

Three-Year Outcomes of the Abre Venous Self-Expanding Stent System in Patients with Symptomatic Iliofemoral Venous Outflow Obstruction

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ABSTRACT

Purpose: To report 36-month outcomes and subgroup analysis of the ABRE study evaluating the safety and effectiveness of the Abre venous self-expanding stent system for the treatment of symptomatic iliofemoral venous outflow obstruction disease.

Methods: The ABRE study was a prospective, multicenter, nonrandomized study that enrolled and implanted Abre venous stents in 200 participants (mean age 51.5 years [SD ± 15.9], 66.5% women) with symptomatic iliofemoral venous outflow obstruction at 24 global sites. Outcomes assessed through 36 months included patency, major adverse events, stent migration, stent fracture, and quality-of-life changes. Adverse events and imaging studies were adjudicated by independent clinical events committee and core laboratories, respectively.

Results: Primary, primary-assisted, and secondary patency through 36 months by Kaplan–Meier estimates were 81.6%, 84.8%, and 86.3%, respectively. The cumulative incidence of major adverse events through 36 months was 10.2%, mainly driven by 12 thrombosis events. Subgroup analyses demonstrated a primary patency of 76.5% in the acute deep vein thrombosis group, 70.4% in the postthrombotic syndrome group, and 97.1% in the nonthrombotic iliac vein lesion group through 36 months. The overall mean lesion length was 112.4 mm (SD ± 66.1). There were no stent fractures or migrations in this study. Quality of life and venous functional assessments demonstrated significant improvements from baseline to 36 months across all patient subsets.

Conclusions: Results from the ABRE study demonstrated sustained patency with a good safety profile after implantation of a dedicated venous stent in patients with symptomatic iliofemoral venous outflow obstruction disease.

ABBREVIATIONS

aDVT = acute deep vein thrombosis, CEAP = Clinical Etiologic Anatomic Pathophysiologic, CEC = clinical events committee, CFV = common femoral vein, CIV = common iliac vein, IDE = investigational device exemption, IRB = institutional review board, MAE = major adverse event, NIVL = nonthrombotic iliac vein lesion, PTS = postthrombotic syndrome, QoL = quality of life, rVCSS = revised Venous Clinical Severity Score, TLR = target lesion revascularization, US = ultrasound, VEINES-QoL/Sym = Venous Insufficiency Epidemiological and Economics Study QoL/Symptoms

Iliofemoral venous obstructive disease is a common condition that affects venous drainage from both the pelvis and lower limbs and is associated with impaired quality of life (QoL) and high economic burden (1,2). The etiology of obstruction may be thrombotic in nature in the case of acute deep vein thrombosis (aDVT) and chronic postthrombotic syndrome (PTS), or nonthrombotic in nature, commonly referred to as May–Thurner syndrome or nonthrombotic iliac vein lesions (NIVLs). The latter results from extrinsic compression from overlying structures, such as the right common iliac artery compressing the left common iliac vein (CIV) (3). Conservative management such as compression

Appendix A and **Tables E1–E6** can be found by accessing the online version of this article on *www.jvir.org* and selecting the Supplemental Material tab.

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RESEARCH HIGHLIGHTS

- The prospective, core laboratory and Clinical Events Committee–adjudicated, ABRE study demonstrated sustained high patency through 36 months after implantation of a dedicated venous stent in patients with symptomatic iliofemoral venous outflow obstruction disease.
- Results also showed low reintervention rates, no stent migration or fracture, and minimal major adverse events.
- Sustained and significant improvements were seen in quality of life (QoL) and functional outcomes through 36 months, including EuroQoL 5 Dimensions, Venous Insufficiency Epidemiological and Economics Study (VEINES)-QoL, VEINES-Symptoms, revised Venous Clinical Severity Score, and Villalta scores.

STUDY DETAILS

Study type: Prospective, observational, cohort study

Level of evidence: 3 (SIR-C)

stockings, medication, and exercise therapies, may be used but are often insufficient to resolve symptoms. Therefore, endovascular interventions, particularly stent placement, have gained popularity in symptomatic patients (4).

The ABRE study was a multicenter, investigational device exemption (IDE) prospective trial designed to evaluate the safety and effectiveness of the Abre, a first-generation dedicated venous stent, for use in patients with symptomatic iliofemoral venous outflow obstruction. The 12-month results were previously reported, and primary safety and effectiveness performance goals were achieved. The study also showed improvements in functional outcomes and QoL with no stent fractures occurring despite a high proportion of stents crossing the inguinal ligament. The aim of this study was to report the 36-month safety and effectiveness outcomes from the ABRE IDE study to evaluate longer-term performance.

MATERIALS AND METHODS

Study Design

A detailed description of the ABRE study design, inclusion and exclusion criteria, and outcomes through 12 months have been previously published (5). The study protocol was approved by institutional review boards (IRBs) or by ethical committees of the respective participating centers. Study participants provided written informed consent before entering the study. An independent clinical events committee (CEC; Syntactx, New York, New York) reviewed and adjudicated endpoint–related adverse events, and independent core laboratories assessed duplex ultrasound (US; VasCore, Boston, Massachusetts) and radiographs, intravascular US, and venography (Syntactx). (https://clinicaltrials.gov/; unique identifier: NCT03038438).

As specified in the protocol and previously reported, participants were enrolled consecutively across 24 international study centers between December 2017 and November 2018. A list of investigators and study sites is provided in **Table E1** (available online on the article's Supplemental Material page at *www.jvir.org*). In total, 200 participants were enrolled who underwent implantation with the Abre venous stent, including 128 participants from 16 sites in the United States and 72 participants from the 8 sites in Europe. Eligible participants included men and women aged between 18 and 80 years who presented with symptomatic iliofemoral venous obstruction. Participants were required to have 1 or more of the following: (*i*) Clinical Etiologic Anatomic Pathophysiologic (CEAP) score of ≥3; (*ii*) moderate leg pain with revised Venous Clinical Severity Score (rVCSS) pain score of ≥2; or (*iii*) suspected DVT. All participants were required to have a nonmalignant venous obstruction within the CIV, external iliac, and/or common femoral vein (CFV) determined by the investigator to be the cause of the presenting symptoms. Venous obstruction was defined as the presence of 1 or more of the following: (*i*) a reduction in diameter by ≥50% on venography or intravascular US, (*ii*) an area reduction by ≥50% with intravascular US, or (*iii*) total venous occlusion. A venous occlusion was defined as the complete occlusion of 1 or more segments of the iliofemoral vein (CIV, external iliac vein, and/or CFV). Based on the implanting physicians' evaluation, the etiology for each participant's venous obstruction was categorized as NIVL, PTS, or aDVT. In the setting of aDVT, stent placement was indicated for residual iliac vein obstruction after successful thrombectomy and/or thrombolysis. Interventions for aDVT and stent implantation had to have been completed within 14 days from symptom onset. In the setting of NIVL, stent placement was indicated after confirmation of clinical manifestations (ie, symptoms and/or signs) in the lower extremities. Patients were excluded if they presented with symptomatic peripheral arterial disease, prior placement of venous stents in the ipsilateral vasculature, bilateral iliofemoral or inferior vena cava lesions, or a contraindication to anticoagulation.

Device and Index Procedure

The Abre venous self-expanding stent (Medtronic, Minneapolis, Minnesota) is indicated for use in iliofemoral veins for treatment of symptomatic venous outflow obstruction and described previously (5).

