



# Venovo venous stent for treatment of non-thrombotic or post-thrombotic iliac vein lesions – long-term efficacy and safety results from the Arnsberg venous registry

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**Summary:** *Background:* Endovascular venous stenting with dedicated venous stents for the treatment of chronic venous outflow obstruction is developing as efficacious alternative to conservative therapy or open surgery. However, so far, mid- and long-term evidence on effectiveness and safety is poor. *Patients and methods:* The prospective, single-center, observational study enrolled consecutive patients with chronic non-thrombotic iliac vein lesions (NIVL) or post-thrombotic iliofemoral obstructions (PTO). From February 2016 to April 2017, patients underwent implantation of open cell, self-expandable dedicated venous stents. Short-term symptomatic improvement, patency, and complication rate were favorable. Evaluation at 2-years included improvement in the revised venous clinical severity score (rVCSS), patency, stent migration, major target limb events, clinically important pulmonary embolism, major bleeding, and all-cause mortality. *Results:* A total of 79 patients (57 ± 16 years, 44 female) were evaluated. At 2 years, rVCSS improved by 4.3 ± 2.7 (p < 0.001). Substantial clinical improvement of ≥ 2 score points was achieved in 86.4% (38 of 44) of patients. Improvement was not associated with thrombotic pathogenesis (regression coefficient [B] with PTO = 0.6 [95%CI: -1.1 to 2.3], p = 0.48). At 2 years, all ulcers (in 8 of 79 patients) were healed and none recurred. Two-year primary patency was 95.5% (95%CI: 86.5 to 98.5) with no difference between NIVL- and PTO-patients (log-rank p = 0.83). Target vessel revascularization was conducted in two PTO- and one NIVL-patients in the period of 34 days to 156 days from index procedure, resulting in a secondary patency of 100%. No stent migration, target limb deep vein thrombosis, major amputation, pulmonary embolism, or death occurred. *Conclusions:* Venovo venous open cell self-expanding stent implantation for chronic outflow obstruction was efficacious and provided a sufficient level of safety throughout 2 years.

**Keywords:** chronic venous disease, endovascular procedures, post-thrombotic syndrome, stents, venous thrombosis

## Introduction

Endovascular stenting with dedicated venous stents of iliofemoral venous outflow obstruction has emerged as efficacious and minimally invasive alternative to standard conservative or open surgical treatment. However, evidence of mid-term effectiveness and safety is poor [1].

Earlier studies reported on considerable symptomatic improvement. Revised venous clinical severity score (rVCSS) decreased from 8 to 2 on average within 21 months [2]. The 2-year ulcer healing rate after endovascular repair was given with 78–100% and primary patency after

stenting with 65–67% [3–5]. However, venous outflow obstructions are supposed to have specific requirements for stent properties including compression resistance, flexibility and exact positioning capability. A recent study on dedicated venous stents revealed a 2-year primary patency of 72% [6].

Ilio-femoral venous outflow obstruction may present as post-thrombotic obstruction (PTO) resulting from deep vein thrombosis (DVT) or as non-thrombotic iliac vein lesion (NIVL) emerging from extrinsic compression such as May-Thurner syndrome. Previous studies found a non-significant tendency of lower primary patency rates in

PTO- than in NIVL-patients [6–8]. Even venous stents showed a somewhat lower primary patency in PTOs of 51% at 2 years (total occlusions) [9] and 68% at 3 years [10].

Different venous stents brands distinguish in material and design and thus, may differ in effectiveness. The prospective Arnsberg venous registry on the VENOVO<sup>®</sup> venous self-expanding, open cell nitinol stent (BARD Peripheral Vascular, Inc., Tempe, AZ, USA) showed primary patency in 97% of NIVL- and in 96% of PTO-patients and led to substantial clinical improvement in 51% of all patients at 6 months [11]. Our purpose was to assess to what extent symptomatic improvement and patency in the Arnsberg venous registry patients sustained throughout 2 years and whether any safety signals will occur over the mid-term.

