Sponsored by Medtronic

Clinical Evidence Behind the VenaSeal™ Closure System

A review of the clinical trials that led to FDA approval of a novel treatment for saphenous vein reflux.

BY KATHLEEN GIBSON, MD, FACS, AND AZAH TABAH, PHD

In the United States, it is estimated that 30 million men and women are affected by chronic venous insufficiency (CVI).[1] CVI is often progressive and can lead to symptoms impacting patient quality of life such as aching, throbbing, and edema.[2] With time, CVI can lead to more serious medical problems such as irreversible skin changes and/or chronic ulceration.[3]

The most common anatomic pattern present in patients with superficial venous insufficiency is incompetence of the great saphenous vein (GSV).[4] In the United States, the previously favored treatment for incompetence of the GSV, surgical stripping, has largely been replaced by endothermal ablation, either with radiofrequency or laser energy.[5] Although endothermal techniques have led to improvements in patient recovery and offer earlier return to normal activities of daily living when compared to surgical stripping,[6] they require tumescent anesthesia and in some centers, are performed using sedation. Additionally, standard clinical practice after endothermal ablation requires the use of compression stockings or wraps for a physician-specified period of time during the recovery period. The VenaSeal™ closure system (VSCS, Medtronic) received CE mark approval in September 2011 and premarket approval from the US Food and Drug Administration (FDA) for closure of incompetent saphenous veins in February 2015. VSCS, utilizing a proprietary cyanoacrylate adhesive, offers a safe and effective method of treating refluxing saphenous veins without the need for tumescent anesthesia or postprocedure compression.*

In the March 2015 issue of *Endovascular Today*, Dr. Nick Morrison described the history of the development of cyanoacrylate adhesives for medical applications. This article outlines the clinical data leading to the premarket approval of the VenaSeal™ closure system.

FEASIBILITY STUDY

The cyanoacrylate adhesive utilized in the VSCS first underwent proof of concept in the rabbit, swine, and goat models.[7,8] Additionally, animal models were used to research biocompatibility, mechanism of action, safety, and effectiveness. In a first-in-man feasibility study published[9] and presented by Dr. Jose Almeida at the American Venous Forum, 38 patients with symptomatic reflux of the GSV were treated with catheter-delivered cyanoacrylate adhesive under ultrasound guidance. No adjunctive procedures were allowed for 6 months, and the post-procedure regimen did not include the use of compression. The primary outcome measure was duplex-verified closure of the GSV at follow-up intervals of 48 hours, 1, 3, 6, and 12 months. Secondary outcome measures were rates of adverse events and change in the Venous Clinical Severity Score (VCSS). A second article reporting follow-up out to 2 years by the same authors in 2014 showed that GSV closure immediately after the procedure and at 48 hours was 100%.[10] Closure rates at 1, 3, 6, and 12 months were 92%. At 2 years, 24 of the original 38 patients were available for follow-up, and the occlusion rate remained at 92% (Table 1). The mean VCSS at the start of the study was 6.1 ± 2.7, and 1.3 ± 1.1, 1.5 ± 1.4, and 2.7 ± 2.5 at 6, 12, and 24 months, showing maintenance of clinical benefit.

A mild and self-limited phlebitis, responding to nonsteroidal analgesia, was reported in 15.8% of patients. Thread-like thrombus extensions into the common femoral vein were seen on duplex ultrasound in eight patients (21.1%). These thrombus extensions resolved without the use of anticoagulants. In this study, the catheter was placed 1.5 to 2 cm caudal to the saphenofemoral junction for the delivery of adhesive. Additionally at this location, two injections of the adhesive were administered. Because of the thrombus extensions seen in the patients in this early

*Some patients may benefit from compression stockings postprocedure.

Sponsored by Medtronic

TABLE 1. DUPLEX CLOSURE RATES

Clinical Study	Closure Rates
FEASIBILITY study[9,10]	12 months: 92% 24 months: 92%
eSCOPE study[13]	6 months: 94.3% 12 months: 92.9%

trial, the technique was changed in the subsequent trials, and the tip of the catheter was positioned farther caudally, 5 cm from the saphenofemoral junction, and the first two injections were delivered 1 cm apart. With this change in technique, no thrombus extensions were seen in subsequent clinical trials.[11,12]

eSCOPE STUDY

The European multicenter study, eSCOPE,[11] was a nonrandomized, prospective trial to evaluate the safety and efficacy of the VSCS in the treatment of symptomatic refluxing GSVs. Seventy patients were treated, and follow-up assessments occurred at 48 hours, 1, 3, 6, and 12 months, and ongoing follow-up at 24 and 36 months. Technique and outcome measures were similar to the feasibility study, with the exception of the more caudal catheter placement, and the allowance of adjunctive measures at 3 months rather than 6 months. No compression therapy was used after the procedures. GSV closure rates were 94.3% at 6 months and 92.9% at 1 year (Table 1); 36-month data have not yet been published. Adverse events included a mild, self-limited phlebitic reaction in 11.4% of patients. No thrombotic events or paresthesias were observed.