Venography and intravascular US were used to determine the extent of the disease and were also used for procedural guidance. The stent was recommended to be placed at least 1 cm cranial and 1 cm caudal to the target lesion(s) to land in a relatively healthy/normal venous segment if the disease allowed; when overlapping stents, overlapping was

Table 1. Baseline Demographic and Clinical Characteristics in the ABRE Study

Demographics	Overall (N = 200)	Primary etiology subgroups		
		aDVT (n = 33)	PTS (n = 95)	NIVL (n = 72)
Age (y)	51.5 ± 15.9 (200)	51.9 ± 16.0 (33)	51.2 ± 15.7 (95)	51.6 ± 16.2 (72)
Female sex	66.5 (133/200)	54.5 (18/33)	68.4 (65/95)	69.4 (50/72)
White race	78.5 (157/200)	75.8 (25/33)	74.7 (71/95)	84.7 (61/72)
BMI (kg/m^2)	29.5 ± 7.1	29.2 ± 5.3	28.8 ± 7.0	30.6 ± 7.8
History of venous thromboembolism	52.0 (104/200)	33.3 (11/33)	87.4 (83/95)	13.9 (10/72)
Target limb	96.2 (100/104)	72.7 (8/11)	100.0 (83/83)	90.0 (9/10)
Nontarget limb	11.5 (12/104)	36.4 (4/11)	6.0 (5/83)	30.0 (3/10)
Known family history of DVT	22.0 (44/200)	21.2 (7/33)	28.4 (27/95)	13.9 (10/72)
Pulmonary embolism	17.0 (34/200)	15.2 (5/33)	26.3 (25/95)	5.6 (4/72)
Thrombophilia	11.5 (23/200)	3.0 (1/33)	20.0 (19/95)	4.2 (3/72)
IVC filter present	5.0 (10/200)	9.1 (3/33)	6.3 (6/95)	1.4 (1/72)
Target limb CEAP classification*				
C0—no visible or palpable signs of venous disease	0.6 (1/166)	NA	0.0 (0/95)	1.4 (1/71)†
C1—telangiectasias or reticular veins	0.6 (1/166)	NA	0.0 (0/95)	1.4 (1/71)†
C2—varicose veins	2.4 (4/166)	NA	1.1 (1/95)†	4.2 (3/71)†
C3—edema	61.4 (102/166)	NA	65.3 (62/95)	56.3 (40/71)
C4a—pigmentation or eczema	12.7 (21/166)	NA	10.5 (10/95)	15.5 (11/71)
C4b—Lipodermatosclerosis or atrophie blanche	6.6 (11/166)	NA	6.3 (6/95)	7.0 (5/71)
C5—healed venous ulcer	6.6 (11/166)	NA	7.4 (7/95)	5.6 (4/71)
C6—active venous ulcer	9.0 (15/166)	NA	9.5 (9/95)	8.5 (6/71)
Venous claudication	30.0 (60/200)	15.2 (5/33)	29.5 (28/95)	37.5 (27/72)
Target limb rVCSS score	8.8 ± 4.7 (199)	8.5 ± 3.7 (33)	8.8 ± 5.0 (95)	9.0 ± 4.5 (71)
Target limb Villalta score	11.2 ± 5.7 (198)	10.8 ± 4.9 (33)	11.1 ± 6.1 (95)	11.6 ± 5.4 (70)

Note–Categorical data are given as the percentage (number/sample); continuous data are presented as the mean ± SD (sample size).
aDVT = acute deep vein thrombosis; BMI = body mass index; CEAP = Clinical Etiologic Anatomic Pathophysiologic; IVC = inferior vena cava; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome; rVCSS = revised Venous Clinical Severity Score; SD = standard deviation.
*PTS and NIVL participants only; CEAP assessment is not applicable for aDVT participants.
†The inclusion for these participants was based on an rVCSS pain score of ≥2.

performed at least 1.5 cm without skipping areas between stents. The distal point of the stent was to be at or above the deep femoral vein, and ending a stent in the inguinal ligament was to be avoided. A stent with a diameter of at least 2 mm more than the chosen reference vessel diameter was recommended to achieve good wall apposition. It was required that lesions were predilated and recommended that stents were postdilated to stent size with the recommendation to use a high-pressure balloon. The anticoagulation recommendations are provided in **Table E2** (available online at *www.jvir.org*); however, anticoagulation decisions were ultimately at the discretion of the investigators.

Baseline Participant Demographic and Lesion Characteristics

Salient baseline demographic, clinical, lesion and procedural characteristics are described in **Tables 1** and **2**. The mean age of participants was 51.5 years (SD ± 15.9 and 66.5% were female. Notable baseline characteristics include a history of venous thromboembolism (52.0% overall), which correlates closely with the high inclusion rate of postthrombotic participants in this trial. The target limb was primarily the left leg (92.0%). PTS and NIVL subgroups presented with varying degrees of chronic venous disease progression. Edema (CEAP score C3) was predominantly noted among these participants (65.3% in the PTS and 56.3% in the NIVL groups). Other common presenting signs of chronic venous disease in the participant population included pigmentation/eczema and lipodermatosclerosis (CEAP score C4a and C4b) and a healed or active venous ulcer (CEAP score C5/C6) (**Table 1**). Venous claudication was reported in 30% of overall participants. The mean lesion length in the overall cohort was 112.4 mm (SD ± 66.1), and the mean stented length was 134.3 mm (SD ± 58.0). The CIV was the most common site for stent implantation (96.0%). The percentage of participants who required stent placement into the CFV was 44.0% (88/200) in the overall cohort and 65.3% (62/95) in the PTS group. The number of stents implanted per participant was 1.5 (SD ± 0.6) in the overall cohort (**Table 2**).

Follow-up

Scheduled follow-up visits were conducted at 30 days and 6, 12, 24, and 36 months after index procedure. Assessments included an interim history with medication review, an assessment for adverse events, physical

Table 2. Lesion and Procedural Characteristics in the ABRE Study

Characteristics	Overall cohort (N = 200)	Primary etiology subgroups		
		aDVT (n = 33)	PTS (n = 95)	NIVL (n = 72)
% Area stesnosis*	74.9 ± 16.8 (189)	82.8 ± 13.3 (31)	78.6 ± 14.9 (86)	67.2 ± 17.5 (72)
% Diameter stenosis†	62.8 ± 28.7 (195)	79.0 ± 23.8 (33)	70.9 ± 27.9 (93)	44.2 ± 21.4 (69)
Lesion length (mm)†	112.4 ± 66.1 (184)	131.2 ± 62.5 (28)	135.7 ± 66.8 (88)	74.5 ± 47.5 (68)
Total stented length (mm)†	134.3 ± 58.0 (192)	137.8 ± 55.9 (32)	160.4 ± 56.5 (92)	97.2 ± 38.3 (68)
Participants with total occlusions†	25.6% (50/195)	45.5% (15/33)	35.5% (33/93)	2.9% (2/69)
No. of Abre stents implanted per participant†	1.5 ± 0.6 (200)	1.5 ± 0.6 (33)	1.8 ± 0.7 (95)	1.2 ± 0.4 (72)
Stented vein location†,‡,§				
Common iliac vein	96.0 (192/200)	100 (33/33)	94.7 (90/95)	95.8 (69/72)
External iliac vein	80.5 (161/200)	81.8 (27/33)	91.6 (87/95)	65.3 (47/72)
Common femoral vein	44.0 (88/200)	45.5 (15/33)	65.3 (62/95)	15.3 (11/72)
Duration of hospital stay (d)	1.5 ± 2.2 (200)	3.9 ± 3.1 (33)	1.5 ± 1.6 (95)	0.5 ± 1.2 (72)
Acute success				
Device success	100 (302/302)	100 (49/49)	100 (168/168)	100 (85/85)
Lesion success	100 (200/200)	100 (33/33)	100 (95/95)	100 (72/72)
Procedure success	99 (198/200)	100 (33/33)	97.9 (93/95)	100 (72/72)

Categorical data are given as the percentage (number/sample); continuous data are presented as the mean ± SD (sample size).
aDVT = acute deep vein thrombosis; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome; SD = standard deviation.
*Intravascular ultrasound core laboratory data (included participants assessed by intravascular US, n = 189).
†Venographic core laboratory data (included participants assessed by venogram, n = 200).
‡Treated area/lesion could encompass more than 1 vein.
§Site data and venographic core laboratory data were used.

examination, duplex US, and QoL questionnaires. At the 30-day follow-up, the first 30 participants underwent multiobliquity pelvic radiography to evaluate for stent fractures. Multiobliquity pelvic radiography was performed on all participants at 12-month, 24-month, and 36-month study visits. A venogram was required at the 12-month visit if the duplex US imaging indicated a ≥50% stent obstruction, if duplex US imaging was nondiagnostic, or if dictated by clinical symptoms.

