American Vein and Lymphatic Society
formerly the American College of Phlebology

Position Statement
Healthcare Policy Committee
Cyanoacrylate Venous Closure

January 17, 2019

Introduction

Historically, treatment options for patients with venous insufficiency and varicose veins primarily consisted of high ligation and stripping of the great saphenous vein (GSV) in association with phlebectomy of individual varicosities. During the past 18 years, such painful interventions, which required general anesthesia along with several days in the hospital and weeks of recuperation, have been supplanted by outpatient office-based endovascular ablation techniques with conscious sedation and/or local anesthesia and an almost immediate return to normal activities of daily living. Such endovascular treatment of venous disease has been primarily performed with thermally-based radiofrequency or laser ablation that require percutaneous, perivenous tumescent anesthesia. They are superior to high ligation and stripping and are recommended by published multi-society guidelines for the treatment of the incompetent superficial axial incompetent veins (GSV, SS, AASV etc.) [Gloviczki P et al. ***The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum***. *J Vasc Surg.* 2011;53(5 suppl):2S-48S] With these approaches, patients achieve excellent vein occlusion rates and more importantly improved quality of life for years after intervention. Newer approaches seek to improve upon these currently available methods by achieving similar clinical outcomes without thermal energy and thus obviate the need for tumescent anesthesia. Elimination of tumescent anesthesia results in less intraoperative pain, no risk of nerve injury and minimal skin damage. The opportunity for physicians to have a choice of treatment options in order to choose the one that is optimal for an individual patient will result in the best outcomes in the treatment of venous insufficiency and varicose veins.

VenaSeal Closure System

On February 20, 2015, the U.S. Food and Drug Administration (FDA) granted premarket approval application (PMA) of the VenaSeal™ Closure System (VSCS) to treat superficial varicosities of the legs through endovascular embolization for adults with clinically symptomatic venous reflux diagnosed by duplex ultrasound. As of March 2018, there have been a total of approximately 9,000 VenaSeal™ Closure Systems sold in the United States.

CPT codes describing cyanoacrylate for the treatment of incompetent veins went into effect on January 1, 2018:

- 36482 - Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (e.g., cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated).
- 36483 - Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (e.g., cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

Overview

The VenaSeal™ Closure System is the only approved non-tumescent, non-thermal, non-sclerosant treatment for patients suffering with symptomatic venous reflux disease in the United States. The VenaSeal™ adhesive, an n-butyl-2-cyanoacrylate (n-BCA) based formulation, is a clear, free-flowing liquid that polymerizes in the vessel upon contact with body fluids or tissue. This acute process halts blood flow through the insufficient vein until the implanted adhesive becomes fibrotically encapsulated to establish a durable, chronic occlusion of the treated vein. It is injected while using high resolution ultrasound imaging.

The procedure has four core phases: catheter insertion, adhesive injection, compression and occlusion. No post-procedure compression stockings are required. This procedure is typically performed in a physician's office setting but can also be provided in a hospital outpatient setting. Medtronic requires an FDA mandated physician training process to ensure the VenaSeal™ adhesive is delivered effectively and consistent outcomes are achieved.

Clinical Evidence

Clinical studies have demonstrated the safety and effectiveness of the VenaSeal™ Closure System as a treatment option for patients suffering from venous reflux disease demonstrating durable results with a 94 % closure rate at 3 years. [1-4]Clinical evidence supporting the safety and effectiveness of the VenaSeal™ Closure System is derived from a combination of clinical studies. The four main studies are:

- Feasibility Study (First in Human Study, December 5, 2010)
- eScope
- VeClose
- WAVES

The below table provides an overview of the above-mentioned studies. A more in-depth analysis of these studies as well as other relevant articles and presentations pertaining to VenaSeal™ Closure System and cyanoacrylate adhesion and a complete bibliography are included in the attached Evidence Compendium.

	eSCOPE Trial[1]*	**Feasibility Study[2]**	**WAVES Trial[3]**	**VeClose Study[4]* (U.S. Pivotal Trial)**
Study Design	Prospective, multi- center, post-market study	Prospective, single-center study	Prospective, single- center, multi-investigator, post- market study	Prospective, multi- center, randomized controlled trial
Patients Enrolled (n)	70	38	50	242*
Closure Rate	**3-year: 88.5 %**	**3-year: 94.7 %**	**1-year: 98%**	**VenaSeal™ System 3-year: 94.4%** **RF 3-year: 91.9 %**

Definition of Closure	No discrete segment of patency >10 cm in the treated vein segment	No discrete segment of patency >5 cm in the treated vein segment	No discrete segments of patency exceeding >5 cm in the treated vein segment	No discrete segment of patency >5 cm in the treated vein segment
Serious Adverse Events Related to Study Device or Procedure	0	0	0	0