VeClose STUDY

The United States pivotal trial, VeClose, was a prospective trial with a 1:1 randomization comparing VSCS to radiofrequency ablation (RFA, ClosureFast™ catheter, Medtronic).[12] The trial was conducted at 10 sites throughout the United States. No adjunctive therapies were permitted for 3 months. To avoid confounding effects, both groups received postprocedure compression. The study objective was to demonstrate the safety and efficacy of VSCS in the treatment of lower extremity truncal reflux by showing noninferiority to RFA

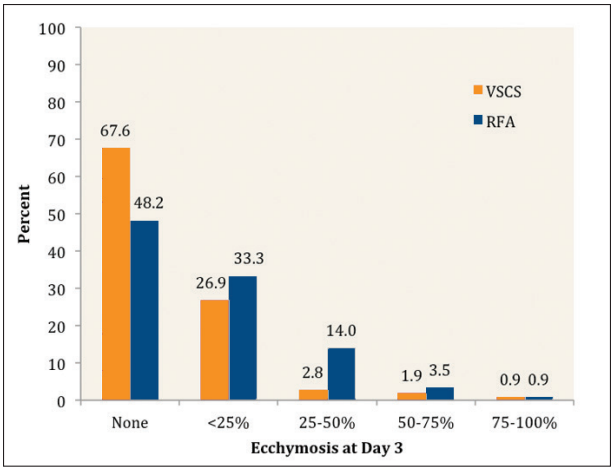

Figure 1. Ecchymosis assessed with a 5-point scale on day 3 by treatment group. Patients treated with VSCS had less ecchymosis at day 3 compared with those treated with RFA ($P < .01$).

at 3 months. There were 242 patients enrolled with 20 roll-in/training cases; 108 patients were treated with VSCS and 114 with RFA. The primary study endpoint was duplex ultrasound closure of the GSV, and secondary endpoints were intraoperative pain, ecchymosis (at day 3), and adverse events (at 1 month). VCSS, Aberdeen Varicose Vein Questionnaires (AVVQ), and EQ-5D were collected at baseline and at follow-up evaluations. Follow-up assessments occurred at day 3, 1 and 6 months, 1 and 2 years, and will conclude at 3 years.

The two treatment groups were well matched in regards to age, gender, body mass index, vein diameter, length of vein treated, and baseline AVVQ. There was no significant difference in intraprocedural pain between the two groups, but there was significantly less ecchymosis in the treated limb at 3 days in the VSCS group ($P = .0013$). No ecchymosis was present in 67.6% of the VSCS patients compared to 48.2% of the RFA patients. When present, the severity of ecchymosis was lower in the VSCS group (Figure 1). In terms of the primary endpoint, the study protocol defined complete closure to mean duplex ultrasound closure along the entire treated segment of the target vein with no discrete segments of patency exceeding 5 cm in length, which also included segments that were compressible, even if they showed

TABLE 2. CLOSURE RATES FROM VeCLOSE STUDY

Duplex Closure Rate	VSCS (n = 108)	RFA (n = 114)	*P* Value
3 months	99%	96%	< .0001
6 months[13]	99%	94%	< .0001

TABLE 3. CHANGE IN VCSS AND AVVQ SCORES BY VISIT AND TREATMENT TYPE

	Treatment	Baseline	1 Month	3 Months	6 Months
VCSS mean (SD)	RFA	5.6 (2.6)	2.6 (2)	2 (2)	1.6 (1.9)
	VSCS	5.5 (2.6)	2.3 (1.7)	1.9 (1.6)	1.5 (1.8)
AVVQ mean (SD)	RFA	19.4 (9.9)	12.6 (8.3)	10.7 (8.6)	9.1 (6.9)
	VSCS	18.9 (9)	11.9 (7.5)	11.6 (7.5)	10.2 (7.2)

no flow with color imaging. Vein closure was adjudicated by an independent core laboratory (VasCore) for the 3-month visit. Closure rates (Table 2) at 3 months and 6 months were 98.9% and 98.9% for VSCS, and 95.4% and 94.3% for RFA, a highly statistically significant finding for noninferiority at these time points ($P < .0001$).[13] There was complete agreement between the core laboratory and the investigator findings. The core laboratory was blinded to the investigator findings.

