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Post-Stent Vein Lumen Shape and Clinical Response in Patients Treated for Iliofemoral Venous Occlusive Disease

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Abstract

Objective: Interventionalists have noted significant venous luminal gain with nitinol venous stents although post-placement lumen shape differed from the circular shape observed with elgiloy stents. The goal of this study was to determine the characteristics of a stented vein lumen that correspond with clinical outcomes, and to identify metrics that might be relevant for stent design by assessing aspect ratio (AR), lumen diameter (LD), lumen area (LA), and stent shape (symmetry and eccentricity) post-implant. **Methods:** This post-hoc analysis evaluated patients from the VIVO US Study (NCT01970007) with pre- and post-stent intravascular ultrasound (IVUS) imaging. Patient characteristics, Venous Clinical Severity Score (VCSS) and Venous Disability Score (VDS) were collected in the study. LD, LA, and stent geometry were measured by the core laboratory. Data were analyzed for linear association between core-laboratory assessed pre and post stent LD, LA, AR, stent eccentricity and symmetry index, and VCSS and VDS change. **Results:** IVUS imaging was available for 29 patients (2 sites) enrolled in the VIVO US Study (55.2% women; mean age: 59.8 ± 17 years). The cohort had post-thrombotic (48.3%), nonthrombotic iliac vein lesion (44.8%) or acute deep vein thrombotic (6.9%) disease. Mean lesion length was 111.8 ± 60.9 mm. Eleven stents extended below the inguinal ligament. Median minimum LD and LA significantly increased after stent placement ($P < 0.001$); median lumen AR changed from 2.0 pre-stent to 1.4 post-stent ($P < 0.001$). Mean VCSS improved from baseline to 12 months (7.6 ± 4.3 to 3.7 ± 2.6). No statistically significant linear relationships were identified between VCSS / VDS change and a specific characteristic of LA, LD, or AR. **Conclusions:** Measures of lumen change pre and post iliofemoral vein nitinol stent placement reflect disease and stent characteristics. After stent placement, minimum LD and LA increased and AR decreased. Stented lumen shape or size with Zilver Vena did not impact 1-year clinical improvement by VCSS.

Keywords

vein stent, lumen shape, stent characteristics, clinical improvement, chronic venous insufficiency

Introduction

Over the last decade, there have been significant advances in the treatment of symptomatic chronic venous hypertension (CVH). Superficial vein ablation along with progress in identifying and treating chronic iliofemoral vein outflow tract obstruction has improved the lives of countless patients. The field is still advancing; revision and optimization of the original groundbreaking techniques and treatment algorithms are ongoing.

The original work around treatment of iliofemoral vein outflow tract obstruction largely focused on the use of the Wallstent. (Boston Scientific, Marlborough, MA).[1,2] Since then, dedicated venous stent designs using nitinol technology have become commercially available, and US and international prospective trials have been completed.[3-6] The Zilver Vena® Venous Self-Expanding Stent (Cook Medical, Limerick, Ireland) was the first commercialized and broadly

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used dedicated venous stent (CE, i.e., European Conformity, marked in 2010).[7] The early experience with the Zilver Vena stent led endovascular interventionalists to note that although the venous luminal gain was significant, the post-nitinol stent venous lumen shape differed from the circular post-stent lumen of elgiloy stents such as the Wallstent. This change, from a previously familiar post-stent circular lumen appearance to a different morphology has been described as an increase in lumen aspect ratio (AR, a measure of the shape of the lumen throughout the target lesion [ratio of maximum diameter to minimum diameter] >1; a complementary measure to lumen cross section area [LA] and lumen diameter [LD] to describe the pre- and post-stent vein lumen).[8,9] (Figure 1) Existing data correlates changes in intravascular ultrasound (IVUS) measured vein LA with clinical improvement.[10] It is unclear whether an elliptical or compressed post-stent lumen with an AR >1 impacts vein stent patency or correlates with a change in symptomatic CVH. Other measures of stent and lumen geometry post intervention such as eccentricity and symmetry index, have been developed to describe coronary and peripheral artery stents and post intervention vessel lumens.[11] These measures have not previously been applied to iliofemoral veins reconstructed with stents.

