Stenting of the venous outflow in chronic venous disease: Long-term stent-related outcome, clinical, and hemodynamic result

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Background: **Stenting of chronic nonmalignant obstruction in the venous outflow tract started in earnest in 1997. Data sets are now available to perform long-term analysis of stent-related outcome and clinical and hemodynamic results of this intervention.**
Materials: **From 1997 to 2005, 982 chronic nonmalignant obstructive lesions of the femoroiliocaval vein were stented under intravascular ultrasound guidance. Median patient age was 54 years (range, 14 to 90 years), the female/male was 2.6:1, and left/right limb symptoms, 2.4:1. Clinical score of CEAP was 2 in 7%, 3 in 47%, 4 in 24%, 5 in 5%, and 6 in 17%; primary/secondary etiology was 518:464. Stent-related outcome (morbidity, thrombotic events, patency, in-stent recurrent stenosis), clinical outcome, quality of life (QOL) as assessed by the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ), and hemodynamics were evaluated before and after intervention.**
Result: **Monitoring for 94% of patients lasted a mean 22 months (range, 1 to 107 months). Stenting was performed with no mortality (<30 days) and low morbidity. Thrombotic events were rare (1.5%) during the postoperative period (<30 days) and during later follow-up (3%). At 72 months, primary, assisted-primary, and secondary cumulative patency rates were 79%, 100%, and 100% in nonthrombotic disease and 57%, 80%, and 86% in thrombotic disease, respectively. Cumulative rate of severe in-stent restenosis (>50%) occurred in 5% of limbs at 72 months (10% in thrombotic limbs, 1% in nonthrombotic limbs). The main risk factors associated with stent occlusion were the presence and severity of thrombotic disease; thrombophilia by itself was not a risk factor. The median pain score and degree of swelling decreased significantly poststent. Severe leg pain (visual analogue scale >5) and leg swelling (grade 3) decreased from 54% and 44% prestent to 11% and 18% poststent, respectively. At 5 years, cumulative rates of complete relief of pain and swelling were 62% and 32%, respectively, and ulcer healing was 58%. The mean CIVIQ scores of QOL improved significantly in all categories. Mean hand-foot pressure differential decreased and mean ambulatory venous pressure improved in stented limbs with no concomitant reflux. The hemodynamic response was modified, depending on the presence of deep and superficial reflux in subsets of patients with adjunct saphenous procedures. No increase in venous reflux was observed.**
Conclusions: **Venous stenting can be performed with low morbidity and mortality, long-term high patency rate, and a low rate of in-stent restenosis. It resulted in major symptom relief in patients with chronic venous disease, which was not consistently reflected in any substantial hemodynamic improvement by conventional measurements. The beneficial clinical outcome occurred regardless of presence of remaining reflux, adjunct saphenous procedures, or etiology of obstruction. (J Vasc Surg 2007;46:979-90.)**

Venous outflow obstruction plays an important role in the clinical expression of chronic venous disease.[1] The combination of reflux and obstruction gives the highest levels of venous hypertension and the most severe symptoms compared with either alone.[2,3] Chronic obstruction of the iliac vein, which is the common outflow tract of the lower limb, results in severe symptoms because of poor compensation by collateral formation.[4,5] Only 20% to 30% of thrombosed iliac veins treated by anticoagulation alone completely recanalize. Five years later, the remaining obstruction results in venous claudication in 44% and venous ulcer in 15% of patients.[6,7] The recanalization process appears to be worse in the presence of an external compression, which has been reported in 80% of limbs with an acute iliofemoral deep vein thrombosis (DVT).[8,9]

The existence of iliac vein compressions and intraluminal webs is in itself more pathogenic than previously thought because they were considered a common finding of little clinical importance. This nonthrombotic iliac vein lesion (NIVL) is found as often as post-thrombotic obstruction in chronic venous disease involving the iliofemoral venous segment. It may occur in both the right and left lower limbs in both sexes at all ages and involve both the common and the external iliac veins. It is a major component of symptomatic primary disease.[10]

Percutaneous endovenous stenting has emerged during the last decade as the method of choice to treat femoroiliocaval venous outflow obstruction due to chronic venous disease. It has replaced bypass surgery as the primary treatment. Stents have also been placed to

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relieve obstruction revealed after removal of acute iliofemoral thrombus or caused by malignant tumors or retroperitoneal thrombosis.[8,9,11,12]

Because the long-term outcome of the stenting procedure is related to the underlying etiology and the clinical situation, this study is limited to assess treatment in patients with chronic, nonmalignant obstructions. Stent placement started in earnest in our institution in 1997, and this experience has formed the basis for several reports on various aspects of venous stenting.[13-18] Data sets are now available to perform long-term analysis of this group of patients; thus, the aim of this study is to evaluate procedure and long-term stent-related outcome, clinical outcome, and hemodynamic before and after results.

