

Two-Year Results of a First-In-Human Study in Patients Surgically Implanted With a Bioprosthetic Venous Valve, the VenoValve in Patients With Severe Chronic Venous Insufficiency

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Abstract

Objective: Two-year follow-up results from a first-in-human study of patients implanted with the VenoValve are evaluated for supporting the long-term clinical safety and performance of the device. **Background:** Chronic Venous Insufficiency (CVI) involves improper functioning of lower limb vein valves and inability of these valves to move blood back towards the heart. CVI symptoms include swelling, varicose veins, pain, and leg ulcers. Currently, there is no cure for this condition and treatment options are limited. This study provides 2-year outcomes for 8 patients who were implanted with the bioprosthetic VenoValve for treating severe CVI with deep venous reflux measured at the mid-popliteal vein. The 6-month and 1-year results were previously published. **Methods:** Eleven patients with C5 & C6 CVI were implanted with VenoValve into the midthigh femoral vein and followed for 2 years. Assessed clinical outcomes include device-related adverse events, reflux time, disease severity, and pain scores. **Results:** All 11 implant procedures were successful. Two-year follow-up data was obtained for 8 subjects: 1 patient died of non-device related causes, 1 was lost to follow-up, and 1 refused to follow-up due to the COVID-19 pandemic. No device-related adverse events occurred between the first and second years of follow-up. Reported 2-year clinical performance outcomes included significant decreases in mean reflux times of the mid-popliteal vein (61%), and significant improvements in mean scores for disease severity rVCSS (56%) and VAS pain (87%). **Conclusions:** Results from this study support long-term safety and effectiveness of the VenoValve for improving CVI severity by reducing reflux and thereby venous pressures in the lower extremities. With limited treatments for valvular incompetence involved in severe, deep venous CVI, the device may be considered as a novel therapy. A pivotal trial in the United States is currently being conducted to assess the device in a larger number of patients.

Keywords

chronic venous insufficiency, venous reflux, bioprosthetic venous valve, valve implant, venovalve, chronic venous disease, venous insufficiency, venous disease, CVI, CVD

Mini-Abstract

A FIH clinical trial was conducted for 11 patients who were implanted with enVVeno's bioprosthetic VenoValve in the midthigh femoral vein for the treatment of severe CVI (C5-C6). Two-year outcomes for 8 of these patients are reported demonstrating overall mean improvements in reflux time of the mid-popliteal vein and in scores for VAS and rVCSS. This is the first publication reporting 2-year results for this novel valve implant.

83.6%.¹ In the United States, approximately 150 000 new patients are diagnosed with CVD annually.² CVI is a subset of CVD and cases of severe, deep venous reflux are classified on the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) scale as C4

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Introduction

The occurrence of chronic venous disease (CVD) is increasing worldwide with a reported global prevalence as high as

to C6 disease. Severe C4 to C6 CVI may lead to complications such as deep venous thrombosis, severe pain, increased risk of infection, and leg ulcerations in up to 3% of patients over 65 years of age. CVI negatively affects a patient's quality of life and contribute to their economic burdens due to loss of work productivity.³ Currently, the available treatment options for deep venous reflux are limited. As the global population is aging and CVI complications worsen with age, the development of novel treatments for CVI are essential.

Currently available treatments that attempt to restore or improve valvular function, such as the use of compression stockings and elevating the legs, are intended for patients with superficial reflux and provide patients with suboptimal results. Some contributing factors to CVI such as poor pump function of the calf muscle and flow obstruction have been managed with exercise regimens, stenting, and thrombolytic agents.⁴ Venous ulcers that are caused by superficial reflux may also be treated with endovenous ablation therapy. As the number of endovenous ablation procedures has skyrocketed during the past couple decades, several medical associations have raised concerns of inappropriate use of these venous procedures.⁵ Nevertheless, effective treatment for patients with deep valvular insufficiency are still needed.