This study is designed to evaluate whether the AR, LD, and LA data specifically, as well as other measures of vein stent lumen geometry, from IVUS generated pre-- and post-stent iliofemoral vein lumen images predict 1-year clinical improvement of symptomatic CVH.

Methods

Study Design

This post-hoc analysis was performed through a retrospective collection of procedural IVUS images from patients enrolled in the investigational study for the treatment of iliofemoral venous outflow obstruction with the Zilver Vena® Venous Stent (VIVO US Study, NCT01970007). In brief, the investigational study was conducted as a prospective, non-randomized, single-arm, multicenter trial. Full study and device details, as well as patient eligibility and clinical definitions, have been published previously.[5] Patients were treated for acute deep vein thrombosis (DVT) or symptomatic CVH due to nonthrombotic iliac vein lesions (NIVL) and post thrombotic stenosis (PTS). Primary safety and effectiveness endpoints were met. All patients were implanted with the Zilver Vena® Venous Self-Expanding Stent (henceforth referred to as the Zilver Vena stent; Cook Medical, Limerick, Ireland), a self-expanding cut nitinol stent indicated for improving LD in the iliofemoral veins for the treatment of

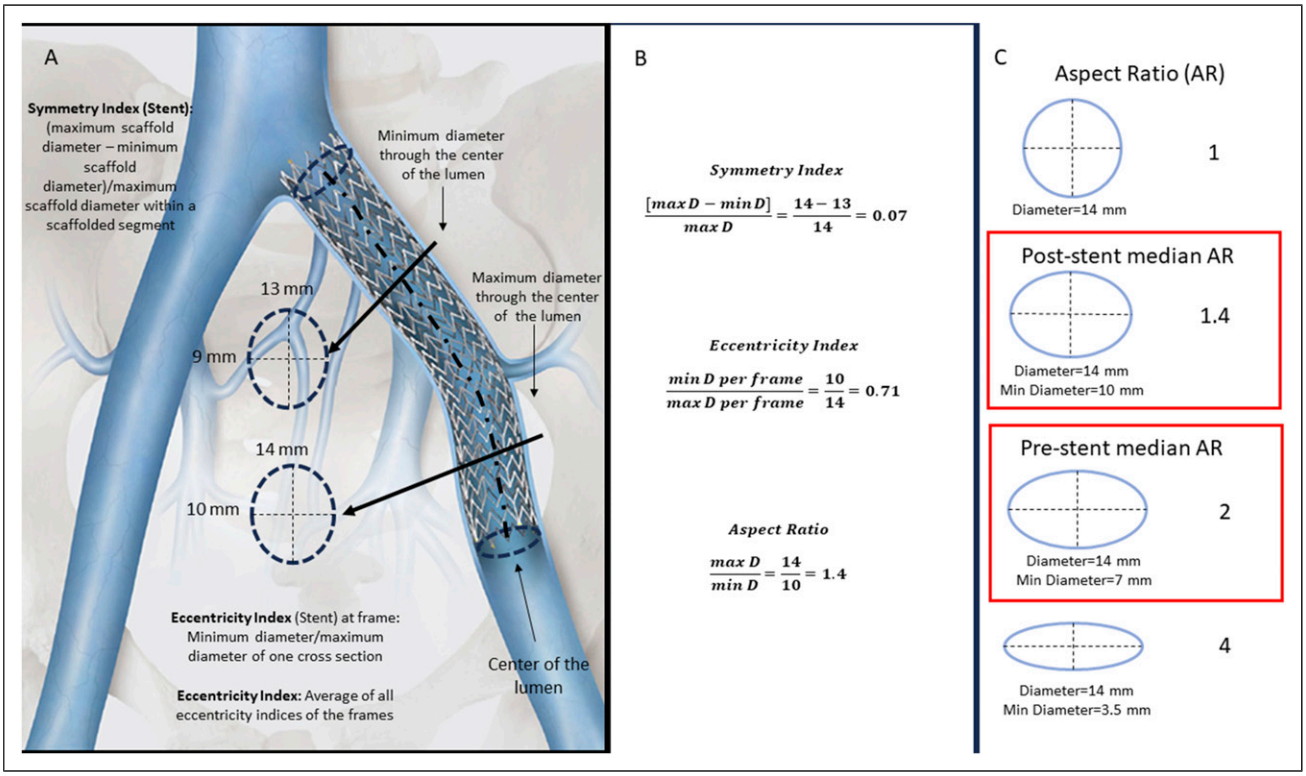

Figure 1. Relationship between symmetry index, eccentricity index, and aspect ratio in an iliofemoral stent. Minimum and maximum diameters over the length of the stent are shown with 2 cross-sections with different eccentricity indices (A). Example calculations of symmetry index, eccentricity index, and lumen aspect ratio are shown (B). An aspect ratio of 1 indicates a circular cross-section and becomes elliptical as the aspect ratio increases (C). The median aspect ratio was 2 prior to stent placement and was 1.4 after stent placement.

symptomatic outflow obstruction. The current analysis includes the subset of patients from the VIVO US study with IVUS imaging to examine if a non-circular lumen impacts clinical outcomes and if the lumen shape after stent placement provides an explanation for clinical improvement.