MATERIAL AND METHODS

From February 1997 to April 2005, 982 consecutive chronic nonmalignant obstructive lesions of the femoroiliocaval vein were treated in 870 patients. Limbs treated by thrombolysis before stenting are excluded. A time-stamped electronic medical records program for patients with venous disease was specifically constructed to prospectively collect comprehensive standardized information on symptoms and physical findings in patients with venous disease.

The limbs were classified using the CEAP classification according to the Reporting Standards of International Society of Cardiovascular Surgery (ISCS)/Society for Vascular Surgery (SVS).[19,20] The obstructive lesion was considered thrombotic when the patient had a known history of previous DVT or when post-thrombotic changes in the lower extremity were found on venogram, or duplex or intravascular ultrasound imaging (IVUS).

The following evaluations were performed before and after the intervention: ascending and transfemoral antegrade venography,[21,22] duplex Doppler study with standardized compression,[23,24] ambulatory dorsal foot venous pressure measurements, arm/foot pressure differential and dorsal foot venous hyperemia-induced pressure increase,[25] and air plethysmography (APG-1000; ACI Medical Inc, Sun Valley, Calif).[26] For a detailed description of the supporting studies see Appendix Table EI (online only). Thrombophilia testing was performed in 683 patients, including levels of proteins C and S, antithrombin III, anticardiolipins immunoglobulin (Ig) M and IgG, and homocysteine, and the presence of lupus anticoagulant, factor V Leiden, homocysteine gene, and prothrombin gene mutation.

Intervention. The diagnosis of obstruction, indications for iliofemoral stenting, technical details of endovenous stenting, and perioperative anticoagulation treatment have been described previously.[13,15,16,27] An ultrasound-guided access to the femoral vein was obtained and a sheath was inserted below the obstruction in symptomatic patients with suspicion of obstruction. After transfemoral venography, IVUS imaging was performed. The crosscut area of the stenosis was measured by IVUS and compared with the area of the normal vein below the stenosis, providing the percentage of stenosis. Stents were placed in limbs shown to have >50% morphologic stenosis by IVUS imaging. The transverse lumen area was obtained by IVUS imaging during the intervention before and after stenting.

The partially obstructed segment was balloon-dilated and stented under IVUS guidance to ensure that the entire lesion was covered (Figs 1 and 2). Occluded post-thrombotic veins required guidewire recanalization before stenting. Wallstents (Boston Scientific, Natick, Mass) were placed in 963 limbs (98%), and 19 limbs (2%) had nitinol stents placed. Stenting of a stenosis adjacent to the confluence of the common iliac veins using Wallstents required that the stent be placed well into the inferior vena cava (IVC) to avoid early restenosis. When two or more stents were inserted, the stents were overlapped by at least 1 cm to ensure adequate stent cover of the diseased vein without skipped areas. Procedure details were collected in a specifically designed database. The stenting was combined with procedures controlling superficial venous reflux (great saphenous vein [GSV] ablation/small saphenous vein [SSV] stripping/stab avulsions) in the same session in 197 limbs (see Appendix Table EII for details, online only). Compression and local ulcer therapy in use preoperatively was continued after intervention until healing. Prolonged use of the compression regimen was generally not encouraged because many considered it a quality-of-life issue. Noncompliant patients were not fitted with new stockings.

Follow-up. Clinical follow-up for treated limbs was at 6 weeks, 3 months, 9 months, and then annually. The study end point of legs with stasis ulceration was complete epithelialization. Primary nonhealing ulcers were marked as such and censored at 3 months. Any breakdown of an ulcer after healing was considered a recurrence. The degree of pain was evaluated perioperatively using a visual analog scale (VAS) from 0 to 10, wherein 10 is the most severe pain.[28] Swelling was assessed according to reporting standards as grade 0, absent; grade 1, pitting, not obvious; grade 2, visible ankle edema; and grade 3, massive, encompassing the entire leg. Patients were asked to complete the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) assessing subjective pain, sleep disturbance, morale and social activities, and routine and strenuous physical activities prospectively before intervention and again at each postoperative visit. The CIVIQ form has a proven specificity and relevance to chronic venous disease.[29] The last available response was used in postoperative outcome analysis. Venous function studies were repeated on follow-up.