## Patients and methods

### Study design

The observational, single-center registry to assess effectiveness and safety of the VENOVO<sup>®</sup> venous stent system in iliofemoral venous outflow obstruction was approved by the Westfalen-Lippe Medical Chamber and the Wilhelms-University ethics committee, Münster, Germany (AZ 2017-382-f-S). The study complies with the Declaration of Helsinki. Patients were included in the registry from February 2016 to April 2017. Clinical follow-up including duplex ultrasonography (DUS) was performed at 30 days, 6, 12, and 24 months after index procedure. Results on clinical presentation, patency up to 6 months, as well as procedure-related complications have been reported earlier [11].

### Patients and procedure

Consecutive patients over 18 years of age with symptomatic, non-malignant, chronic, non-thrombotic iliac vein lesions (NIVL) or post-thrombotic venous obstruction (PTO), were eligible. We excluded patients with previous venous stent implantation and those with extension of the lesion into the inferior vena cava. Venous iliofemoral outflow obstruction was confirmed by DUS, computed tomography venography, and magnetic resonance venography. The study device consisted of the dedicated venous VENOVO<sup>®</sup> self-expanding nitinol stent with open cell design, pre-mounted on a delivery system. Detailed description of device and procedure had been provided earlier [11]. Venous access was achieved under ultrasound guidance. Examination of lesion properties was conducted using digital subtraction venography and intravascular ultrasound (IVUS). Venous stents were implanted according to manufacturer's instruction for use. Pre- and post-dilation were mandatory. Patients received 5000 IU heparin at the time of procedure. Subsequently, anticoagulation therapy with vitamin K antagonists or novel oral

anticoagulants was prescribed for at least 6 and 12 months in NIVL- and PTO-patients, respectively. Patients with recurrent DVT in the past remained on anticoagulation indefinitely.

### Study outcome measures

Clinical improvement at 2 years was assessed on the basis of change in rVCSS and CEAP (clinical findings, etiological factors, anatomical cause, pathophysiological cause) clinical class. In patients with bilateral disease, rVCSS did not differ between limbs at every follow-up and thus, was included in analyses only once per patient. Primary patency referred to cumulative incidence of patients with modulated flow through the stent lumen and absence of > 50% diameter obstruction as measured by DUS without prior surgical or percutaneous revascularization of the target vessel. Secondary patency applied in patients without permanent loss of patency irrespective of any interventions after the index procedure. Safety outcome measures at 2 years were target vessel revascularization (TVR) defined as any clinically driven surgical or percutaneous revascularization of the target vessel, target limb deep vein thrombosis (DVT), clinically relevant pulmonary embolism, major bleeding, major target limb amputation, and mortality.

### Statistics

Categorical variables are given as counts and percentages and continuous variables as means and standard deviations (SD). Differences were assessed with Mann-Whitney U test, Wilcoxon signed-rank test, Fisher's exact test, or chi-square test. Linear regression and analysis of variance were used for univariable analysis. Kaplan-Meier analysis was performed to estimate primary patency. Survival functions were compared by log-rank test. A 2-sided value of  $p < 0.05$  was considered as statistically significant. Statistical analysis was performed using SPSS Statistics (Version 22.0. IBM, Armonk, NY, USA).

## Results

### Study population and treatment

A total of 79 patients (29 NIVL with May-Thurner syndrome, 50 PTO) who underwent implantation of VENOVO<sup>®</sup> venous stents for the treatment of iliofemoral NIVL or PTO were included in the single center Arnsberg venous registry (56% female, aged  $57 \pm 16$  years). Two-year follow-up ( $708 \pm 112$  days) was completed in 55.7% patients (44 [22 NIVL, 22 PTO] of 79), (ESM 1, Table). Half of all patients had hypertension (51%) and a clinical history of deep vein thrombosis (47%). Seventeen percent of patients were current or former smokers and 14% had diabetes. PTO-patients were older and more frequently affected by chronic renal failure or preceding cancer than NIVL-patients. In addition, at baseline, both rVCSS and clinical