Outcome Measures and Definitions

Outcomes assessed through 36 months included primary patency, target lesion revascularization (TLR, including clinically driven and nonclinically driven), and major adverse events (MAEs). Primary patency was defined as freedom from occlusion, freedom from restenosis of ≥50% of the stented segment, and freedom from clinically driven TLR measured through 36 months after index procedure. "Clinically driven" was defined as the recurrence of symptoms present at baseline or the onset of new symptoms, including but not limited to ipsilateral venous pain, swelling, stasis dermatitis, or ulceration. TLR was defined as any reintervention of the stented segment of the target lesion. MAE was defined as a composite of all-cause death, clinically significant pulmonary embolism, procedure-related major bleeding adverse events, and stent thrombosis and/or stent migration, as confirmed by imaging within 36 months of the index procedure.

Additional endpoints evaluated through 36 months included major bleeding adverse events related to bleeding that occurred during the index procedure, delayed stent migration, and stent fracture. These endpoints were adjudicated by CEC or confirmed by imaging core laboratory. QoL and venous functional assessments were assessed using validated scoring systems (6–11). QoL was evaluated using EuroQoL Five Dimensions (EQ-5D) and Venous Insufficiency Epidemiological and Economics Study QoL/Symptoms (VEINES-QoL/Sym). Venous functional outcomes were measured before and after treatment using the rVCSS and the Villalta score.

Other clinical end points assessed include primary-assisted and secondary patency through 36 months. The detailed definitions of the important outcomes of this study are described in **Methods** in **Appendix A** (available online at *www.jvir.org*).

Statistical Analysis

Baseline characteristics and outcomes were summarized descriptively using percentages and frequencies for categorical variables and the mean, standard deviation or standard error, and number of observations for continuous variables. Analyses were based on evaluable data where applicable. Nonparametric Kaplan–Meier estimates were used to report time-to-event outcomes: patency end points, reinterventions, and MAEs. Participants were censored at the time of withdrawal, loss to follow-up, or death. Confidence intervals (95% CIs) were derived for time-to-event outcomes with standard error formula introduced by Peto et al (12).

A repeated-measures mixed model was analyzed for the VEINES-QoL/Sym, EQ-5D Index Score, Villalta score, and rVCSS using data available at baseline and at 6, 12, 24, and

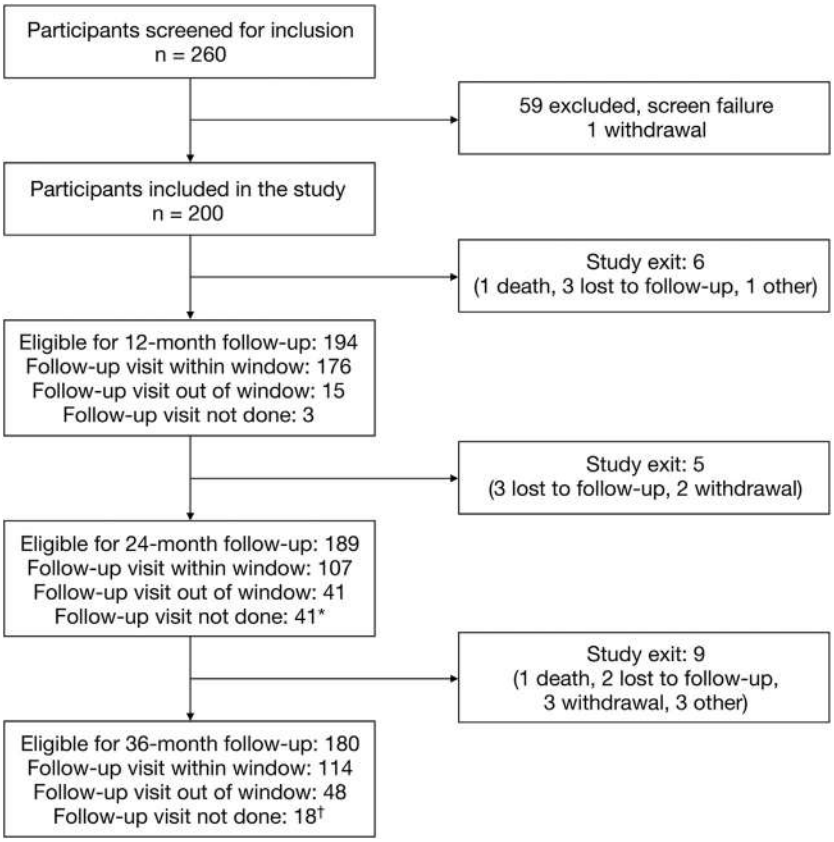


Figure 1. Participant flowchart in the ABRE study through 36 months. *Of the 41 participants who did not complete planned clinic follow-up at 24 months (31 due to COVID-19–related issues), 30 completed telephonic follow-up; 1 had imaging available. †Of the 18 participants who did not complete planned clinic follow-up at 36 months (10 due to COVID-19–related issues), 16 completed telephonic follow-up.

36 months. Please refer to **Methods** in **Appendix A** (available online at *www.jvir.org*) for the details of this analysis.

Annual cutoffs for the statistical analysis used 360 days per year (eg, 1,080 days for the 36-month cutoff). No adjustments were made for multiple comparisons and a significance level of 0.05 was used. Statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina) version 9.4 or higher.

RESULTS

The participant flow chart in the ABRE study is shown in **Figure 1**. Two hundred participants were included in the study. A total of 20 participants had exited the study before the 36-month follow-up: 3 died, 5 withdrew consent, 8 were lost to follow-up, and 4 exited for other reasons (1 participant was incarcerated, 2 moved away, 1 refused to schedule their 36-month follow-up visit). Of the 180 participants eligible for follow-up at 36 months, 162 (90.0%) completed planned clinic visit follow-up, and 16 participants completed telephonic follow-up. Follow-up visits were significantly impacted by COVID-19; 31 and 10 participants did not have planned clinic follow-up visits at 24 and 36 months, respectively, owing to COVID-19–related issues.

Follow-up Outcomes

Effectiveness Outcomes through 36 Months. The 36-month assessments were conducted as secondary analyses without formal hypothesis testing. The primary patency through 36 months was 81.6% (95% CI: 76.0%–87.2%) in the overall cohort (**Table 3** and **Fig 2a**). Subgroup analyses demonstrated primary patency of 76.5% (95% CI: 61.3%–91.8%) in the aDVT group, 70.4% (95% CI: 60.6%–80.2%) in the PTS group, and 97.1% (95% CI: 93.1%–100.0%) in the NIVL group (**Table 3** and **Fig 2b**). The primary patency rate in participants with stents extending into the CFV was 67.9% (95% CI: 57.7%–78.1%) in the overall cohort (70.7% aDVT, 61.0% PTS, and 100.0% NIVL) (**Table 3**). The primary-assisted patency and secondary patency rates through 36 months are reported in **Table 3**. Kaplan–Meier estimated freedom from TLR rates

Table 3. Principal Effectiveness Outcomes in the ABRE Study

Outcomes	Overall (N = 200)	aDVT (n = 33)	PTS (n = 95)	NIVL (n = 72)
12-mo outcomes				
Primary patency	93.2 (13)	100.0 (0)	86.4 (12)	98.6 (1)
Freedom from occlusion of the stented segment of the target lesion	96.4 (7)	100.0 (0)	93.3 (6)	98.6 (1)
Freedom from restenosis (≥50%) of the stented segment	93.8 (12)	100.0 (0)	87.6 (11)	98.6 (1)
Freedom from clinically driven target lesion revascularization	93.2 (13)	100 (0)	86.4 (12)	98.6 (1)
Primary patency extending into the CFV*	86.8 (11)	100.0 (0)	81.0 (11)	100.0 (0)
Primary-assisted patency	97.0 (6)	100.0 (0)	94.6 (5)	98.6 (1)
Secondary patency	99.0 (2)	100.0 (0)	97.8 (2)	100.0 (0)
24-mo outcomes				
Primary patency	86.2 (26)	83.3 (5)	76.8 (20)	98.6 (1)
Freedom from occlusion of the stented segment of the target lesion	95.3 (9)	96.6 (1)	92.0 (7)	98.6 (1)
Freedom from restenosis (≥50%) of the stented segment	86.7 (25)	83.3 (5)	77.9 (19)	98.6 (1)
Freedom from clinically driven target lesion revascularization	91.1 (17)	93.2 (2)	84.0 (14)	98.6 (1)
Primary patency extending into the CFV*	73.1 (22)	78.6 (3)	66.7 (19)	100.0 (0)
Primary-assisted patency	90.2 (19)	84.4 (5)	85.8 (13)	98.6 (1)
Secondary patency	91.8 (16)	87.5 (4)	88.0 (11)	98.6 (1)
36-mo Outcomes				
Primary patency	81.6 (34)	76.5 (7)	70.4 (25)	97.1 (2)
Freedom from occlusion of the stented segment of the target lesion	94.1 (11)	92.8 (2)	90.8 (8)	98.6 (1)
Freedom from restenosis (≥50%) of the stented segment	82.1 (33)	76.5 (7)	71.5 (24)	97.1 (2)
Freedom from clinically driven target lesion revascularization	89.3 (20)	89.6 (3)	81.5 (16)	98.6 (1)
Primary patency extending into the CFV*	67.9 (26)	70.7 (4)	61.0 (22)	100.0 (0)
Primary-assisted patency	84.8 (29)	78.0 (7)	77.6 (20)	97.1 (2)
Secondary patency	86.3 (26)	81.1 (6)	79.7 (18)	97.1 (2)