The VIVO US study was conducted in accordance with the Declaration of Helsinki II and in compliance with the Health Insurance Portability and Accountability Act. Each participating institution had approval from their Institution Review Boards or Ethics Committee; IVUS data for this subanalysis came from 2 institutions, UNC Rex Healthcare (Schulman Associates, IRB #201407350) and Norwalk Hospital (Norwalk Hospital, IRB #13-14, Western Institutional Review Board, IRB #20132239). All patients provided written informed consent before study enrollment.

IVUS Imaging

Multiplane venography was the principal imaging mode used in this investigational device exemption (IDE) study to determine vein stenosis and extent of occlusive disease. IVUS was used routinely as an adjunctive imaging modality for each patient at the 2 high enrolling sites, and the IVUS images from these 2 sites constitute the clinical images used for this analysis. Clinical assessments, including Venous Clinical Severity Score (VCSS) and Venous Disability Score (VDS), were completed preprocedurally and at 1, 6, and 12 months.

The Volcano Core™ Mobile Precision Guided Therapy System (Philips, Amsterdam, Netherlands) with the Visions PV 0.035 IVUS catheter (Philips) was used to interrogate the deep venous system. The inferior vena cava (IVC), ipsilateral common iliac vein (CIV), external iliac vein (EIV), and common femoral (CFV) and femoral vein segments were assessed with the IVUS catheter over an 0.035 wire. A recorded pullback from the level of the renal veins to the femoral vein was performed. The veins were evaluated for lumen size and stenosis, quality of the vein wall, and intraluminal filling defects or scars.

Imaging Analysis

Only patients with adequate IVUS imaging were included in this analysis. Adequate image quality was assessed at the core laboratory (Medstar Health Research Institute, Hyattsville, MD) through 2 independent physician reviews. All IVUS images were processed using QIVUS (version 3.1, Medis Medical Imaging Systems, Leiden, Netherlands), a semi-automated offline analysis software. Any available venograms were also provided to the core lab to aid in the IVUS imaging review process.