The degree of in-stent restenosis and patency was assessed by an antegrade transfemoral venogram. In-stent restenosis, if present, was assessed as the percentage diameter reduction of the patent lumen of the stent. An ascending venogram through a dorsal foot vein and duplex ultrasound imaging was also used to evaluate stent patency but not in-stent restenosis. The investigations were performed at 2 to 3 months, 9 months, and then annually after stenting.

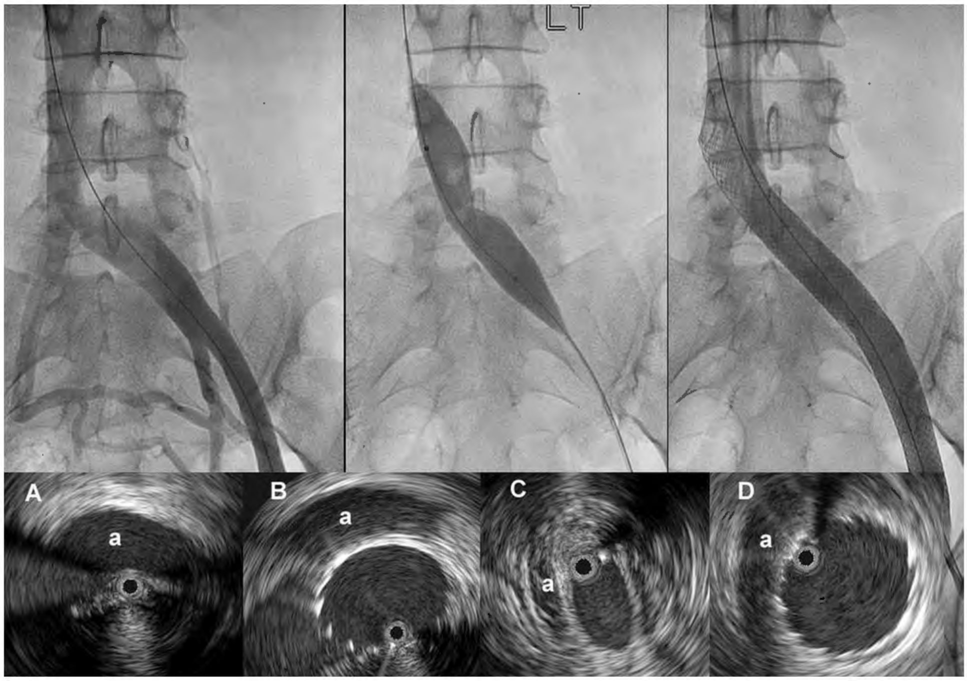

Fig 1. Left panel, Transfemoral venogram shows a typical nonthrombotic iliac vein lesion (NIVL) with prestent translucency at the vessel-crossing and transpelvic collaterals. **A and B,** Inserts show corresponding intravascular ultrasound (IVUS) image of the left panel before and after stenting. **Middle panel,** Waisting of balloon during inflation by the stenosis at predilation before stent placement. **Right panel,** A venogram after stenting shows no stenosis or collaterals. Note that the Wallstent is placed well into the inferior vena cava to prevent retrograde migration. The stent is carried into the external iliac vein because a significant stenosis was found on IVUS at the external and internal iliac vein confluence. **C and D,** Inserts show before and after stenting IVUS. (*a,* artery; the *black circle* within the vein is the IVUS catheter.)

Statistical analysis. Individual data are given as median with range or mean ± SD, unless otherwise indicated. Continuous variables were analyzed by *t* test or nonparametric Wilcoxon rank test for paired and unpaired data, depending on skewness, and the Fisher exact test for categoric variables. Primary, assisted primary (patency after preemptive intervention), and secondary patency (patency after intervention for occlusion) rates as defined by the reporting standards of the ISCVS/SVS[19] were calculated using survival analysis with the Kaplan-Meier method. Cumulative survival analysis was also used to analyze and compare recurrence of pain, swelling, and ulcer after the treatment. The log-rank test was used to compare cumulative curves Commercially available statistical programs Graph Pad Prism 3.0 (GraphPad Software, San Diego, Calif) and SAS 9.1 (SAS Institute, Inc, Cary, NC) were used for analysis. Results are reported using *P* values and either effect or odds ratio for continuous and categoric variables, respectively. A $P < .05$ was considered significant.