Note–Values are percentages, calculated based on Kaplan–Meier estimates (numbers are count of participants with the earliest occurrence of an event). aDVT = acute deep vein thrombosis; CFV = common femoral vein; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome.
*Overall, 88 participants underwent stent placement extended into the CFV: 15 aDVT, 62 PTS, 11 NIVL.

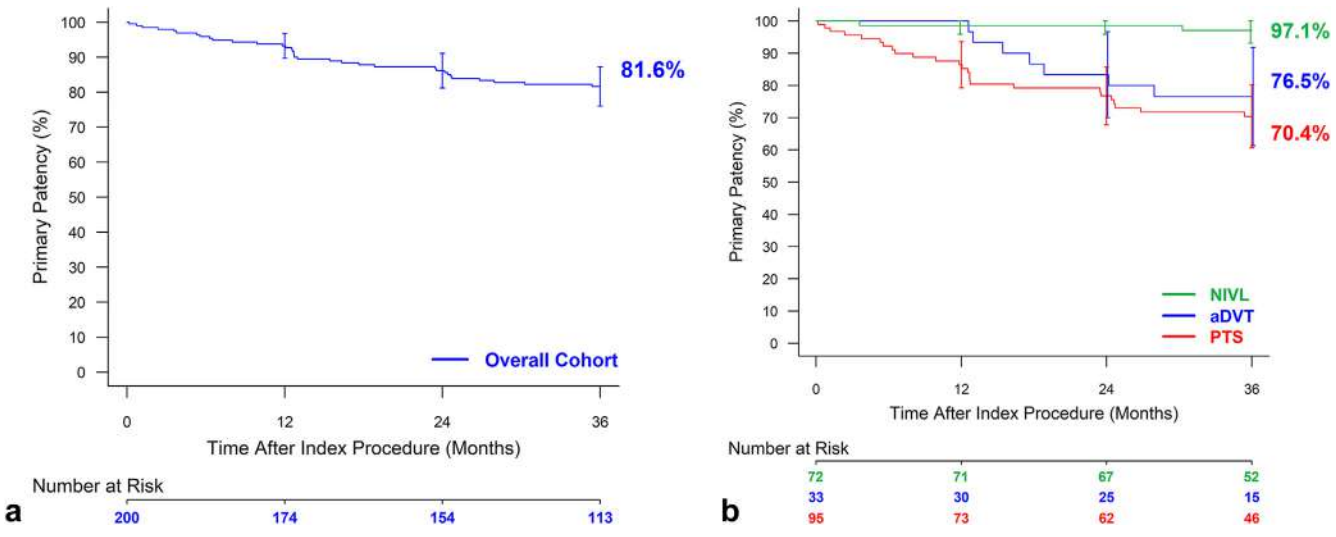


Figure 2. Primary patency rates by Kaplan–Meyer estimate through 36 months in the ABRE study: **(a)** overall cohort and **(b)** subgroups. Bars represent the 95% confidence intervals. aDVT = acute deep vein thrombosis; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome.

through 36 months were 83.7% (95% CI: 78.5%–88.9%) in the overall cohort (81.2% aDVT, 74.1% PTS, and 97.2% NIVL) (Fig 3).

Safety Outcomes through 36 Months. The 36-month cumulative incidence of MAE, a composite of all-cause death, clinically significant pulmonary

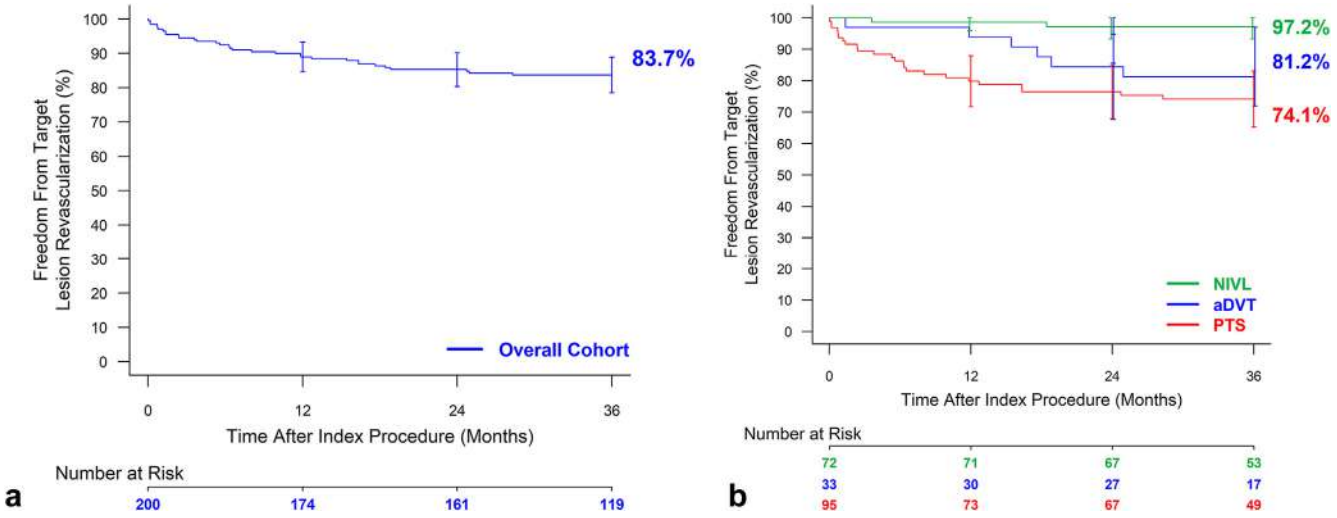


Figure 3. Freedom from target lesion revascularization (clinically driven and nonclinically driven) by Kaplan–Meyer estimate through 36 months in the ABRE study: **(a)** overall cohort and **(b)** subgroups. Bars represent the 95% confidence intervals. aDVT = acute deep vein thrombosis; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome.

embolism, procedure-related major bleeding adverse events, and stent thrombosis and/or stent migration, was 10.2% (Table 4). Three participants died through 36 months of follow-up, 2 in the PTS group and 1 in the NIVL group. All 3 deaths were adjudicated by the CEC as not related to the procedure or study device. Through the 36-month follow-up, clinically significant pulmonary embolism was experienced by 4 participants; 2 in the aDVT group, 2 in the PTS group, and none in the NIVL group. One participant in the PTS group experienced a major bleeding adverse event (not related to the index procedure). Of the 12 participants who experienced stent thrombosis, 10 were in the PTS group. There were no cases of stent migration or stent fracture in this study through the 36 months of follow-up.

Quality of Life and Functional Outcomes. QoL and venous functional assessments were conducted using the VEINES-QoL/Sym, EQ-5D (Index Score), Villalta, and rVCSS scores. All QoL and functional measures demonstrated statistically significant improvements at 6 months that were sustained through 36 months compared with those at baseline (Fig 4; Tables E3–E6, available online at *www.jvir.org*). In the overall cohort, the least square mean differences from baseline to 36 months for VEINES-QoL and VEINES-Sym were 20.79 (95% CI: 17.08–24.50; $P < .001$) and 20.00 (95% CI: 16.28–23.72; $P < .001$), respectively. The EQ-5D index score least square mean difference from baseline to 36 months was 0.13 (95% CI: 0.09–0.16: $P < .001$). Similarly, the least square mean differences for Villalta and rVCSS scores from baseline to 36 months were −6.29 (95% CI: −7.07 to −5.52; $P < .001$) and −4.47 (95% CI: −5.05 to −3.89; $P < .001$), respectively. The number of participants with active venous leg ulcers on the target limb decreased from 15 at baseline to 5 at 36 months.