**Table 1.** Baseline patient and procedure characteristics

Characteristics	Overall (n = 79)	NIVL (n = 29)	PTO (n = 50)	P-Value
Patients				
Age, years	57 ± 16	50 ± 15	61 ± 16	p = 0.001
Gender, female	44 (56)	14 (48)	30 (60)	p = 0.18
Smoking (current and former), n = 78	13 (17)	6 (21)	7 (14)	p = 0.53
Diabetes	11 (14)	4 (14)	7 (14)	p > 0.99
Hypertension	40 (51)	13 (45)	27 (54)	p = 0.49
Chronic renal failure	6 (8)	0 (0)	6 (12)	p < 0.003
Previous DVT (iliofemoral/femoropopliteal)	37 (47)	12 (41)	25 (50)	p = 0.49
Previous cancer	9 (11)	1 (3)	8 (16)	p = 0.03
Previous CVD event	4 (5)	0 (0)	4 (8)	p > 0.99
Previous PE	7 (9)	1 (3)	6 (12)	p = 0.25
Proximal target vessel				p = 0.21
CIV	71 (90)	27 (93)	44 (88)	
EIV	7 (9)	1 (3)	6 (12)	
CFV	1 (1)	1 (3)	0 (0)	
Target vessel, n <sub>o</sub> /limb				p = 0.002
1	32 (41)	19 (66)	13 (26)	
2	33 (42)	6 (21)	27 (54)	
3	14 (18)	4 (14)	10 (20)	
Left limb affected	55 (70)	27 (93)	28 (56)	p < 0.001
Bilateral venous disease	6 (8)	2 (7)	4 (8)	p > 0.99
Total occlusion	17 (22)	4 (14)	13 (26)	p = 0.26
Active ulcer	8 (10)	1 (3)	7 (14)	p = 0.25
rVCSS	9.1 ± 4.2	7.7 ± 2.7	9.8 ± 4.6	p = 0.02
≥ 8	39 (49)	8 (28)	31 (62)	p = 0.01
CEAP (clinical class)	3.5 ± 0.8	3.2 ± 0.6	3.6 ± 0.9	p = 0.03
≥ C5	8 (10)	1 (3)	7 (14)	p = 0.25
Procedure				
Total stented length, mm	144 ± 91	131 ± 95	151 ± 89	p = 0.15
Stent extension into CFV	21 (27)	6 (21)	13 (26)	p = 0.79
Stents, n <sub>o</sub> /limb				p = 0.78
1	55 (70)	21 (72)	34 (68)	
2	22 (28)	8 (28)	14 (28)	
3	2 (3)	0 (0)	2 (4)	

Data presented as counts (percentage) or mean ± standard deviation. CEAP: comprehensive classification system for chronic venous disease; CIV: common iliac vein; EIV: external iliac vein; CFV: common femoral vein; CVS: cardiovascular disease; NIVL: non thrombotic iliac vein lesion; DVT: deep vein thrombosis; deep PE: pulmonary embolism; PTO: post-thrombotic venous obstruction; rVCSS: revised venous clinical severity score.