Full study imaging definitions are provided in Supplemental Table 1,[12] and are adopted from analyses of stents in other vascular beds.[12] 3 measurements (1 in each frame) were obtained prior to stent placement in each vessel segment (CFV, EIV, and CIV) and within the stented region post-stent placement to ascertain mean, minimum, and maximum LD and LA. An AR of 1 indicates a circular shape and a diversion from 1 indicates a more elliptical shape (Figure 1). An AR of ≥ 2.0 (i.e. 50% diameter stenosis) is considered a hemodynamically significant stenosis.[13] Concentric expansion of the stent was assessed by calculating the device eccentricity, defined as $\frac{maximum\ stent\ diameter}{minimum\ stent\ diamter} - 1$ at the location of the minimum stent area, with device eccentricity for a perfectly concentric expansion equal to zero. Device eccentricity index of 0.68 or less was considered oval.[14] Stent symmetry index was defined as:

$$\frac{(maximum\ stent\ diameter - minimum\ stent\ diameter)}{maximum\ stent\ diameter}$$

Data Analysis

A centralized data-coordinating center, Cook Research Incorporated (West Lafayette, IN), managed and analyzed study data. Data from the core laboratory physician review team were transferred to the data-coordinating center. Statistical analyses were performed with Statistical Analysis Software (SAS) for Windows (release 9.4 or higher; SAS Institute, Cary, NC). Continuous variables were summarized as median with 25th and 75th percentiles or as mean ± standard deviation, as appropriate. Statistical differences between pre-procedural and post-procedural imaging were assessed by Wilcoxon signed-rank test to compare the median of the 2 samples with α level of 0.05. Linear relationships between study variables were assessed by Pearson's coefficient statistic with α level of 0.05. Generalized linear mixed models were fitted to assess the effect of VCSS improvement of ≥2 and VDS improvement of ≥1, regarding changes from baseline measurements to 12-month with respect to LD, LA, and AR measurements. Additionally, deep vein thrombosis (DVT) status (past and/or current) was assessed with post-stent placement device symmetry index, AR, and eccentricity by fitting generalized mixed models. All *P*-values reported have been adjusted for multiple comparisons using False Discovery Rate (FDR).

Results

Of the 243 patients who were enrolled in the VIVO Clinical Study, 35 patients had pre- and post-procedure IVUS imaging available. After review of the imaging data for those 35 patients, 29 patients (mean age: 59.8 ± 17 [21-89], 55.2% female) had pre- and post-IVUS imaging adequate for analysis and were included in this study IVUS cohort. Six patients were excluded due to poor image quality. Demographic and pre-procedural clinical variables for the overall VIVO Clinical Study population[5] and the IVUS cohort are presented in Table 1. The most common indication for stent placement in the IVUS cohort was iliac vein compression by the iliac artery (69.0%, 20/29). Most lesions were located in either the CIV

Table 1. Demographics and Preprocedural Clinical Variables.

Variable	Percent of patients or Mean ± SD (min-max)	
	VIVO clinical study N = 243	IVUS cohort N = 29
Age, years	53.0 ± 15.3 (18-89)	59.8 ± 17 (21-89)
Female	70.0% (170)	55.2% (16)
BMI, kg/m^2	31.3 ± 8.5 (17.5-64.8)	30.3 ± 8.4 (19.9-52)
Condition		
PTS	43.2% (105)	48.3% (14)
NIVL	32.5% (79)	44.8% (13)
Acute DVT	24.3% (59)	6.9% (2)
Hypertension	42.6% (106)	58.6% (17)
Hypercholesterolemia	31.7% (77)	41.4% (12)
Presence of venous reflux	18.1% (44)	27.6% (8)
Existing tissue loss related to venous disease	4.5% (11)	6.9% (2)
Bleeding diathesis or coagulopathy	7.0% (17)	3.4% (1)
Family history of clotting disorder	7.9% (19)	17.2% (5)
Family history of DVT	9.9% (24)	6.9% (2)
DVT	18.5% (45)	20.7% (6)
Past current	38.3% (93)	27.6% (8)
Past and current	10.7% (26)	6.9% (2)
Pulmonary embolism	13.6% (33)	20.7% (6)
Past current	1.2% (3)	0% (0)
History of cancer	16.9% (41)	17.2% (5)
Smoking status	62.1% (151)	65.5% (19)
Never	24.7% (60)	27.6% (8)
Past current	13.2% (32)	6.9% (2)
Preprocedural study leg VCSS	8.0 ± 4.2 (1-24)	7.6 ± 4.3 (2-24)
Preprocedural study leg VDS		
0	5.3% (13)	13.8% (4)
1	28.0% (68)	34.5% (10)
2	41.6% (101)	44.8% (13)
3	25.1% (61)	6.9% (2)