DISCUSSION

This study reports the final 3-year safety and effectiveness outcomes of the overall cohort and subsets of disease etiology in the ABRE study. Results demonstrated a 3-year primary patency of 81.6%, freedom from TLR rate of 83.7%, and a 10.2% cumulative incidence of MAE with no stent migration or stent fracture after the Abre stent placement. Most importantly, sustained and significant improvements in QoL and functional outcomes were seen through 3 years, including EQ-5D, VEINES-QoL/Sym, rVCSS, and Villalta scores. Considering the real-world representation of patients in this study, the findings support a durable clinical benefit and safety profile of the Abre venous stent for use in patients with symptomatic iliofemoral venous disease. This adds to the accumulated data from the published IDE trials and separate publications that venous stent placement provides a meaningful clinical improvement in patient QoL (13). This is important because only 1 randomized controlled trial has been conducted in this space recognizing the difficulty in randomizing patients (14).

At the time of writing, the 3-year follow-up results have been published for VIRTUS and VERNACULAR (15,16) and presented for VIVO (17). All 4 IDE trials showed promising results and increased the availability of data for treatment analysis in these populations. The ABRE study prospectively enrolled participants representing all etiology of iliofemoral venous obstruction, which included aDVT, PTS, and NIVL. PTS (47.5%), the largest subgroup in this study, is known to be a complex disease and challenging to treat with lower patency rates in this group (18). This

Table 4. Principal Safety Outcomes in the ABRE Study

Outcomes	Overall (N = 200)	aDVT (n = 33)	PTS (n = 95)	NIVL (n = 72)
12-mo outcomes				
MAE*	6.0 (12)	0.0 (0)	11.6 (11)	1.4 (1)
All-cause death	1.0 (2)	0.0 (0)	2.1 (2)	0.0 (0)
Clinically significant pulmonary embolism	0.5 (1)	0.0 (0)	1.1 (1)	0.0 (0)
Major bleeding adverse event†	0.5 (1)	0.0 (0)	1.1 (1)	0.0 (0)
Stent thrombosis confirmed by imaging	4.0 (8)	0.0 (0)	7.4 (7)	1.4 (1)
Stent migration confirmed by imaging	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Stent fracture‡,§	0.0 (0/180)	0.0 (0/30)	0.0 (0/85)	0.0 (0/65)
Delayed stent migration§,¶	0.0 (0/181)	0.0 (0/30)	0.0 (0/85)	0.0 (0/66)
Target lesion revascularization#	11.1 (22)	6.2 (2)	20.2 (19)	1.4 (1)
Major bleeding related to index procedure**	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
24-mo outcomes				
MAE*	8.6 (17)	9.4 (3)	13.8 (13)	1.4 (1)
All-cause death	1.0 (2)	0.0 (0)	2.1 (2)	0.0 (0)
Clinically significant pulmonary embolism	1.5 (3)	6.3 (2)	1.1 (1)	0.0 (0)
Major bleeding adverse event†	0.5 (1)	0.0 (0)	1.1 (1)	0.0 (0)
Stent thrombosis confirmed by imaging	5.6 (11)	3.1 (1)	9.7 (9)	1.4 (1)
Stent migration confirmed by imaging	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Stent fracture‡,§	0.0 (0/130)	0.0 (0/23)	0.0 (0/64)	0.0 (0/43)
Delayed stent migration§,¶	0.0 (0/131)	0.0 (0/24)	0.0 (0/64)	0.0 (0/43)
Target lesion revascularization#	14.7 (29)	15.5 (5)	23.5 (22)	2.8 (2)
Major bleeding related to index procedure**	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
36-mo outcomes				
MAE*	10.2 (20)	9.4 (3)	16.0 (15)	2.9 (2)
All-cause death	1.5 (3)	0.0 (0)	2.1 (2)	1.5 (1)
Clinically significant pulmonary embolism	2.1 (4)	6.3 (2)	2.2 (2)	0.0 (0)
Major bleeding adverse events†	0.5 (1)	0.0 (0)	1.1 (1)	0.0 (0)
Stent thrombosis confirmed by imaging	6.1 (12)	3.1 (1)	10.8 (10)	1.4 (1)
Stent migration confirmed by imaging	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Stent fracture‡,§	0.0 (0/145)	0.0 (0/26)	0.0 (0/66)	0.0 (0/53)
Delayed stent migration§,¶	0.0 (0/145)	0.0 (0/26)	0.0 (0/66)	0.0 (0/53)
Target lesion revascularization#	16.3 (32)	18.8 (6)	25.9 (24)	2.8 (2)
Major bleeding related to index procedure**	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Note–Percentages were calculated based on Kaplan–Meier estimates (numbers are count of participants with the earliest occurrence of an event), except for delayed stent migration and stent fracture, in which percentages were calculated as proportion rates (number of participants with each event/number of participants with data). All-cause death, clinically significant (ie, symptomatic and confirmed by CT pulmonary angiography) pulmonary embolism, bleeding adverse events, and TLR were CEC adjudicated; stent thrombosis, stent migration, stent fracture, and delayed stent migration were reported by core laboratories.
aDVT = acute deep vein thrombosis; CEC = clinical events committee; CT = computed tomography; MAE = major adverse event; NIVL = non-thrombotic iliac vein lesion; PTS = post-thrombotic syndrome; TLR = target lesion revascularization.
*Definitions of the individual MAE components are described in Supplementary Methods.
†Major bleeding adverse event (MAE component): procedural at 30 d; postprocedural at 6, 12, 24, and 36 mo.
‡Radiography for the 30-d visit was only required for the first 30 participants.
§Stent fracture and delayed stent migration within 12, 24, and 36 mo included participants who had scheduled visit-based evaluable imaging and unscheduled imaging up to Day 420, 780, and 1140, respectively.
¶Delayed stent migration within 12, 24, and 36 mo was defined as position change of a stent with an imaging modality of >1 cm from its original location at the conclusion of the index procedure, as determined regarding a reference anatomic structure.
#Included both clinically driven and nonclinically driven target lesion revascularizations.
**Major bleeding related to index procedure was defined as a blood loss leading to transfusion of whole blood or red cells provided hemoglobin drop of 3 g/dL (1.86 mmol/L) or more is related to bleeding occurring during the index procedure through 36 months post-index procedure.

prospective categorization allowed prespecified subgroup analyses of aDVT, PTS, and NIVL in the ABRE study. As described in the limitations, VIRTUS did not enroll patients with aDVT (15,16). VERNACULAR enrolled 14 participants with aDVT; however, they were evaluated as part of the PTS cohort (16). VIVO initially enrolled patients in the trial as acute (<30 days) or chronic (>30 days); however, a recent publication (19) and a post hoc analysis presentation (20) recategorized the patients into aDVT, PTS, and NIVL subgroups. Although the revised categorization of VIVO patients improved data analysis overall, subgroup definitions used were different from comparable subgroups used in ABRE. These described differences make it difficult to make direct comparisons between these studies and indicate a need for explicit definitions to ensure future work can be compared.