There were no deep vein thromboses or pulmonary emboli reported in either treatment group. Phlebitis occurred in 20% of VSCS-treated patients and 14% of RFA-treated patients ($P = .36$). In both groups, the majority of the cases of phlebitis were mild and transient, and were successfully treated with anti-inflammatory medications such as ibuprofen. The reaction within the VSCS cohort was seen in all three studies, and it has a presentation that is different in terms of both physical signs and duration and quality of symptoms compared to phlebitis that can occur following endothermal heat ablation. Whereas phlebitis after endothermal ablation typically presents as a firm and focally tender cord along the course of the treated vein that may take weeks to resolve, patients with symptoms following VSCS presented with a rosy cutaneous erythema in the medial thigh, with mild diffuse tenderness that dissipated over several days. Some patients with phlebitis presented without symptoms, having only the visual appearance.

It is increasingly recognized that the use of surrogate outcome measures (such as duplex closure of the GSV) to judge the success or failure of a treatment for venous disease is insufficient if they are not accompanied by demonstration of improvement in a patient's symptoms/quality of life. The improvements seen in VCSS and the AVVQ in the VeClose trial therefore are critically important findings. In the two treatment groups, the VCSS and AVVQ showed significant and sustained improvement. There were no differences in the improvement in VCSS and AVVQ in patients treated with VSCS compared with those treated with RFA (Table 3). Data collection in this trial is ongoing and will continue for 36 months after treatment.

CONCLUSION

The three described clinical trials demonstrate that VSCS is a safe and effective therapy for the closure of incompetent truncal veins. The closure rates across all of the trials have been consistently demonstrated. Side effects were minor and well tolerated. There have been no documented cases of deep venous thrombosis or pulmonary embolism in any trial. As shown in the feasibility and eSCOPE trials, patients treated with VSCS do not require post-procedure compression stockings.* Additionally, VSCS does not require use of tumescent anesthesia. The FDA approval of VSCS for the treatment of superficial venous insufficiency gives physicians a new and important tool to treat their patients suffering from symptoms caused by varicose veins. ■

Kathleen Gibson, MD, FACS, is with Lake Washington Vascular Surgeons in Bellevue, Washington. She has disclosed that she is a consultant for Medtronic and is a Principal Investigator in the VeClose US Pivotal trial. Dr. Gibson may be reached at drgibson@lkwv.com.

Azah Tabah, PhD, is a Scientific Communications Manager for Medtronic in Minneapolis, Minnesota.

1. McLafferty RB, Passman M, Caprini J, et al. Increasing awareness about venous disease: the American Venous Forum expands the National Venous Screening Program. J Vasc Surg. 2008;48:394-399.
2. Pannier F, Rabe E. Progression in venous pathology. Phlebology. 2015;30(1 suppl):95-97.
3. Robertson L, Lee AJ, Gallagher K, et al. Risk factors for chronic ulceration in patients with varicose veins. J Vasc Surg. 2009;49:1490-1498.
4. Labropoulos N, Leon M, Nidolaides A, et al. Superficial venous insufficiency: correlation of anatomic extent of reflux with clinical symptoms and signs. J Vasc Surg. 1994;20:953-958.
5. US Markets for Varicose Vein Treatment Devices. 2013. Medtech360, Millennium Research Group, INC.
6. Rasmussen LH, Lawaetz M, Bjoern L, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg. 2011;98:1079-1087.
7. Almeida JI, Min RJ, Raabe R, et al. Vein closure using cyanoacrylate adhesive: 60 day swine model results. Vasc Endovascular Surg. 2011;45:631-635.
8. Min RJ, Almeida JI, McLean DJ, et al. Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results. Phlebology. 2012;27:398-403.
9. Almeida JI, Javier JJ, Mackay EG, et al. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg: Venous and Lymph Dis. 2013;1:174-180.
10. Almeida JI, Javier JJ, Mackay EG, et al. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence [published online ahead of print April 30, 2014.]. Phlebology .
11. Proebstle TM, Alm J, Rasmussen L, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg: Venous and Lym Dis. 2013;1:101.
12. Morrison N, Gibson K, McEnroe S, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg. 2015;61:985-994.
13. Gibson K. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). Presented at the German College of Phlebology, September 2014.

*Some patients may benefit from compression stockings postprocedure.