast system, 171 completed 24 months of follow-up, with GSV closure rates of 95.3% and 94.0% in the CAC and radiofrequency ablation groups, respectively ($P = .0034$ for noninferiority). There were no significant device- or procedure-related adverse events in either group, and there were similar significant improvements in quality of life scores.
- **Recommendation:** CAC can be recommended as a safe and effective method for GSV closure out to 2 years.

METHODS

Trial design and participants. VeClose is a prospective, randomized controlled, multicenter trial conducted under an investigational device exemption from the U.S. Food and Drug Administration at 10 trial centers in the United States. The design, eligibility criteria, and outcomes through month 3 have been described in detail previously.[11] The target population was adult patients with symptomatic moderate to severe varicosities (CEAP clinical classification of symptomatic C2-C4b) and incompetence of the GSV, with reflux time of >0.5 seconds assessed in the standing position with duplex ultrasound. Patients with clinically significant reflux of the small saphenous vein or anterior accessory GSV, prior treatment of the target GSV, symptomatic peripheral arterial disease, history of deep venous thrombosis or pulmonary embolism, or aneurysm of the target GSV >12 mm in diameter were excluded. All patients underwent baseline examination consisting of physical examination, completion of CEAP and VCSS assessments,[18] and duplex ultrasound of both legs. In addition, patients completed the Aberdeen Varicose Vein Questionnaire (AVVQ) and EuroQoL-5 Dimension (EQ-5D) QoL survey.[19,20] Enrollment took place between March and September 2013. All participating sites obtained central Institutional Review Board approval before enrollment, and each patient provided trial-specific informed consent before treatment.

Randomization. There were 222 patients who were randomized in a 1:1 fashion to either CAC performed with the VenaSeal Closure System (n = 108) or RFA. Randomization was stratified by trial site and used random block sizes of 4 or 6; assignments were obtained through an automated telephone service connected to a password-protected randomization table. In addition, the trial included a roll-in group (n = 20), described more completely elsewhere,[21] composed of the first two patients at each site who were not randomized but rather treated with CAC to ensure familiarity with the procedure and trial requirements.

Devices and procedures. Endovenous treatment of the GSV with CAC was performed with VenaSeal Closure System as described previously.[11] Briefly, the refluxing