The ABRE study also reports a high number of stents placed in the CFV (44.0%), reflecting the complexity of the

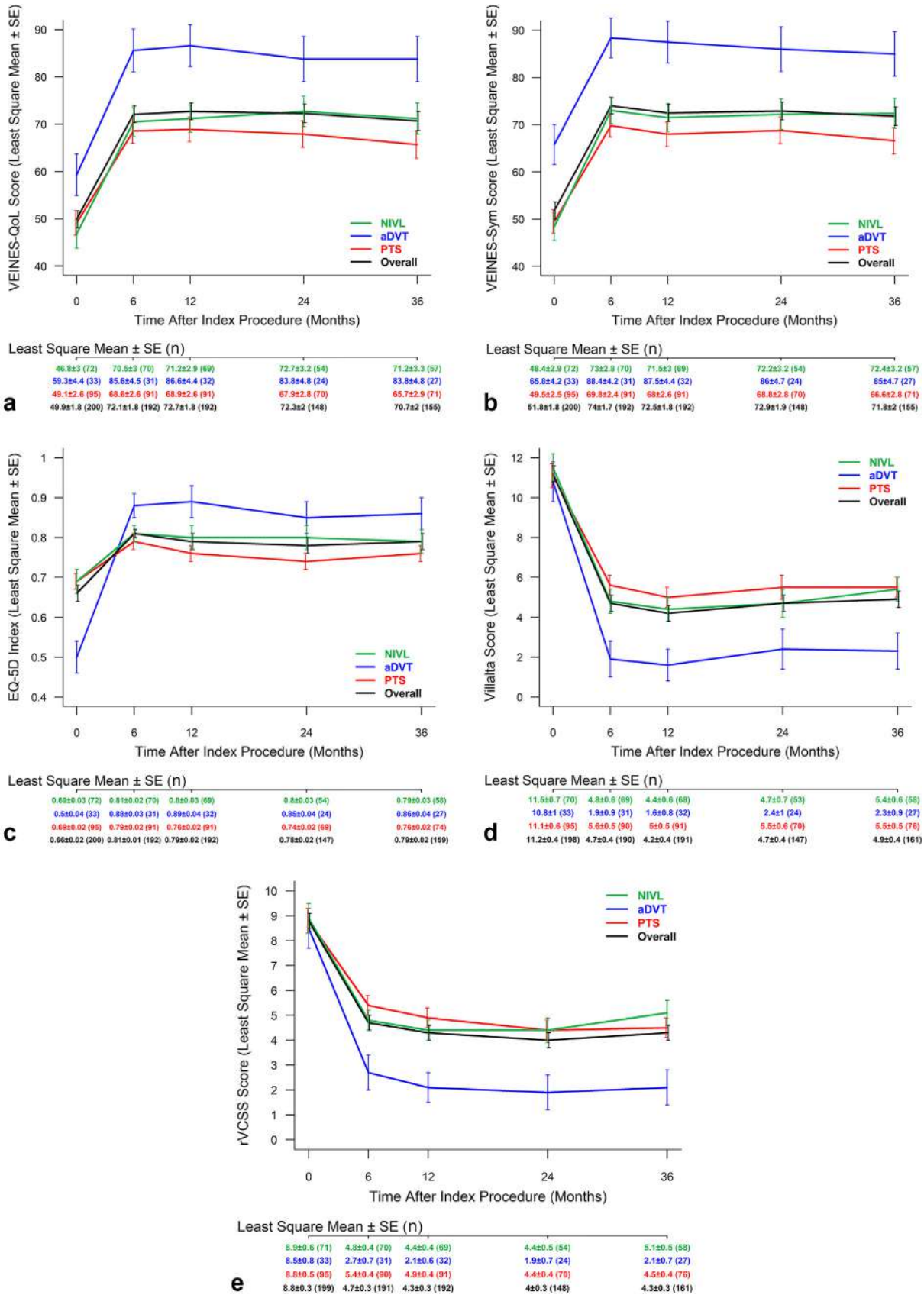


Figure 4. Functional outcomes were assessed at baseline and at 6, 12, 24, and 36 months. Values presented are least square mean ± standard error (number of participants with available data at the time point). Least square mean differences showed statistically significant improvements at all time points compared with those at baseline. *P* values are provided in **Tables E3–E6** (available online at *www.jvir.org*). **(a)** Venous Insufficiency Epidemiological and Economics Study Quality of Life (VEINES-QoL), **(b)** VEINES-Symptoms, **(c)** EuroQoL Five Dimensions (EQ-5D) index score, **(d)** Villalta score, **(e)** Revised Venous Clinical Severity Score (rVCSS). aDVT = acute deep vein thrombosis; NIVL = nonthrombotic iliac vein lesion; PTS = postthrombotic syndrome.

participant population in this study. This also means that a meaningful analysis of stent fracture could be made because the principal site for stent fracture occurs in patients with extension of stents beyond the inguinal ligament into the CFV (21). Approximately 11% (20% in PTS) of participants in the ABRE study also experienced thrombophilia; however, this did not appear to impact the results (22). Despite these complexities, the study met the prespecified performance goals, and encouraging 12-month primary and secondary outcomes were reported previously (5). The 3-year analysis continued to demonstrate sustained effectiveness with a primary patency rate of 81.6% based on Kaplan–Meier estimate for the overall cohort. The 3-year primary patency rates have been previously published from VIRTUS and VERNACULAR studies: 71.7% (proportion rate, VIRTUS) and 84.0% (Kaplan–Meier estimate, VERNACULAR) (15,16). The present study also reports patency rates in subgroups. It was a requirement of the study for inflow to be evaluated; however, a significant reduction in patency was still identified in the subgroup of patients requiring stent extension to the CFV, particularly among patients with PTS. This underlies the complexity of the group with advanced disease and reinforces that more work is needed to optimize inflow in these patients.

The reintervention rates are consistent across all 4 IDEs. The drive for reintervention in venous disease has anecdotally tended to be any buildup of thrombus within the stented segment at ≥50%. However, it is noted that not all patients exhibit symptoms. In the absence of any reliable objective measurements, it has evolved that many patients may in fact not require secondary interventions. It is clear that more work is needed to establish a standardized approach to reintervention, and in particular, we need a better understanding of flow dynamics and the impact of restenosis on long-term patency.

The ABRE study assessed QoL and venous functional outcomes in all patient subgroups and collectively through 3 years, including VEINES-QoL, VEINES-Sym, EQ-5D, Villalta, and rVCSS scores. Sustained improvements were observed through 3 years compared with the baseline in all parameters assessed. These findings are bolstered by additional reports of improved QoL after venous stent placement procedures in patients with chronic venous disease (13,23). Importantly, these improvements spanned across all patient subgroups, including aDVT and PTS, which highlight the value of treating these patients despite increased patency loss in these subgroups.

All 4 venous IDE studies reported low adverse event rates through 1–3 years. A small number of stent fractures (3.3%) were reported through 1 year in VIRTUS, but the authors mentioned that no clinical sequelae were observed in these patients. There were no stent fractures in this study (ABRE) through 3 years despite the high number of CFV stents (44%). VIVO and VERNACULAR studies also did not report any stent fractures through 1 and 3 years, respectively (16,19). In the case of VERNACULAR, the low number of stents crossing the ligament makes it difficult to draw conclusions regarding the risk of fracture with this stent. Overall, the stent fracture rates for these dedicated stents from the IDE studies are encouraging. However, it is important to note that the evaluation of fracture resistance will need to be an ongoing process as more experience is gained with these stents over time. Stent migration is a pertinent adverse event in deep venous obstructive disease treatment. The causes of stent migration are multifactorial, including mismatch between stent, vein diameter, cephalad hemodynamic displacement forces, properties of the stent, and operator errors (24). Previous literature suggested a stent migration rate of 6%, but a recent meta-analysis of studies with dedicated venous stents reported a rate of 0.17% at 12 months (25). Among the IDE studies, VERNACULAR reported no stent migration through 3 years; 4 instances of stent migration were site-reported in VIRTUS through 3 years; and 1 clinical stent migration was reported in VIVO through 1 year. No stent migration was found in the ABRE study through 3 years. There were 3 all-cause deaths in this study. None were related to the device or the index procedure as adjudicated by the CEC. There were 12 confirmed stent thrombosis events in this study, 10 of which were in the PTS group. Stent thrombosis, an unfortunate but common, non–life-threatening sequela of stent placement in patients with PTS (26), was also the main driving cause of the 10.2% MAE rate reported in this 3-year follow-up study. Nonetheless, these results require further investigation to understand the etiology of stent thrombosis but point to the residual inflow disease and a need for improving PTS management understanding and guidelines. The occlusion rate in the PTS population has been similar in all IDE studies in what was a carefully screened patient population. This ultimately highlights that work is still needed to understand the etiology of stent failure and support efforts to maintain longer-term patency.

There were limitations in this study. First, this study was a single-arm study with no comparator arm. The primary assessments were hypothesis driven and statistically powered at 12 months; however, additional secondary analyses out to 3 years were observational only. The study follow-ups were significantly impacted by the COVID-19 pandemic: 31 and 10 participants did not have planned clinic follow-up due to COVID-19–related issues at 2 and 3 years, respectively. Given the impact to follow-up, if missing data at follow-up are not missing at random, estimates may be biased. Finally, the results of this study may not be generalizable to other venous stents owing to differences in the design and performance.