Surgical correction of deep venous reflux is a valuable adjunct for patients requiring treatment and several developments have been documented throughout the history of vascular surgery. Dating back to as early as 1960, Palma and Esperon conducted a femoropopliteal bypass with saphenous vein for treating obstruction of the iliac vein.⁶ The first deep venous valve reconstruction was performed by Kistner in 1968, establishing that the technical feasibility of surgical correction of abnormal venous valves were possible.⁷ In 1982, Taheri et al conducted vein valve transplants as an alternative treatment for reflux due to post-thrombotic syndrome. However, there were no improvements in venous pressure or clinical symptoms, indicating that maintenance of venous pressure may involve other valves or muscles.⁸

In 1990, Ulloa proposed the surgical implantation of prosthetic valves for treating deep vein insufficiency. In Latin America, he implanted prosthetic valves in 5 patients with good results including improvements in distal venous pressures, clinical symptoms, and ulcer healing.⁹ A 2002 study using cryopreserved allograft monocusp patches surgically implanted into the common femoral vein was conducted for treating non-thrombotic valvular insufficiency. Unfortunately, a high failure rate of 33% was observed at 1-year follow-up.¹⁰

Maleti and Lugli later in 2006 developed a neovalve, monoscusp construction technique to treat patients with deep venous incompetence affected by post-thrombotic syndrome. A total of 40 neovalve constructions were carried out in 36 patients. Due to causes of failure, the technique was modified in the second group of patients and results in the second group seemed to demonstrate improvements in valve continence.¹¹ In patients with CVI, popliteal vein external banding at the valve-free segment may also result in hemodynamic

improvement but this surgical technique does not restore valve function.^{12,13}

When direct valve repair is possible, current recommendations suggest valvuloplasty as the standard treatment. However, for many patients where this option is not feasible, other techniques may be necessary.¹⁴ In addition, several valvuloplasty studies have resulted in high rates of postoperative segmental thromboses or have failed due to the inability to architecturally preserve the venous valve leaflets.¹⁵⁻¹⁷ Novel minimally invasive techniques such as the BlueLeaf System are being explored as an endovenous method for treating symptomatic deep venous reflux without an implant. As the device's results look promising for ulcer healing and decreasing disease severity, the patient population is small and reflux improvement was not observed.¹⁸

Although our understanding of treatment options for CVI has greatly evolved over the years, there are currently no devices available to effectively replace malfunctioning venous valves. Few studies on venous valve devices have been completed in humans and there is a lack of high-quality evidence to demonstrate the long-term clinical safety and effectiveness of medically available treatments.⁵ Consequently, developing an effective treatment for severe cases of CVI with deep valvular incompetence remains a medical challenge.

In order to contribute to providing patients with a viable medical treatment, the VenoValve was developed by enVVeno Medical Corporation (formerly known as Hancock Jaffe Laboratories in Irvine, CA). The VenoValve is a bioprosthetic monocuspid venous valve comprised of a non-antigenic, anti-thrombogenic porcine aortic leaflet sewn onto a stainless-steel frame, and is terminally sterilized by gamma radiation (Figure 1). The monocusp design allows the valve to open and close with the unique hemodynamic conditions that exist in the deep venous system. The valve is surgically implanted into the femoral vein in the midthigh position, and prevents or reduces reflux in the lower extremity deep venous system, thereby reducing elevated venous pressure in the diseased lower extremity.

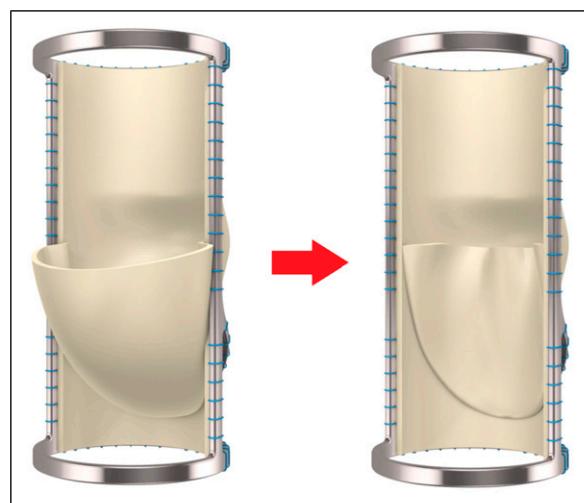


Figure 1. VenoValve (enVVeno medical corporation).