*The VeClose study has had it's 24 and 36-month results reported. The 24-month manuscript has been submitted for publication and the 36-month manuscript is in a draft status. The eSCOPE 36-month data has been reported and the manuscript has been submitted for publication. UPDATE THIS SECTION

Patient Outcomes

The VeClose Trial, a 10-center randomized, controlled study demonstrated 94% closure rate at 3 years.[4] It demonstrated excellent patient outcomes without the need for tumescent anesthesia, multiple needle sticks, thermal nerve injury and post-procedure compression stockings. Patients were able to return to normal activities following the treatment and reported minimal bruising.[1-4] Patient satisfaction at 1 year in the WAVES trial was 98%.[3] The VenaSeal™ Closure System can be considered as a device that achieves desirable patient outcomes and shows demonstrated performance in the treatment of patients with symptomatic, incompetent lower extremity truncal veins (GSV and SSV) with improvement in QoL parameters[9]

Return to Work:

Return to full normal activity (including full exercise routine) [3]

Secondary Endpoint	Duration
Mean return to work	0.2 ± 1.1 days
Mean return to normal activities	2.4 ± 4.1 days

Assessments related to venous disease severity:

Change in VCSS scores[3]

Assessments related to QOL:

Change in **AVVQ** scores
Change in **EQ-5D** scores

CLINICAL OUTCOMES AND QUALITY OF LIFE INDICES					
	Baseline	**1 Month**	**3 Months**	**12 Months**	**P Value (Baseline 3-mo)**
VCSS	6.5 ± 2.4 (3-14)	1.8 ± 1.4 (0-6)	1.8 ± 1.4 (0-6)	1.1 ± 1.3 (0-4)	<.001
AVVQ	17.3 ± 7.9 (2.5-47.1)	8.9 ± 6.6 (0-24.8)	6.5 ± 7.2 (0-28.1)	5.6 ± 7.3 (0-38.1)	<.001
EQ-5D	84 ± 12 (30-100)	88.3 ± 8.7 (65-100)	88.6 ± 10.6 (40-100)	90.1 ± 10.0 (45-100)	.002

Conclusion

Based on current evidence, there is data to support the conclusion that VenaSeal is as good as and in some cases better than the currently reimbursed thermal modalities. Occlusion rates are equal and improved quality of life measurements are equal as well. VenaSealTM Closure System should be allowed and covered in the armamentarium of interventions that we can offer to our patients suffering from venous disease. We request equitable reimbursement for this procedure when physicians choose to use it to treat their patients. Attached are the clinical data and references to substantiate these recommendations.

A. Bibliography

Study Design	# of Studies	Study Citation

Prospective	16	1. Proebstle TM. The European Multicenter Study on Cyanoacrylate Embolization of Refluxing Great Saphenous Veins without Tumescent Anesthesia and without Compression Therapy. Results presented at: Charing Cross; 2016; London, UK. 2. Almeida JI, Javier JJ, Mackay EG, Baustista C, Cher DJ, Probestle TM. Thirty-sixth- month follow-up of first-in-human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *J Vasc Surg: Venous and Lym Dis*. 2017;1-9. https://doi.org/10.1016/j.jvsv.2017.03.016Proebstle TM, Alm J, Rasmussen L, et al. 3. Carr. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: a post-market evaluation of the VenaSeal™ system (Waves trial): 12 months data. Medtronic [Internal data on file]. 2017;1-19. 4. Morrison N. VenaSeal™ closure system vs. radiofrequency ablation for incompetent great saphenous veins. 36-month results. IVC. Medtronic [Internal data on file]. 2017;1- 19. 5. 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(4):985-994. 6. Gibson K. A randomized, controlled study comparing cyanoacrylate adhesive embolization with radiofrequency ablation for treatment of incompetent great saphenous veins. German society of phlebology Munich. Medtronic [Internal data on file]. 2014;1-26. 7. Kolluri R, Gibson K, Cher D, Madsen M, Weiss R, Morrison N. Roll-in phase analysis of clinical study of cyanoacrylate closure for incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2016;4(4):407-415. 8. Morrison N, Kathleen G, Michael V, et al. VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2017;5(3):321-330. 9. Gibson K. VeClose randomized controlled trial-quality of life (QoL) assessment. Medtronic [Internal data on file]. 2017;1-17. 10. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *J Vasc Surg Venous Lymphat Disord*. 2013;1(2):174-180. 11. Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Two-year follow- up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. *Phlebology*. 2015;30(6):397-404. 12. The European multicenter study on cyanoacrylate embolization of refluxing great saphenous Veins without Tumescent Anesthesia and without Compression Therapy. *J Vasc Surg Venous Lymphat Disord*. 2013;1(1):101. 13. Proebstle TM, Alm J, Dimitri S, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2015;3(1):2-7. 14. Gibson K and Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: Initial outcomes of a post-market evaluation of the VenaSeal System (the Waves Study). *Vascular*. 2017;25(2)149–156. 15. Gibson. Cyanoacrylate closure of incompetent great, small and accessory saphenous

veins without the use of post-procedure compression: a post-market evaluation of the
VenaSeal™ system (waves trial): three month data. Medtronic [Internal data on file].
2017;1-24.
16. Toonder IM, Lam YL, Lawson J, Wittens CH. Cyanoacrylate adhesive perforator embolization (CAPE) of incompetent perforating veins of the leg, a feasibility study.
Phlebology. 2014;29(1S):49–54.