BMI, body mass index; DVT, deep vein thrombosis; NIVL, non-thrombotic iliac vein lesion; PTS, post-thrombotic syndrome; VCSS, Venous Clinical Severity Score; VDS, venous disability score.

(72.4%, 21/29) or the EIV (62.1%, 18/29). Mean lesion length was 111.8 ± 60.9 mm. Eleven stents extended below the inguinal ligament. Additional details on the indication for placement and lesion information are presented in Table 2.

The Wilcoxon Signed Ranks Test demonstrated that median values for post-stent minimum LD and mean LD were statistically higher than pre-stent minimum LD and mean LD (P_{adj} = 0.002) Table 3. Additionally, the same analysis indicated that median values for post-stent minimum LA and mean LA were statistically significantly higher than pre-stent measurements (P_{adj} = 0.002). The resulting pre and post percent gain for the minimum LD and minimum LA was 104 ± 70.2 (29, -22 - 247.2) and 191.2 ± 124 (29, 39.4 - 495.7), respectively. Overall lumen shape (e.g., circularity vs oval/ellipse), as described by the median AR, significantly changed from more oval (2.0) at pre-procedure to more circular after stent placement (1.4; P_{adj} = 0.002). Additional evidence of the VCSS improvement regarding AR is further illustrated in Figure 2. However, post-stent AR was not significantly correlated with mean LA, either pre- (P_{adj} = 0.8352) or post-stent placement (P_{adj} = 0.8352). While device eccentricity and symmetry are traditional measurements in the arterial space, the relevance to veins is less clear. However, both measures were obtained for this analysis. Post-stent placement, median device eccentricity index at the minimum stent area (MSA) frame was 0.7 and device symmetry index was 0.5 consistent with the improvement of the AR post-stent (Table 3, Figure 1).

Clinical Benefit and Relation to Shape

Pre-procedural VCSS was 7.6 ± 4.3 (29, 2 - 24) and improved following stent placement, to 5.1 ± 4.3 (29, 0 - 20) at 1 month and further to 3.7 ± 2.6 (23, 0 - 8) at 12 months. There was no statistical difference among patients with VCSS improvement of ≥2 for patients who had stents with an oval device shape vs a circular device shape (P_{adj} = 0.8352). There was no statistical significance among patients with VCSS improvement of ≥2 and post procedure device symmetry index (P_{adj} = 0.9205).

Table 2. Indication(s) for Placement and Core Laboratory-Reported Lesion Information.

Variable	Percent of patients (n/N) or mean ± STD (N, min-max)
Indication(s) for stent placement[a]	
Iliac vein compression by iliac artery	69.0% (20/29)
Stenosis due to chronic obstruction	44.8% (13/29)
Stenosis after treatment for acute DVT	3.4% (1/29)
Iatrogenic stenosis	0% (0/29)
Extrinsic compression from mass	0% (0/29)
Other[b]	10.3% (3/29)
Lesion location[a]	
Common iliac vein	72.4% (21/29)
External iliac vein	62.1% (18/29)
Common femoral vein	24.1% (7/29)
Femoral vein	6.9% (2/29)
Lesion length (mm)	111.8 ± 61 (28, 9.7-220)
Thrombus present at baseline	27.6% (8/29)
Stent below the inguinal ligament	37.9% (11/29)

[a]Patients may be categorized by more than 1 indication for stent placement or more than 1 lesion location.
[b]Extrinsic compression from an unknown source, not the iliac artery; external iliac compression from an unknown source; compression of external iliac vein, which, compared with a dilated vein at the inguinal ligament at the transition from the common femoral to the external iliac vein, measured greater than 50% stenosis.