An original FIH clinical study was conducted on 11 patients who were implanted with the VenoValve in the midthigh femoral vein. Six-month and 1-year clinical outcomes from the study were previously published, noting significant improvements in safety and performance outcomes.^{19,20} In 2020, the 6-month results of the trial were published in the Journal of Vascular Surgery demonstrating 100% technical success, 40% decrease in reflux time, 61% improvement in rVCSS, and 57% improvement in VAS scores when compared to pre-operative values. Few adverse events were noted, and none were associated with the device.¹⁹ Recently in 2021, the 1-year results of the VenoValve trial were published in the journal of Vascular and Endovascular Surgery, demonstrating sustained improvements in clinical outcomes including 54% decrease in reflux time, 56% improvement in rVCSS, and 76% improvement in VAS pain levels. At 1-year, there were no reports of adverse events, and significant patient benefits were noted associated with the device.²⁰

This study reports follow-up data for 8 patients, two years after implantation of the VenoValve. Reported clinical outcomes were assessed to evaluate the functional benefit of the VenoValve in patients with significant CVD and venous hypertension to determine improvement in deep venous reflux.

Methods

Trial Design and Oversight

Eleven patients with severe deep venous CVI (classified as C5-C6) were enrolled in the original VenoValve FIH study. The first implant occurred on February 6, 2019 and the last on December 11, 2019. Patient selection criteria and procedural details were reported in prior publications.^{19,20} These 11 patients completed the 1-year FIH study and were then enrolled in a longer-term follow-up observational study to continue evaluating assessments for device safety and effectiveness through 48 months post-implantation.

This follow-up observational study was approved by the local institutional ethics committee and written consent forms were obtained by all patients. The principal investigator (Ulloa JH) and study authors had unrestricted access to the data and attest to the completeness and accuracy of the data and analyses.

Clinical Assessments and Analysis

Patients enrolled in the original FIH were assessed for DVT after implantation of the bioprosthetic at the following post-procedural time points: 24-hours, 7 days, 4 weeks, then 3-month intervals through 1 year. Results from the assessments and analysis were reported in prior publications.^{19,20}

The primary endpoints for the observational study include: improvement of reflux in the deep venous system measured at the mid popliteal vein by reflux time; improvement in rVCSS; and improvement in VAS pain scores.

The clinical assessments for reflux time are measured at the mid-popliteal vein via direct venous duplex scan measurement, rVCSS scores were calculated and observed by the principal investigator, and VAS scores are recorded based on patient reporting. Follow-up evaluations are scheduled at 6-month intervals until study completion. Each follow-up visit includes a physical exam and assessment of valve patency of the ipsilateral femoral vein.

Two-year follow-up study data for the midterm results reported in this manuscript was collected through January 2022. The clinical parameters were compared to the baseline pre-operative levels to determine measurements of improvement.

The descriptive statistical analysis was performed using Stata/SE 16.0 (StataCorp LP, College Station, Tex) with linear regression and measures of central tendency (median, average) for continuous variables. Long-term assessments for clinical safety outcomes included reporting any and all serious and non-serious device-related adverse events.

Results

Implantation of the VenoValve into the midthigh femoral vein was successful for all 11 patients in the FIH clinical trial. Procedural details and results were provided in previous publications reporting the 6-month and 1-year results, which included significant decreases in mean reflux time in the popliteal vein (40% at 6 months; 54% at 1 year), significant average improvements in rVCSS for disease severity (61% at 6 months; 56% at 1 year), and significant average decreases in VAS scores for pain (57% at 6 months; 76% at 1 year).^{19,20}

Patient Demographics and Follow-Up

Details for patient demographics and the post-procedure follow-up protocol were summarized in the first study publication reporting 6-month results.¹⁹ The implanted patients were followed for 2 years. Clinical outcomes at the 2-year timepoint were obtained for 8 of the 11 implanted patients: 1 patient died due to natural causes unrelated to the device, 1 patient refused to follow-up due to the upsurge of COVID-19 and high hospital occupancy in Colombia, and one patient was lost to follow-up (patient numbers 4, 5, 6; see Table 1). Of these 8 patients who reached 2-year follow-up, 5 were male and 3 were female with an average age of 64.9 years. At baseline, the CEAP classification was C5 for 4 patients, and C6 for 4 patients (Table 1).