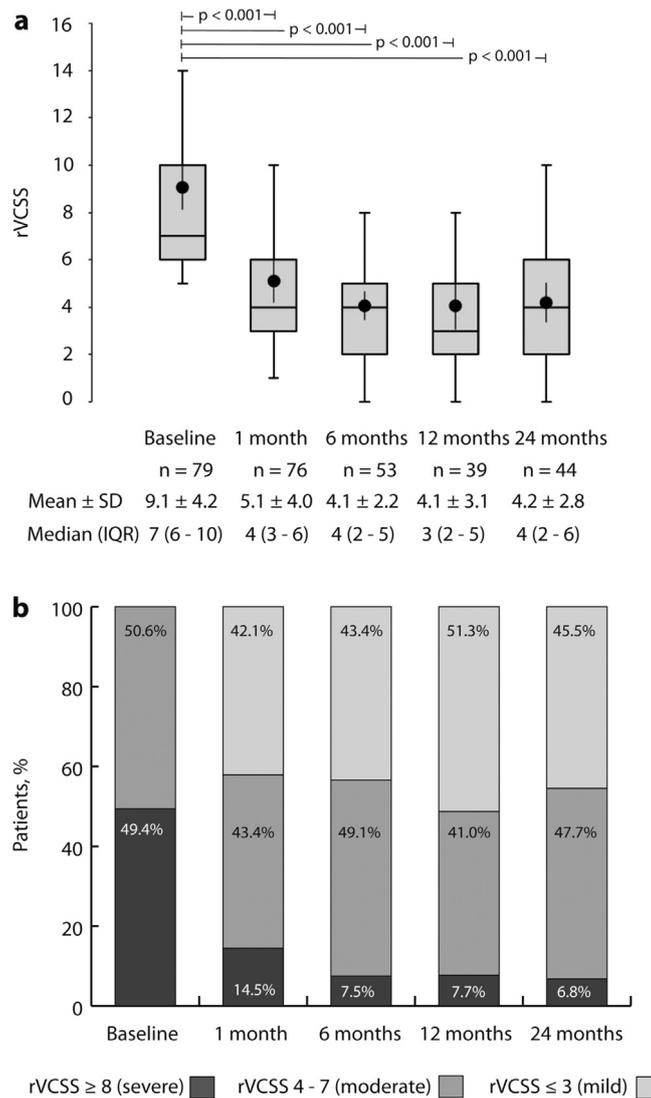
CEAP class was higher in PTO than in NIVL-patients. Pain and venous edema were present in all, and varicose veins in 99% of patients. Almost all patients (99%) were treated with compression therapy. Skin pigmentation, inflammation, induration, and active ulcer occurred in 21%, 20%, 16%, and 10% of patients, respectively. In 18% of patients all three vessels, CIV, EIV, and CFV were affected. A total of 1.4 stents comprising a total stented length of 144 ± 91 mm were implanted per patient (Table 1).

## Clinical improvement

Revised VCSS improved from 9.1 ± 4.2 at baseline to 4.2 ± 2.8 at 2 years (decrease by 4.3 ± 2.7, p < 0.001). Proportion of patients with severe symptoms (rVCSS ≥ 8) decreased

from 49.4% to 6.8% (p < 0.001), (Figure 1). Substantial clinical improvement in rVCSS by ≥ 2 points occurred in 86.4% (38 of 44 patients; NIVL: 91% [20 of 22], PTO: 82% [18 of 22], p = 0.38). Clinical CEAP class improved from 3.4 ± 0.8 at baseline to 3.0 ± 1.0 at 2 years (decrease by 0.5 ± 0.7, p = 0.001). Improvement of varicose veins, venous edema, and induration was somewhat greater in NIVL- than in PTO-patients (Figure 2). At baseline, venous ulcers were present in 8 patients (1 NIVL and 7 PTO-patients). None of the ulcers persisted until the 2-year follow-up.

Linear regression neither revealed an association of decrease in rVCSS with thrombotic pathogenesis (regression coefficient [B] for PTO vs. NIVL: 0.6 [95%CI: -1.1 to 2.3], p = 0.48) nor with total stented length (B coefficient per 10 mm: -0.09 [95%CI: -0.2 to 0.02], p = 0.10) or total



**Figure 1.** Improvement in rVCSS (a) and rVCSS distribution (b) at baseline and follow-ups. rVCSS: revised venous clinical severity score.

occlusion ( $-1.7$  [95%CI:  $-3.7$  to  $0.2$ ],  $p = 0.08$ ). In contrast, number of stents per limb was associated with improvement, and increasing age with deterioration of rVCSS (B coefficient:  $-2.7$  in case of more than 1 stent [95%CI:  $-4.3$  to  $-1.1$ ,  $p = 0.002$ ] and  $0.7$  per 10 years of age [95%CI:  $0.1$  to  $1.3$ ,  $p = 0.02$ ], respectively). In addition, diabetes and a clinical history of cancer tended to increase the rVCSS (B coefficient vs. no diabetes  $2.0$  [95%CI:  $-0.3$  to  $4.4$ ,  $p = 0.09$ ], and vs. no cancer  $2.8$  [95%CI:  $-0.04$  to  $5.5$ ,  $p = 0.05$ ], respectively).