Table 3. Core Laboratory-Reported Vessel and Lumen Shape After Stent Placement.

	Median (N, 25th −75th percentile)		
Variable	Preprocedure N = 29	Post-stent placement N = 29	*P* value[a]
Maximum vessel diameter (mm)	23.4 (29, 20.7 – 25.7)	22.2 (29, 20.8 – 24.6)	0.71
Minimum vessel diameter (mm)	6.1 (29, 5.1 – 6.5)	11.5 (29, 10.1 - 13)	<0.001
Mean vessel diameter (mm)	12.5 (29, 11.1 – 14.5)	16.7 (29, 15.1 – 17.7)	<0.001
Maximum vessel area (mm^2)	251.5 (29, 185.1 – 283.7)	286.2 (29, 257.1 – 318.7)	0.004
Minimum vessel area (mm^2)	60.1 (29, 42.4 – 88.4)	173.6 (29, 140.2 – 218.7)	<0.001
Mean vessel area (mm^2)	131.1 (29, 102.5 – 169.9)	221.9 (29, 179.0 – 245.8)	<0.001
Maximum lumen diameter (mm)	21.2 (29, 18.6 – 24.2)	19 (29, 17.9 – 21.3)	0.08
Minimum lumen diameter (mm)	4.5 (29, 3.8 – 5.3)	8.8 (29, 7.3 – 10.4)	<0.001
Mean lumen diameter (mm)	11.3 (29, 9.7 – 12.3)	13.8 (29, 12.3 – 14.8)	<0.001
Maximum lumen area (mm^2)	195.6 (29, 160.6 – 225.1)	194 (29, 179.5 - 218)	0.70
Minimum lumen area (mm^2)	39.3 (29, 26.7 – 57.0)	110.7 (29, 83.6 – 147.0)	<0.001
Mean lumen area (mm^2)	106.2 (29, 84.2 – 124.5)	154.9 (29, 119.9 – 171.7)	<0.001
Percent residual area stenosis	75.8 (28, 54.5 – 83.1)	34.2 (27, 21.8 - 46.9)	<0.001
Percent diameter stenosis	67.6 (28, 59.3 – 75.7)	43.8 (27, 28.0 – 52.0)	<0.001
Lumen aspect ratio	2 (29, 1.8 – 2.5)	1.4 (29, 1.3 – 1.6)	<0.001
Acute lumen gain (%)	-	79.2 (29, 68.2 – 113.2)	-
Post-eccentricity index at the minimum stent area	-	0.7 (29, 0.5 – 0.8)	-
Post-symmetry index	-	0.5 (29, 0.4 – 0.6)	-
		Mean ± standard deviation (N, Min-Max)	
Minimum lumen diameter pre/post gain (%)	-	104 ± 70.2 (29, -22 – 247.2)	-
Minimum lumen area pre/post gain (%)	-	191.2 ± 124 (29, 39.4 – 495.7)	-

[a]α<0.05, Wilcoxon signed-rank test.

Additionally, VCSS improvement of ≥2 was not significant with any of the following covariates that were evaluated in the mixed model: post-procedure AR (P_{adj} = 0.9205), post-procedure LA (P_{adj} = 0.8352) and post-procedure mean LD (P_{adj} = 0.8352). Similarly, VDS improvement of ≥1 was not significant with any of the following covariates that were evaluated in the mixed model: post-procedure AR (P_{adj} = 0.8352), post-procedure mean LA (P_{adj} = 0.8352), post-procedure mean LD (P_{adj} = 0.8352).