In conclusion, results from this prospective, core laboratory, and CEC-adjudicated study demonstrated sustained patency, low reintervention rates, no stent migration, or fracture, acceptable MAE rates, and improved QoL through

3 years after implantation of the Abre venous stent in patients with symptomatic iliofemoral venous obstructive disease.

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S.Bl. and E.M. are co-global principal investigators of this study.

*A complete list of investigators is available in **Table E1**. The collaborators are co-authors.

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APPENDIX A. LIST OF SUPPLEMENTARY FILES

I. Methods
II. References
III. Table E1. ABRE Study Site and Investigators
IV. Table E2. Medication Recommendations
V. Table E3. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in the Overall Cohort
VI. Table E4. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in Participants with Acute Deep Vein Thrombosis
VII. Table E5. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in Participants with Postthrombotic Syndrome
VIII. Table E6. Least Square Mean Differences Over Time from Repeated-Measures Model for Functional Outcomes in Participants with Nonthrombotic Iliac Vein lesions

METHODS

Key Outcomes Definitions

Device success: Assessed at the time of procedure, successful delivery, and deployment of the Abre stent in the target lesion with successful removal of the delivery system.

Lesion success: Assessed at the time of procedure, venographic evidence of <50% final residual stenosis of the stented segment of the target lesion after dilation, when applicable, and as assessed by core laboratory.

Procedure success: Lesion success without procedure-related major adverse events before hospital discharge within 30 days.

Note–If core laboratory was unable to assess the venographic evidence, site-reported data were used.

Clinically driven: Defined as the recurrence of symptoms present at baseline or the onset of new symptoms including but not limited to venous pain, swelling, dermatitis, or ulceration related to the target limb.

Major adverse events: A composite of the following:

- All-cause death occurring postprocedurally
- Clinically significant (ie, symptomatic, confirmed by computed tomography (CT) pulmonary angiography) pulmonary embolism
- Major bleeding adverse event (procedural for primary safety end point; postprocedural for secondary safety end point)
- Stent thrombosis confirmed by imaging as assessed by core laboratory
- Stent migration confirmed by imaging as assessed by core laboratory

Note–Migration excludes stent dislodgment at the index procedure as may occur with undersizing of a stent.

Major bleeding adverse event (procedural): A blood loss leading to transfusion of whole blood or red cells provided hemoglobin drop of 3 g/dL (1.86 mmol/L) or more is related to bleeding occurring during the index procedure through 30 days postindex procedure (1).

Major bleeding adverse event (postprocedural): A blood loss leading to transfusion of whole blood or red cells provided hemoglobin drop of 3 g/dL (1.86 mmol/L) or more is related to bleeding occurring at 30 days through 36 months postindex procedure (1).

Major bleeding adverse event related to index procedure: A blood loss leading to transfusion of whole blood or red cells provided hemoglobin drop of 3 g/dL (1.86 mmol/L) or more is related to bleeding occurring during the index procedure through 36 months postindex procedure (1).

Stent thrombosis: Occlusion of the stented venous segment occurring at any time after stent placement. Stent thrombosis may be diagnosed by Duplex ultrasound (US). It needs to be confirmed by venogram or intravascular US.

Stent migration: Stent migration (as part of primary safety and secondary major adverse event end points): position change of a properly sized venous stent observed with an imaging modality, with displacement of the stent outside of the intended treatment segment after the conclusion of the index procedure, as determined regarding a reference anatomic structure. Stent migration occurs following the proper deployment of a venous stent after the index procedure (ie, stent movement or dislodgment during the index procedure will not be noted as stent migration).

Delayed stent migration: Delayed stent migration within 12, 24, and 36 months was defined as position change of a stent with an imaging modality of >1 cm from its original location at the conclusion of the index procedure, as determined regarding a reference anatomic structure.

Primary patency: Freedom from occlusion of the stented segment of the target lesion, freedom from restenosis of ≥50% of the stented segment, and freedom from clinically driven target lesion revascularization

Primary-assisted patency: Uninterrupted patency of the stented segment of the target lesion with a secondary intervention, also known as an adjunctive treatment (eg, balloon venoplasty and subsequent stenting).

Secondary patency: Patency of the stented segment of the target lesion after subsequent intervention for an occlusion. Note–Confirmed by duplex US, evaluated by independent core laboratory. In cases where both duplex US and venography were used simultaneously, venography would be used for the primary assessment.

Target lesion: The target lesion is defined as nonmalignant venous obstruction within the common iliac, external iliac, and/or common femoral vein: the proximal point of the obstruction may extend to the iliac venous confluence of the inferior vena cava and the distal point may be at or above the deep femoral vein.

Target lesion revascularization: Any reintervention of the stented segment of the target lesion.

Stent fracture: Fracture or breakage of any portion of the stent.

Stent Fracture Classification: Determined by x-ray (assessed by core laboratory) as follows:

- Type 0—No strut fractures
- Type I—Single tine fracture
- Type II—Multiple tine fractures
- Type III—Stent fracture(s) with preserved alignment of the components
- Type IV—Stent fracture(s) with malalignment of the components
- Type V—Stent fracture(s) in a transaxial spiral configuration

Supplementary Statistics Methods

A repeated measures mixed model was analyzed for the VEINES-QoL/Sym, EQ-5D Index Score, Villalta score, and rVCSS using data available at baseline, 6-months, 12-monhts, 24-months, and 36-months. Correlation was enabled through the covariance matrix of the residuals and an unstructured covariance matrix was specified. The denominator degrees of freedom was computed using the method of Kenward and Roger.[2] An overall Type III F-statistic was computed to test the null hypothesis that the mean at all visits (including baseline) was equal. The overall test had a p-value less than 0.001, subsequently, the difference of the least square means were computed for comparing baseline to 6-, 12-, 24-, and 36-months, respectively. No adjustments were made for multiple comparisons and a significance level of 0.05 was used.

SUPPLEMENTARY REFERENCE

1. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123:2736–2747.
2. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983–997.

Table E1. ABRE Study Site and Investigators

Clinical site	Location	Principal investigator
Europe		
Hôpital Européen Georges-Pompidou	Paris, France	Marc Sapoval
Hôpital Nord Marseille	Marseille, France	Olivier Hartung
University Hospital RWTH Aachen	Aachen, Germany	Houman Jalaie
Klinikum Arnsberg	Arnsberg, Germany	Michael Lichtenberg
Galway University Hospital	Galway, Ireland	Gerard O'Sullivan
Hesperia Hospital	Modena, Italy	Marzia Lugli
St Thomas' Hospital	London, United Kingdom	Stephen Black
University College London	London, United Kingdom	Steve Bandula
United States		
Lake Washington Vascular	Bellevue, WA	Kathleen Gibson
Carolinas Medical Center	Charlotte, NC	Erin Murphy
Sentara Vascular Specialist	Norfolk, VA	David Dexter
OhioHealth Riverside Methodist Hospital	Columbus, OH	Raghu Kolluri
Saint Joseph Hospital	Orange, CA	Mahmood Razavi
North Carolina Heart and Vascular	Raleigh, NC	Dorian deFreitas
The Vascular Experts	Darien, CT	Paul Gagne
Piedmont Atlanta Hospital	Atlanta, GA	Charles Ross
Cardiac Center of Texas	McKinney, TX	M. Akram Khan
The Mount Sinai Hospital	New York, NY	Windsor Ting
Holy Name Medical Center	Teaneck, NJ	John Rundback
Stony Brook University Hospital	Stony Brook, NY	Antonios Gasparis
University of Michigan Health System	Ann Arbor, MI	David Williams
Albany Medical Center	Albany, NY	Jeffrey Hnath
NYU Langone Medical Center	New York, NY	Todd Berland
Mayo Clinic	Rochester, MN	Haraldur Bjarnason

Table E2. Medication Recommendations

Antithrombotics	
Preprocedure	Stop anticoagulation regimen prior to index procedure (ensure appropriate transition regimen)
Periprocedure	• Institute full anticoagulation before beginning the index procedure • Maintain anticoagulation during index procedure • Suggested regimen for chronic participants: ○ a heparin bolus of 5,000 units, after placement of the sheath in the access vessel; ○ followed by a bolus of 5,000 units or infusion of 100 U/kg to keep ACT > 200 s for full systemic anticoagulation
Postprocedure*	• Commence full anticoagulation within 4 h of completion of the index procedure • When using warfarin, an INR of >2.0 with appropriate bridging cover is recommended. DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) can be used instead of warfarin. • Suggested duration: ○ For chronic participant: anticoagulate for at least 12 mo ○ For nonthrombotic participant: anticoagulate for at least 6 mo
Antiplatelets	
Dual antiplatelet therapy, in addition to anticoagulation, should be carefully considered to minimize bleeding risks. If used, dual antiplatelet therapy should be limited to the first 6 weeks after the index procedure. After discontinuation of anticoagulation therapy, consider switching participants to antiplatelet therapy (if not currently ongoing)	

Note–Participants with acute deep vein thrombosis and postthrombotic syndrome recruited at the France site received oral anticoagulant along with clopidogrel at least for 6 mo postprocedurally as per local guidelines. However, participants with nonthrombotic iliac vein lesion received low-molecular-weight heparin along with clopidogrel for 3 wk after the procedure.
ACT, activated clotting time; DOAC, direct oral anticoagulants; INR, international normalized ratio.