## Primary patency

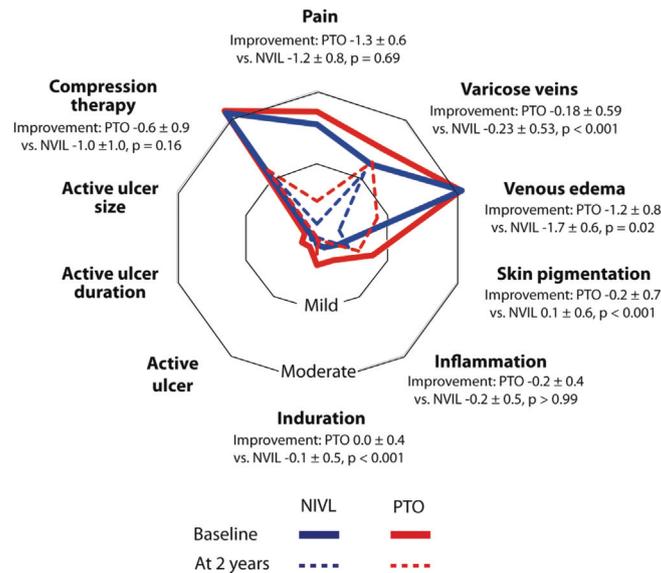
At 2 years, primary patency was 95.5% (95%CI: 86.5 to 98.5). Restenosis ( $> 50\%$  diameter stenosis by DUS) occurred in 2 PTO-patients (at 34 and 59 days) and in one NIVL-patient (at 156 days). Primary patency did not differ between groups (NIVL: 95.5% [SE 3.9], PTO: 96.0% [SE 3.1], log-rank  $p = 0.83$ ), (Figure 3). After TVR in 2 PTO and 1 NIVL patients, secondary patency was 100%.

## Safety

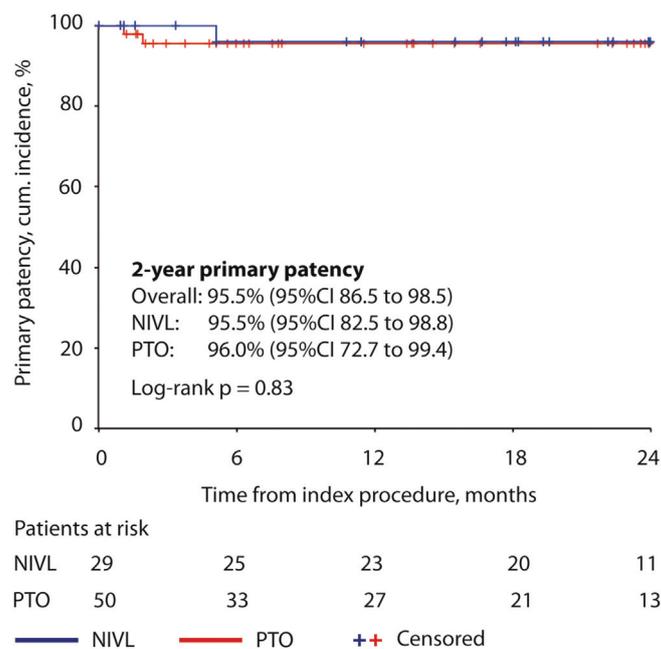
Procedure related complications were reported previously [11]. These were four access site complications with minor hematomas, and one infection. Two PTO-patients who experienced thrombotic stent-occlusion at 34 and 59 days were treated with endovascular mechanical thrombectomy and stent-in-stent implantation. Restenosis in a NIVL-patient at 156 days that went along with target limb pain and edema was resolved by repeat angioplasty. No stent migration, clinically important pulmonary embolism, or target limb DVT occurred and none of the patients underwent major target limb amputation or died within 2 years after stent implantation.

## Discussion

The Arnsberg venous registry revealed a favorable 2-year primary patency after implantation of an open cell, self-expanding nitinol stent (VENOVO<sup>®</sup> venous stent) both in



**Figure 2.** Radar chart on symptom severity following the revised venous clinical severity score (rVCSS; severity 0: none, 2: moderate). Average improvement in every category was compared between NIVL- and PTO-patients. Continuous lines indicate baseline- and dashed lines 2-year data. Blue lines denote NIVL- and red lines PTO patients. NIVL: non-thrombotic iliac vein lesions; PTO: post-thrombotic venous obstruction.