Performance Outcomes

Performance outcomes for the 8 patients who completed 2-year follow-up are summarized. As described, there were 3 patients (patients 4, 5, 6) who did not reach 2-year

follow-up and were therefore excluded from the 2-year analyses. Clinical outcomes included mean improvements in performance parameters measured from pre-operative levels for all patients. Significant mean improvements over 2 years were observed in reflux time (61%), disease severity rVCSS (56%), and VAS pain scores (87%) (Table 2).

Measurements for reflux times at baseline (pre-operative), and post-valve implantation at 6 months, 1 year, and 2 years

are illustrated (Figure 2A). Improvements were observed at each follow-up for all patients except for 1 patient (patient 6) who thrombosed shortly after 90 days due to non-compliance with anticoagulation therapy. However, the previous reflux times recorded for this patient at 30-day, 60-day, and 90-day follow-ups demonstrated significant improvements from baseline.^{19,20} Two-year average reflux values for the remaining 8 patients demonstrated 61% improvement from pre-operative values (Figure 2B).

Table 1. Patient Demographics.

Gender	Avg. Age (y)			
Male (n = 5)	59.8			
Female (n = 6)	73.3			
Demographics details				
Pt. No.*	Age (y)	Male/Female	CEAP class	2-Yr follow-up
1	52	F	C5	Y
2	82	F	C5	Y
3	61	M	C5	Y
4	87	F	C5	N
5	81	F	C6	N
6	52	F	C6	N
7	58	M	C6	Y
8	86	F	C6	Y
9	65	M	C6	Y
10	69	M	C5	Y
11	46	M	C6	Y
Avg. Age	67.2	—		

Pt. No., patient number.

*Two-year follow-up data not available for patients no. 3, 4, 5

Table 2. Two-Year Post-Implantation Results.

Pt No.	Reflux time in popliteal vein (mm/sec)				rVCSS				VAS score			
	Pre-Op	1 Year	2 Years	% Decrease	Pre-Op	1 Year	2 Years	% Improvement	Pre-Op	1 Year	2 Years	% Decrease
1	1.5	0.4	0.2	87	16	1	6	63	8	2	1	88
2	1	0.7	0.9	7	10	4	3	70	7	2	0	100
3	1	0.2	0.1	90	12	3	6	50	6	2	4	33
4	1.7	0.6	—	—	9	5	—	—	6	3	—	—
5	1	0.7	—	—	16	11	—	—	8	6	—	—
6	1.7	2.2	—	—	18	8	—	—	8	1	—	—
7	3	0.5	0.1	97	21	5	5	76	10	3	0	100
8	2	1.2	1.0	52	13	12	9	31	8	1	2	75
9	2	0.4	0.6	70	16	4	5	69	5	0	0	100
10	2.4	0.7	2.1	14	6	4	5	17	8	0	0	100
11	2.7	0.8	0.8	71	13	4	4	69	6	0	0	100
Avg	1.8	0.8	0.7	61	13.4	5.5	5.4	56	7.3	1.8	0.9	87

Percentages determined from pre-operative levels compared with those at 2 years (730 days). Average 2-year follow-up: 811 days for all 8 patients