RESULTS

This study includes 982 limbs in 870 patients, of whom 112 patients (13%) had bilateral treatment with stents for obstruction of the femoroiliocaval vein. Median age was 54 years (range, 14 to 90 years). Female gender and left lower limb involvement were more than twice as common as male gender and right lower limb (female/male ratio, 2.6:1; left/right symptomatic limb ratio, 2.4:1). The CEAP clinical score was class 2 in 7% of limbs, class 3 in 47%, class 4 in 24%, class 5 in 5%, and class 6 in 17%. Thus, almost half of the patients had lower limb hyperpigmentation, dermatitis, lipodermatosclerosis, healed venous ulcer, or active ulcer. Most patients complained of limb pain (76%) and swelling (82%). Limbs of C class 2 were chosen for the procedure because of their associated pain. The etiology (*E* in CEAP) was primary (NIVL) in 518 limbs and secondary (post-thrombotic) in 464.

Obstruction of the deep venous outflow with no reflux (*P* in CEAP) was found in 353 limbs (obstruction, 36%; reflux/obstruction, 64%). Guidewire recanalization was necessary in 62 occluded iliac veins in 464 post-thrombotic limbs (13%). In the 629 limbs with reflux and obstruction, reflux was found in 164 (26%) in the deep system alone, in 396 (63%) in the superficial system alone, and in 67 (11%) of limbs in combined systems (A in CEAP: deep veins, 53%; deep and superficial veins, 47%). Deep reflux was found in 24% of all limbs (236 of 982) and found to be axial (Kistner grade 3 to 4) in 75% (177 of 236). The median multisegment score was 1.8 (range, 1 to 7). Grade 2 to 4 obstruc-

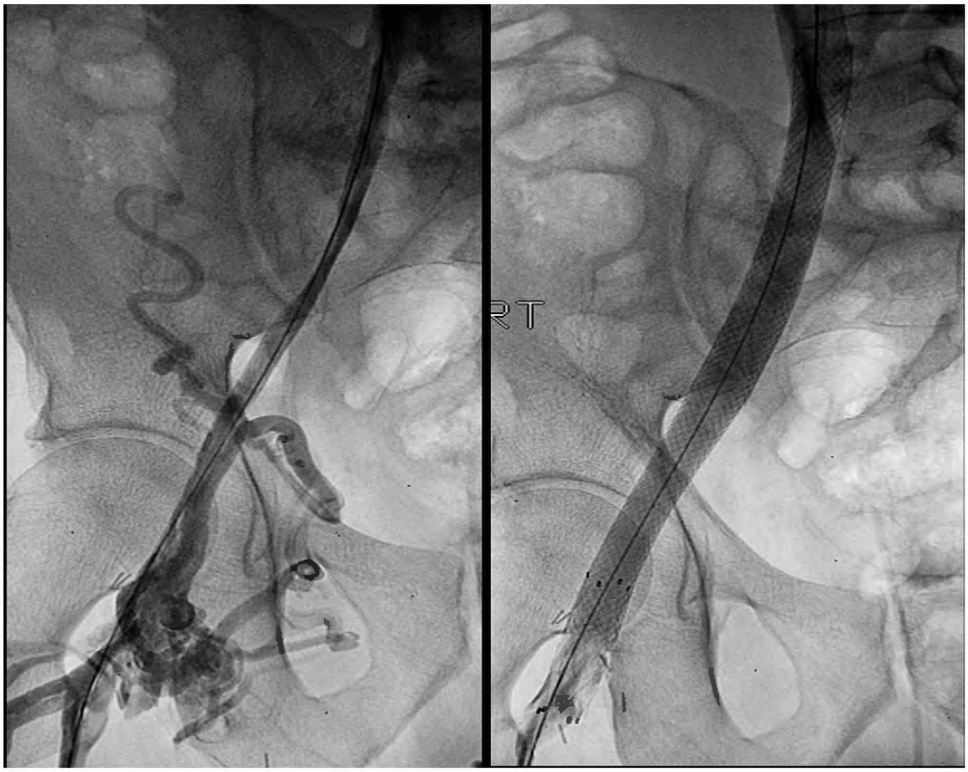

Fig 2. Chronic iliofemoral thrombotic stenosis before and after stenting. The stenting is carried into the common femoral vein to ensure an adequate inflow to prevent later occlusion.

tion (Raju classification) was present in 26% of limbs, and an additional 36% had reduced phasicity of the femoral vein without pressure changes before stenting.