Study Design	# of Studies	Study Citation
		17. Chan YC, Law Y, Cheung GC, Ting AC, Cheng SW. Cyanoacrylate glue used to treat great saphenous reflux: Measures of outcome. *Phlebology*. 2017;32(2):99-106.
Retrospective	8	18. Zierau UT. VenaSeal® versus RFITT® History study over 18 months on 590 saphenous veins. *Vasomed*. 2014;26(4):178-183. 19. Zierau UT. Sealing Veins with the VenaSeal® sapheon closure system Results for 795 treated truncal veins after 1000 Days. *Vasomed*. 2015;27(3):124-127. 20. Zierau UT. Vein adherence closure Radiofrequency therapy for varicose veins Course study over 36 months with 1139 treatments. *Vasomed*. 2016;28(5):212-216. 21. Alm J. VenaSeal™ closure treatment of saphenous varicosis indication, technique, initial results. *Phlebology.* 2014;43(5):242–248. 22. Liu. Cyanoacrylate embolization for the treatment of saphenous vein reflux: ultrasound appearance and correlative findings of comparative model histology. Medtronic [Internal data on file]. 2014. 23. Raju A, Mallick R, Campbell C, Carlton R, O'Donnell T, Eaddy M. Real-World Assessment of interventional treatment timing and outcomes for varicose veins: A retrospective claims analysis. *J Vasc Interv Radiol.* 2016;27(1):58-67. 24. Mallick R, Raju A, Campbell C, et al. Treatment patterns and outcomes in patients with varicose veins. *Am Health Drug Benefits*. 2016;9(8):455-464. 25. Chan YC, Law Y, Cheung GC, Cheng SW. Predictors of recanalization for incompetent great saphenous veins treated with cyanoacrylate glue. *J Vasc Interv Radiol*. 2017;28(5):665-671.
Review	5	26. Almeida JI. Nonthermal ablation for the treatment of varicose veins the evolving minimally invasive methods for saphenous vein ablation. *Evtoday*. 2011;34-38. 27. Lawson J, Gauw S, Vlijmen CV, et al. Sapheon: the solution? *Phlebology.* 2013;28(suppl 1):2-9. 28. Gibson K, Tabah A. Clinical evidence behind the VenaSeal™ closure System. *Evtoday*. 2015;33-35. 29. Bootun R, Lane TRA, Davies AH. A comparison of thermal and non-thermal ablation. *Reviews in Vascular Medicine*. 2016;4(5);1–8. 30. Proebstle T, Bos R. Endovenous ablation of refluxing saphenous and perforating veins. *Vasa.* 2017;46(3):1–8.
Case Reports	2	31. Lane TRA, Kelleher D, Moore HM, Franklin IJ, Davies AH. Cyanoacrylate glue for the treatment of great saphenous vein incompetence in the anticoagulated patient. *J Vasc Surg: Venous and Lym Dis*. 2013;1:298-300. 32. Anwar M A, Lane T R, Franklin I J, et al. Cyanoacrylate for the treatment of small saphenous vein venous incompetence. *Cureus*. 2014;6(10):221.

Pre-clinical Studies	2	33. Almeida JI, Min RJ, Raabe R, McLean DJ, Madsen M. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. *Vasc Endovascular Surg.* 2011;45(7):1-5. 34. Min RJ, Almeida JI, McLeanDJ, Madsen M, Raabe R. Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results. *Phlebology.* 2012;27(8):398-403.
Editorial	1	35. Chan YC, Ting AC, Yiu WK, Cheng SW. Cyanoacrylate superglue to treat varicose veins: truly office based and minimally invasive? *Eur J Vasc Endovasc Surg*. 2013;45(2):176-177.
Book Chapter	1	36. Raabe R Madsen M. The use of cyanoacrylate for treating venous reflux disease. Charing cross. 2014
Expert Opinion	1	37. Carr J, Jennifer W. The VenaSeal™ System in clinical practice. *Evtoday*. 2016;15(7):30- 31.

Study Design	# of Studies	Study Citation
Clinical Practice Article	1	38. Liu DM, Klass D, John Chung J, Gagnon J. How we incorporated the VenaSeal™ closure system into our vein practice. *Evtoday*. 2015;36-40.