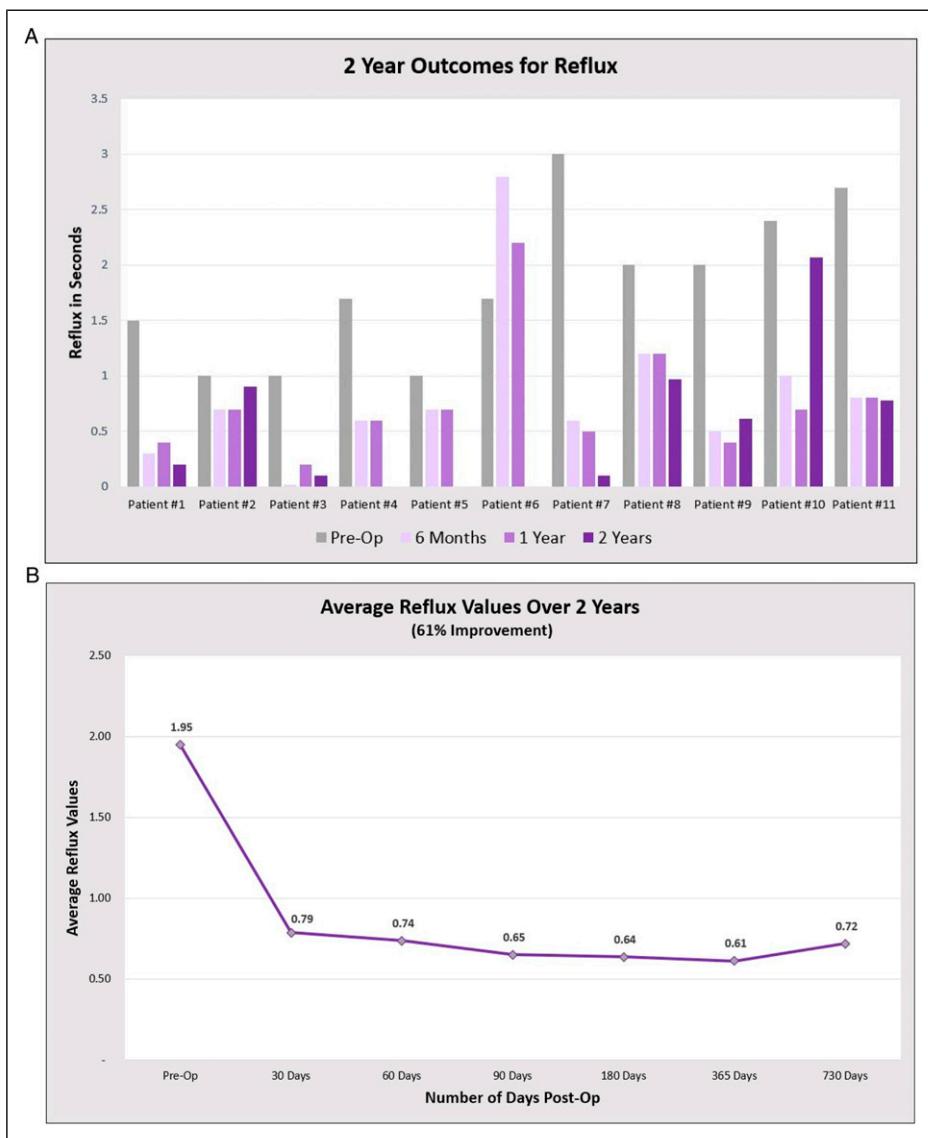


Figure 2. Two-year outcomes for reflux. (2A) Reflux outcomes for patients at baseline (pre-op), 6 months, 1 year, and 2 years. (2B) Average reflux values for 8 patients from baseline through 2 years demonstrating overall 63% improvement.

Measurements for disease severity (rVCSS) at baseline (pre-operative), and post-valve implantation at 6 months, 1 year, and 2 years are illustrated. Improvements in rVCSS were observed in all patients at each follow-up measurement when compared to pre-operative values (Figure 3A). Over 2 years, there was a 56% improvement in average rVCSS, noting an average decrease of 8 points from pre-operative levels (Figure 3B).

Measurements for pain scores (VAS) at baseline (pre-operative), and post-valve implantation at 6 months, 1 year, and 2 years are illustrated. Improvements in VAS pain scores were reported by all patients at each follow-up when compared

to pre-operative scores (Figure 4A). Over 2 years, there was an 87% improvement in average VAS scores from pre-operative levels (Figure 4B).

Safety Outcomes

Prior to the procedure, ulcers were only observed in patients with C6 disease. All ulcers had healed with an average healing time of 90 days. Between years 1 and 2 of follow-up, there were no serious adverse events, adverse events related to the device, or hospitalizations. In addition, there were no occurrences or recurrence of ipsilateral ulcers. At 2 years post-