Table E3. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in the Overall Cohort

Outcomes	Mean difference	95% CI bounds		*P*
		Lower	Upper	
Baseline to 6 mo				
rVCSS	−4.08	−4.60	−3.56	<.001
VEINES-symptoms	22.26	18.87	25.66	<.001
VEINES-QoL	22.16	18.55	25.77	<.001
Villalta score	−6.49	−7.27	−5.70	<.001
EQ-5D index score	0.15	0.12	0.19	<.001
Baseline to 12 mo				
rVCSS	−4.53	−5.13	−3.93	<.001
VEINES-symptoms	20.72	17.31	24.14	<.001
VEINES-QoL	22.75	19.20	26.31	<.001
Villalta score	−6.97	−7.74	−6.19	<.001
EQ-5D index score	0.14	0.10	0.17	<.001
Baseline to 24 mo				
rVCSS	−4.81	−5.47	−4.16	<.001
VEINES-symptoms	21.13	17.21	25.05	<.001
VEINES-QoL	22.32	18.27	26.38	<.001
Villalta score	−6.49	−7.37	−5.62	<.001
EQ-5D index score	0.12	0.08	0.16	<.001
Baseline to 36 mo				
rVCSS	−4.47	−5.05	−3.89	<.001
VEINES-symptoms	20.00	16.28	23.72	<.001
VEINES-QoL	20.79	17.08	24.50	<.001
Villalta score	−6.29	−7.07	−5.52	<.001
EQ-5D index score	0.13	0.09	0.16	<.001

EQ-5D = EuroQoL 5 Dimensions; rVCSS = Revised Venous Clinical Severity Score; VEINES-QoL = Venous Insufficiency Epidemiological and Economics Study Quality of Life.

Table E4. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in Participants with Acute Deep Vein Thrombosis

Outcomes	Mean difference	95% CI bounds		*P*
		Lower	Upper	
Baseline to 6 mo				
rVCSS	−5.80	−7.06	−4.54	<.0001
VEINES-symptoms	22.67	14.24	31.10	<.0001
VEINES-QoL	26.27	17.33	35.20	<.0001
Villalta score	−8.91	−10.81	−7.02	<.0001
EQ-5D index score	0.38	0.31	0.45	<.0001
Baseline to 12 mo				
rVCSS	−6.38	−7.82	−4.93	<.0001
VEINES-symptoms	21.71	13.28	30.14	<.0001
VEINES-QoL	27.30	18.56	36.04	<.0001
Villalta score	−9.27	−11.15	−7.39	<.0001
EQ-5D index score	0.39	0.31	0.47	<.0001
Baseline to 24 mo				
rVCSS	−6.60	−8.20	−4.99	<.0001
VEINES-symptoms	20.26	10.56	29.95	<.0001
VEINES-QoL	24.46	14.47	34.44	<.0001
Villalta score	−8.44	−10.59	−6.29	<.0001
EQ-5D index score	0.35	0.26	0.44	<.0001
Baseline to 36 mo				
rVCSS	−6.38	−7.77	−5.00	<.0001
VEINES-symptoms	19.21	10.18	28.24	<.0001
VEINES-QoL	24.42	15.43	33.40	<.0001
Villalta score	−8.56	−10.43	−6.69	<.0001
EQ-5D index score	0.36	0.28	0.44	<.0001

EQ-5D = EuroQoL 5 Dimensions; rVCSS = Revised Venous Clinical Severity Score; VEINES-QoL = Venous Insufficiency Epidemiological and Economics Study Quality of Life.

Table E5. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in Participants with Postthrombotic Syndrome

Outcomes	Mean difference	95% CI bounds		*P*
		Lower	Upper	
Baseline to 6 mo				
rVCSS	−3.42	−4.17	−2.69	<.0001
VEINES-symptoms	20.36	15.42	25.30	<.0001
VEINES-QoL	19.56	14.32	24.80	<.0001
Villalta score	−5.47	−6.58	−4.36	<.0001
EQ-5D index score	0.10	0.06	0.14	<.0001
Baseline to 12 mo				
rVCSS	−3.87	−4.72	−3.02	<.0001
VEINES-symptoms	18.59	13.62	23.56	<.0001
VEINES-QoL	19.85	14.70	25.00	<.0001
Villalta score	−6.08	−7.19	−4.97	<.0001
EQ-5D index score	0.07	0.02	0.11	.0061
Baseline to 24 mo				
rVCSS	−4.38	−5.32	−3.44	<.0001
VEINES-symptoms	19.38	13.66	25.09	<.0001
VEINES-QoL	18.79	12.91	24.67	<.0001
Villalta score	−5.59	−6.85	−4.32	<.0001
EQ-5D index score	0.05	−0.01	0.10	.0785
Baseline to 36 mo				
rVCSS	−4.28	−5.11	−3.46	<.0001
VEINES-symptoms	17.16	11.71	22.61	<.0001
VEINES-QoL	16.64	11.23	22.06	<.0001
Villalta score	−5.64	−6.75	−4.54	<.0001
EQ-5D index score	0.07	0.02	0.11	.0068

EQ-5D = EuroQoL 5 Dimensions; rVCSS = Revised Venous Clinical Severity Score; VEINES-QoL = Venous Insufficiency Epidemiological and Economics Study Quality of Life.

Table E6. Least Square Mean Differences over Time from Repeated-Measures Model for Functional Outcomes in Participants with Nonthrombotic Iliac Vein Lesions

Outcome	Mean difference	95% CI bounds		*P*
		Lower	Upper	
Baseline to 6 mo				
rVCSS	−4.16	−5.00	−3.31	<.0001
VEINES-symptoms	24.58	18.94	30.22	<.0001
VEINES-QoL	23.74	17.76	29.72	<.0001
Villalta score	−6.73	−8.01	−5.44	<.0001
EQ-5D index score	0.12	0.07	0.17	<.0001
Baseline to 12 mo				
rVCSS	−4.55	−5.53	−3.57	<.0001
VEINES-symptoms	23.05	17.37	28.74	<.0001
VEINES-QoL	24.50	18.60	30.39	<.0001
Villalta score	−7.07	−8.36	−5.79	<.0001
EQ-5D index score	0.11	0.05	0.16	.0001
Baseline to 24 mo				
rVCSS	−4.56	−5.65	−3.48	<.0001
VEINES-symptoms	23.78	17.26	30.30	<.0001
VEINES-QoL	25.92	19.21	32.63	<.0001
Villalta score	−6.80	−8.26	−5.34	<.0001
EQ-5D index score	0.12	0.06	0.18	.0002
Baseline to 36 mo				
rVCSS	−3.82	−4.77	−2.87	<.0001
VEINES-symptoms	23.95	17.79	30.11	<.0001
VEINES-QoL	24.46	18.34	30.58	<.0001
Villalta score	−6.10	−7.39	−4.82	<.0001
EQ-5D index score	0.11	0.05	0.16	.0002

EQ-5D = EuroQoL 5 Dimensions; rVCSS = Revised Venous Clinical Severity Score; VEINES-QoL = Venous Insufficiency Epidemiological and Economics Study Quality of Life.