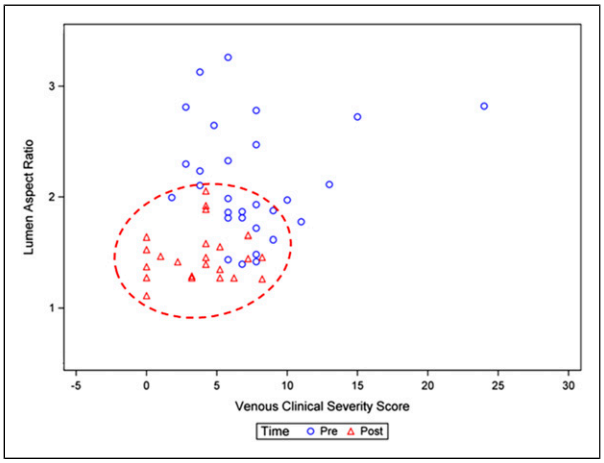

Figure 2. Scatter plot demonstrating a reduction in the lumen aspect ratio observed after stent placement associated with lower clinical severity scores (red triangles), compared to lumen aspect ratio and higher clinical severity scores prior to stent placement (blue circles).

Pre-procedure DVT status (i.e., past and/or current) was not significant with any of the following variables that were evaluated in the mixed model: device eccentricity index (P_{adj} = 0.9205), post-stent placement device symmetry index (P_{adj} = 0.8352) or post-stent placement AR (P_{adj} = 0.8352).

Discussion

Though nitinol venous stents are less likely than Wallstents to form perfect ovals in diseased and stenosed deep veins, interventionalists have found them more reliable in deployment and lumen gain.[7] This has led to widespread adoption of nitinol venous stents for iliofemoral venous reconstruction. Like coronary and peripheral artery stents before them, the quality of repair after use of deep venous stents is being evaluated. There is little rigorous data on how the function of a venous stent will impact post-procedure clinical improvement. Neglen and Raju observed that successfully stenting a stenosed vein with a Wallstent resulted in a notable increase in cross section area when evaluated with IVUS.[2] This was associated with improvement of CVH symptoms.[2,15] The results of the VIDIO study, which also used Wallstents, suggested that in nonthrombotic iliac vein stenosis, gains in post-stent lumen area and diameter best correlated with a decrease in symptomatic CVH.[10]

Overall, results of nitinol venous stent trials have been consistently reliable. Four IDE trials of dedicated nitinol venous stents with different stent properties, and slightly different patient populations and imaging, have been completed with only small differences in the primary clinical outcome.[3-6] Though differences in stent flexibility and radial force exist among the available nitinol venous stents, resistance to crush and fracture seems to be uniformly good among the commercially available stents given the low incidence of reported problems.[3,5,6] This study examines if a non-circular shape of the lumen associated with nitinol venous stents impacts clinical outcome and, more specifically, if the lumen shape post-stent placement could predict a lack of clinical improvement. The impetus of this study is the early results of the VIRTUS nitinol vein stent trial. Lichtenberg and Kabnick[8,9] suggested that the higher the AR post-venous stent placement, the less reliable the clinical improvement. That report on the first 27 patients, however, has not been supported with subsequent published data from the larger VIRTUS patient cohort[16] or other nitinol vein stent trials.[4,6] Additionally, given some anecdotal reports of stent erosion in the tortuous pelvic venous anatomy, we wanted to determine if a more flexible stent with a less circular lumen when implanted would impact clinical outcomes. In the VIRTUS treatment cohort, the IVUS determined post-stent median AR was 1.3,[8,9] similar to the median AR in this IVUS subset of VIVO of 1.4. So, the more flexible Zilver Vena Stent had a post-stent AR not notably different than that of the less flexible stent studied in the VIRTUS trial. In the IVUS cohort of the VIVO US study, diameter and area stenosis improved from a median of 67.6% to 43.8% and 75.8% to 34.2% post-stent, respectively. These patients experienced substantial clinical improvement, suggesting a relationship between lumen increase and clinical improvement. AR decreased closer to 1 post-stent placement, as clinical symptoms improved. Since the change in lumen size and AR occurred simultaneously, this study could not determine how the change in AR specifically impacted clinical improvement. All metrics improved together. What is evident is that an AR >1 did not correlate with diminished clinical improvement compared to similar nitinol stent trials.[3-6]