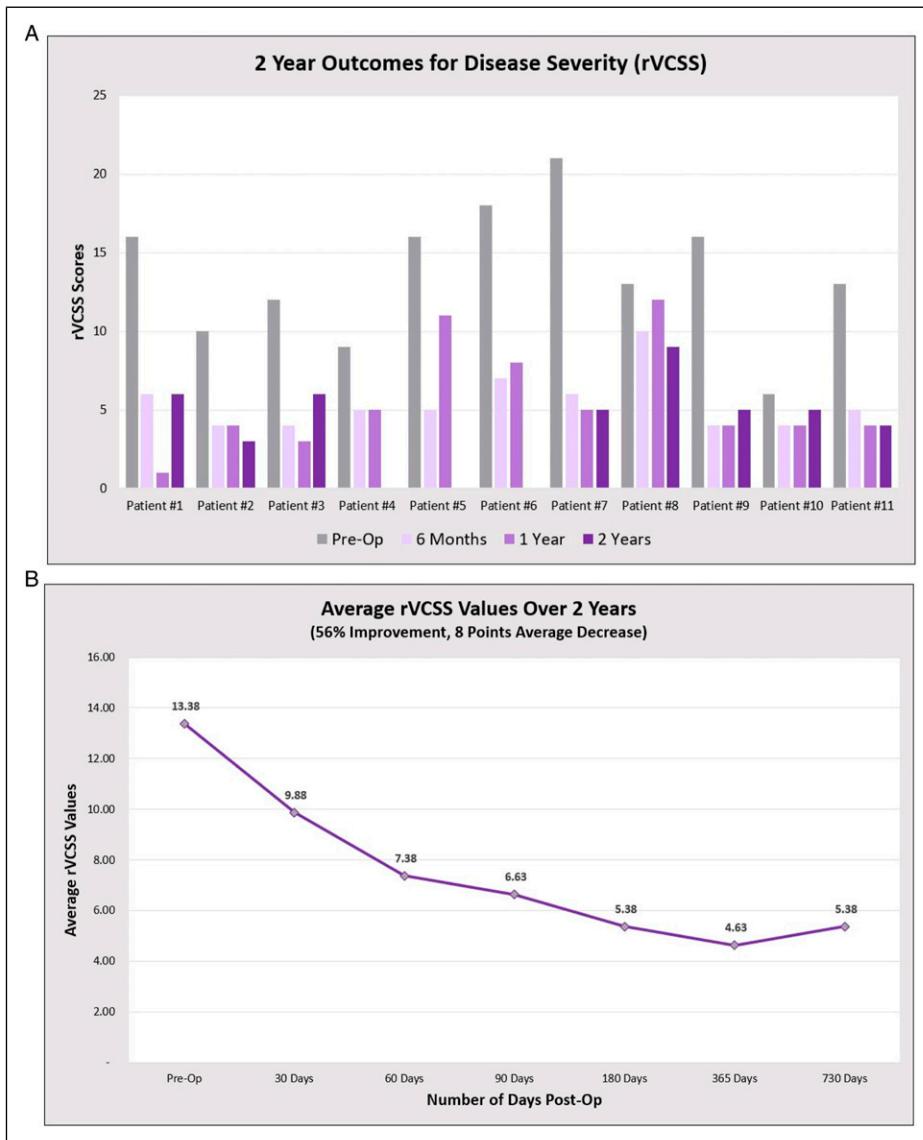


Figure 3. Two-year outcomes for disease severity (rVCSS). (3A) rVCSS scores for patients at baseline (pre-op), 6 months, 1 year, and 2 years. (3B) Average rVCSS values for 8 patients from baseline through 2 years demonstrating overall 56% improvement, 8 points decrease.

valve implantation, 50% of the patients improved in their CEAP classifications from C6 to C5. Classifications for the other 50% did not vary.

Discussion

This FIH clinical trial evaluates patients implanted with the bioprosthetic VenoValve device for the treatment of CVI. These 2-year clinical results provide objective evidence that the long-term safety and performance of the VenoValve was sustained. Remarkably, the patients obtained wound healing without ulcer recurrence. Significant improvements in reflux time, disease severity, pain scores, and the reclassification of

patient diagnosis from severe to mild disease, provide further support that the device may serve as a possible effective treatment for patients with severe CVI. With these promising findings, in August 2021 the VenoValve received Breakthrough Designation by the United States Food and Drug Administration (FDA). Additionally in August 2021, these results were presented at the Society for Vascular Surgery Annual Meeting 2021 in San Diego, CA in the United States.