**Figure 3.** Kaplan-Meier estimate of 2-year primary patency after venous stent implantation for treatment of non-thrombotic or thrombotic venous obstruction. NIVL: non-thrombotic iliac vein lesions; PTO: post-thrombotic venous obstruction.

non-thrombotic and post-thrombotic venous obstruction. Risk of major adverse events was low. Substantial improvement of clinical symptoms (decrease of VCSS by  $\geq 2$  points) sustained throughout 2 years in the majority of patients. Neither primary patency nor symptomatic improvement differed considerably between NIVL- and PTO-patients. Increasing age, diabetes, and a clinical history of cancer were associated with less and the number of stents with greater symptomatic improvement.

Although, 2 of 3 re-occlusions in our study occurred in PTO-patients, 2-year primary patency did not differ from that of NIVL-patients. Overall, 2-year patency was higher

and symptomatic improvement greater than previously reported after dedicated venous stent [6]. This might be due to different stent properties (open versus closed design), or due to different patient and lesion characteristics (including inflow differences), particularly regarding the share of PTO-patients. Duration of anticoagulant medication and compression treatment after stenting also might have contributed to different outcomes across studies. In only about one quarter of our patients, stents extended into the CFV. However, there is still controversy whether stent site below the inguinal ligament increases the risk of restenosis [1].

Adverse effect of thrombotic pathogenesis on thrombotic events after stenting is supported by an earlier meta-analysis of 14 studies on dedicated venous stents [12]. Additionally, another study on PTO-patients that entailed indefinite anticoagulation reported on considerably lower primary and secondary patency rates compared to our study (51% and 82%, respectively) [9]. However, in contrast to our study, decision on reintervention in the later study initially was taken independently of clinical symptoms. Although a previous long-term evaluation revealed events of late restenosis in the period between 24 and 48 months after the index procedure [13], loss of patency most frequently was reported within the first 6 months from the index procedure [6, 9, 13].

In our study, improvement of venous edema was greater in NIVL- than in PTO-patients. This might have been due to persistent valvular insufficiency despite stenting in chronically thrombotic disease.

Results of the Arnsberg venous registry on successful ulcer healing after stenting were in line with earlier reports [1, 6, 10]. Yin et al. found a significantly improved recurrence free ulcer healing rate after stenting compared to conservative treatment [14]. The rate of ulcer healing after venous stenting is reported with 72% and the recurrence rate with 9% [12].

According to published studies, perioperative complications with venous stenting are rare [12, 15, 16]. Our study also did not give rise to concerns regarding safety.

## Limitations

Our study has several limitations. First of all, only 55.7% of patients completed the 2-year follow-up. Whether results would have applied for the total study cohort remains uncertain. In addition, we did not include a control group. Thus, treatment effect cannot be clearly attributed to stenting alone. Since no direct comparison was conducted, our study does not allow for conclusion on comparative effectiveness of venous stents. Furthermore, results on NIVL- and PTO-patients were based on a non-randomized comparison. As was to be expected, baseline condition of PTO patients was worse than that of NIVL-patients. However, separate consideration of disease presentation can be meaningful for clinical implementation of venous stenting. Finally, we neither assessed Villalta score in PTO-patients nor quality of life.

## Conclusions

In conclusion, our study revealed that implantation of VENOVO<sup>®</sup> venous stents for the treatment of venous outflow obstructions was efficacious regarding symptomatic improvement in the medium term in both NIVL- and PTO patients. Primary and secondary patency sustained

from 6 months to 24 months after index procedure. Except from an increased risk of bleeding due to anticoagulant medication, no safety signal occurred.

## Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at <https://doi.org/10.1024/0301-1526/a000893>

**ESM 1.** Baseline and procedure characteristics of patients who completed the 2-year follow-up (Table).

## References

1. Seager MJ, Busuttill A, Dharmarajah B, Davies AH. Editor's Choice – A systematic review of endovenous stenting in chronic venous disease secondary to iliac vein obstruction. *Eur J Vasc Endovasc Surg.* 2016;51(1):100–20.
2. Blanch Alerany M, Izquierdo Lamoca LM, Ramirez Ortega M, Lago Rivas I, Zotta Desboeufs R, Stefanov Kiuri S. Endovascular treatment of iliofemoral chronic post-thrombotic venous flow obstruction. *J Vasc Surg Venous Lymphat Disord.* 2014; 2(1):2–7.
3. Kolbel T, Lindh M, Akesson M, Wasselius J, Gottsater A, Ivancev K. Chronic iliac vein occlusion: Midterm results of endovascular recanalization. *J Endovasc Ther.* 2009;16(4): 483–91.
4. Raju S, Ward M Jr, Kirk O. A modification of iliac vein stent technique. *Ann Vasc Surg.* 2014;28(6):1485–92.
5. Catarinella FS, Nieman FH, De Wolf MA, Toonder IM, De Graaf R, Wittens CH. Quality-of-life in interventional treated patients with post-thrombotic syndrome. *Phlebology.* 2015; 30(Suppl 1):89–94.
6. Stuck AK, Reich T, Engelberger RP, Sebastian T, Kucher N. Endovascular treatment of post-thrombotic and non-thrombotic iliofemoral venous outflow obstructions with self-expanding nitinol stents. *Vasa.* 2018;47(4):319–25.
7. De Wolf MAF, Arnoldussen CW, Grommes J, Hsien SG, Nelemans PJ, De Haan MW, et al. Minimally invasive treatment of chronic iliofemoral venous occlusive disease. *J Vasc Surg Venous Lymphat Disord.* 2013;1(2):146–53.
8. Liu Z, Gao N, Shen L, Yang J, Zhu Y, Li Z, et al. Endovascular treatment for symptomatic iliac vein compression syndrome: A prospective consecutive series of 48 patients. *Ann Vasc Surg.* 2014;28(3):695–704.
9. Black S, Gwozdz A, Karunanithy N, Silickas J, Breen K, Hunt B, et al. Two year outcome after chronic iliac vein occlusion recanalisation using the Vici Venous Stent(R). *Eur J Vasc Endovasc Surg.* 2018;56(5):710–8.
10. Qiu P, Zha B, Xu A, Wang W, Zhan Y, Zhu X, et al. Systematic review and meta-analysis of iliofemoral stenting for post-thrombotic syndrome. *Eur J Vasc Endovasc Surg.* 2019;57(3): 407–16.
11. Lichtenberg MKW, De Graaf R, Stahlhoff WF, Ozkapi A, Rassaf T, Breuckmann F. Venovo venous stent in the treatment of non-thrombotic or post-thrombotic iliac vein lesions – Short-term results from the Arnsberg venous registry. *Vasa.* 2019;48(2): 175–80.
12. Wen-da W, Yu Z, Yue-Xin C. Stenting for chronic obstructive venous disease: A current comprehensive meta-analysis and systematic review. *Phlebology.* 2016;31(6):376–89.
13. Ignatyev IM, Pokrovsky A, Gradusov E. Long-term results of endovascular treatment of chronic iliofemoral venous obstructive lesions. *Vasc Endovascular Surg.* 2019;53(5): 373–8.

14. Yin M, Shi H, Ye K, Lu X, Li W, Huang X, et al. Clinical assessment of endovascular stenting compared with compression therapy alone in post-thrombotic patients with iliofemoral obstruction. *Eur J Vasc Endovasc Surg.* 2015; 50(1):101–7.
15. Razavi MK, Jaff MR, Miller LE. Safety and effectiveness of stent placement for iliofemoral venous outflow obstruction: Systematic review and meta-analysis. *Circ Cardiovasc Interv.* 2015;8(10):e002772.
16. Lichtenberg M, Breuckmann F, Stahlhoff WF, Neglén P, Rick G. Placement of closed-cell designed venous stents in a mixed cohort of patients with chronic venous outflow obstructions – Short-term safety, patency, and clinical outcomes. *Vasa.* 2018;47(6):475–81.

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#### Conflicts of interests

Michael K. W. Lichtenberg and Rick de Graaf received speaker honoraria from BD Bard, the manufacturer of the Venovo venous stent.

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