To evaluate potential new metrics for evaluating vein stent function that may aid future stent design or stent function we examined common measures of small artery stent design and function. Stent symmetry or eccentricity had no statistically identified relation to clinical outcomes in the VIVO patient cohort studied. New metrics for analyzing large vein stents for tortuous, scarred or compressed pelvic veins need to be defined.

Future vein stent trials should prospectively evaluate changes in vein lumen diameter, area, and AR post stent to assess whether these variables are individually important for long-term clinical improvement and safety. To date, no other measure of vein stent characteristics or performance such as shape, flexibility, crush resistance, or fracture has been correlated with stent patency or clinical outcome. Additionally, the lack of a comparative trial between the commercially available venous stents makes identifying true differences in clinical outcomes impossible.

Limitations: The standard of care imaging for deep vein interventions when the VIVO US Study protocol was written and implemented was pre-operative axial imaging and intraoperative multiplanar venography. Though IVUS had been

described,[15] it was not yet considered an essential tool. For that reason, only a subset of VIVO study sites performed pre- and post-stent IVUS imaging for this IVUS post-hoc analysis.

This subset evaluation of the VIVO US study is admittedly limited by the number of VIVO patients who had comprehensive pre- and post-stent IVUS imaging, and the rare technical and clinical failures (e.g. n = 1 patency failure at 12 months; n = 1 stent misplacement) observed. Small study numbers for this IVUS cohort makes developing strong conclusions correlating stent performance and clinical improvement difficult. However, this analysis provides a framework for the systematic analysis of other venous stent data or future trials to gain insight about deep vein interventions for optimal patient outcomes.

Conclusion

Until further data is available about how stent performance impacts clinical outcomes, we are left with stent size, length, and flexibility as quantitative and qualitative metrics to assess the currently available stents. How these characteristics, and others yet to be defined, will best address specific deep vein pathologies awaits to be seen. The 1-year outcome data of the IVUS cohort described in this analysis reflects the 1-year outcome data of the full cohort of the VIVO study. These data support the concept that lumen gain at iliofemoral vein stenoses with the flexible Zilver Vena Stent results in clinical improvement. We cannot yet explain the specific metrics of the lumen gain that explains why this clinical efficacy occurs. Further refinement in how we measure vein stent performance may one day guide individual patient treatment for uniformly better results.

Author Notes

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Author Contributions

Paul Gagne: Study design, data analysis, manuscript preparation, Kayode O. Kuku: Data analysis, manuscript preparation, Robert Mendes: Manuscript preparation, Amy Griggs: Study design, data analysis, and manuscript preparation, Edem Segbefia: data analysis and manuscript preparation, Lawrence Hofmann: Manuscript preparation, Anthony Comerota: Manuscript Preparation, Hector Garcia-Garcia: data analysis and manuscript preparation.

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Trial Registration

VIVO US Clinical Study (NCT01970007); https://clinicaltrials.gov/search?term=NCT01970007

Ethical Statement

Ethical Approval

The VIVO US study was conducted in accordance with the Declaration of Helsinki II and in compliance with the Health Insurance Portability and Accountability Act. Each participating institution had approval from their Institution Review Boards or Ethics Committee; IVUS data for this subanalysis came from 2 institutions, UNC Rex Healthcare (Schulman Associates, IRB #201407350, approved on February 9, 2015) and Norwalk Hospital (Norwalk Hospital, IRB #13-14, approved on November 6, 2013; Western Institutional Review Board, IRB #20132239, approved on September 17, 2018). All patients provided written informed consent before study enrollment.

Informed Consent

All patients provided written informed consent before study enrollment.

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Supplemental Material

Supplemental material for this article is available online.

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