Continued assessment of these patients through long-term follow-up will be essential to further evaluate the long-term functionality and effectiveness of the VenoValve as a novel treatment for severe, deep venous CVI. As study limitations

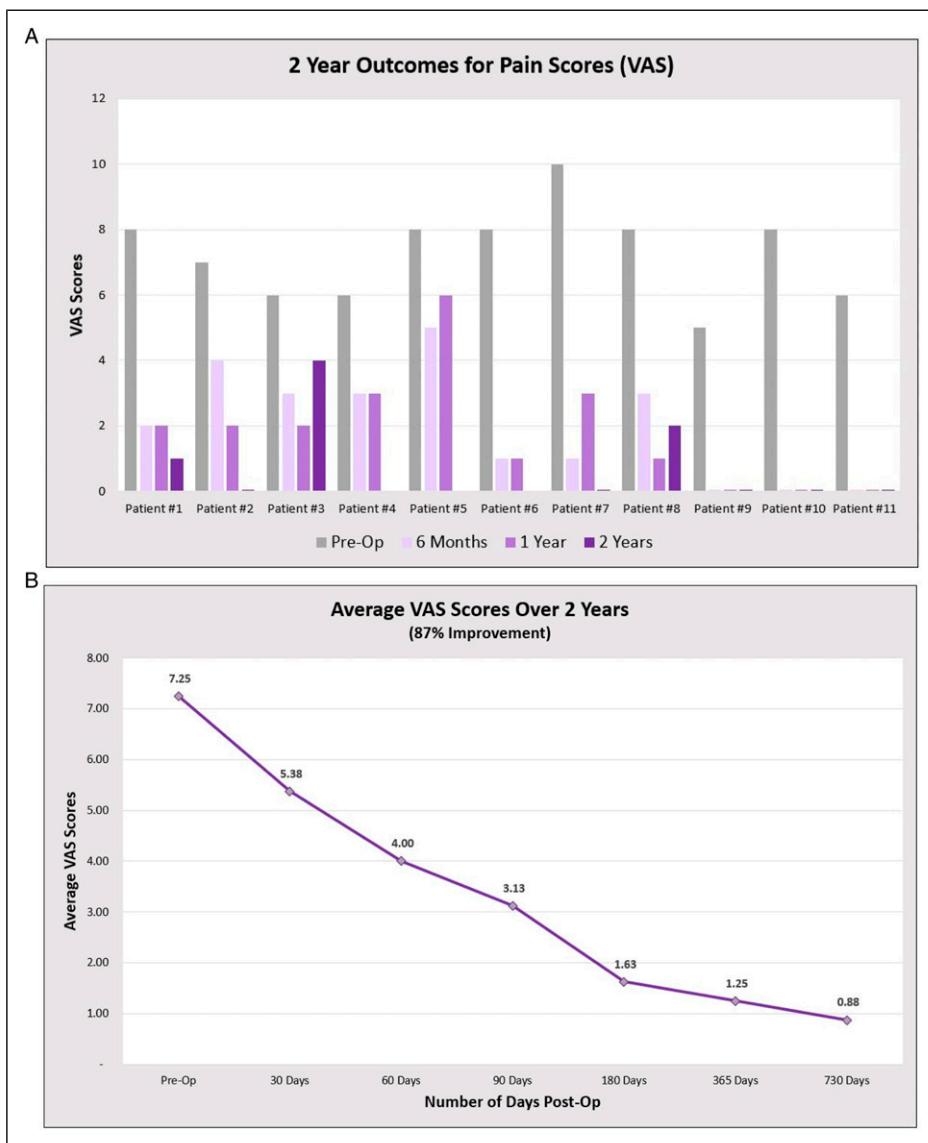


Figure 4. Two-year outcomes for pain scores (VAS). (4A) VAS scores for patients at baseline (pre-op), 6 months, 1 year, and 2 years. (4B) Average VAS scores for 8 patients from baseline through 2 years demonstrating overall 87% improvement.

include the derivation of results from a small patient population, a large pivotal, open, single-arm, multi-center clinical trial is currently being conducted in the United States to assess the safety and effectiveness of the VenoValve in larger group of 75 patients with CVI. The trial is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT04943172?term=hancock+jaffe&draw=2&rank=1) under identifier: NCT04943172 (<https://clinicaltrials.gov/ct2/show/NCT04943172?term=hancock+jaffe&draw=2&rank=1>).

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Trial registration

The clinical trial is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT04943172?term=hancock+jaffe&draw=2&rank=1) under identifier: NCT04943172 (<https://clinicaltrials.gov/ct2/show/NCT04943172?term=hancock+jaffe&draw=2&rank=1>).

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