Post-stenting complications. The stenting procedures were performed with no mortality (<30 days). In the first 29 cases, two access-related complications occurred (7%) (1 retroperitoneal bleeding, 1 femoral artery injury requiring open repair). Ultrasound-guided access in the next 953 limbs limited cannulation complications to three femoral artery pseudoaneurysms, which were treated by thrombin injection, and an arteriovenous fistula, which closed spontaneously (0.004%). In one patient the guidewire became caught in the stent, which was pulled to the femoral vein and then openly removed. During the follow-up period, 47 thrombotic events occurred in 982 patients (5%).

All early thrombotic events (<30 days). Early thrombosis of the stented iliac vein occurred in 8 limbs, of the contralateral iliac vein in 4 limbs, at the femoral access site in 2 limbs, and was limited to the calf in 1 limb, for an overall rate of 1.5%. All 12 iliac thrombi occurred in post-thrombotic limbs. All the contralateral DVTs were lysed successfully. Six limbs with stent occlusions had thrombolysis, which was successful in three. A Palma crossover bypass was performed in one patient. One patient with occluded stent had an immediate thrombectomy, but this rethrombosed after 3 weeks. One of the access-related femoropopliteal vein thrombi was successfully lysed. The calf DVT was treated by anticoagulation only.

All late thrombotic events. Occlusion of the stented iliofemoral vein occurred at a median of 13 months (range, 2 to 77 months) after stenting in 23 limbs, for an overall rate of 3%. In nine limbs, the occlusion was found at routine follow-up and treated only by anticoagulation. Early onset (<7 days) occurred in 13 limbs, and thrombolysis was attempted. This was successful in only four limbs, and the other limbs remained occluded. One patient had an open thrombectomy, which occluded in the postoperative period. Late acute thrombotic events occurred in the contralateral iliofemoral vein in seven limbs: one at the ipsilateral receiving femoral site of an old axillary vein transfer, and one nonocclusive thrombus was found attached to the proximal site of a stent in the IVC. The latter two limbs were treated only by anticoagulation. The IVC thrombus could not be detected at a later investigation. All limbs with contralateral proximal occlusions received thrombolysis, which was successful in five of seven limbs.

Contralateral iliac vein thrombosis. As already described, contralateral iliofemoral thrombosis occurred in 11 of 982 patients (1%) during the observation period. Three limbs were stented for NIVL and eight limbs for thrombotic obstructions. Nine of 11 limbs were successfully lysed.

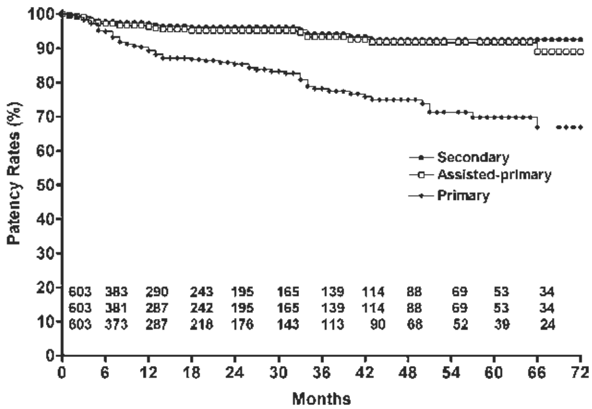

Fig 3. Cumulative primary, assisted-primary, and secondary patency rates of 603 limbs after iliofemoral stenting. The lower numbers represent limbs at risk for each time interval (all standard error of the mean <10%).

Stent patency. Venography or iliofemoral venous ultrasound imaging was performed one or several times in 610 limbs (62%) to verify patency at a mean of 30 months (range, 1 to 107 months) after stent placement. Ipsilateral early or late stent occlusion occurred in 31 limbs and was successfully lysed in seven; thus, 24 stents remained occluded. Overall primary, assisted-primary, and secondary cumulative patency rates at 72 months were 67%, 89% and 93%, respectively (Fig 3). During the observation period, 149 secondary procedures were performed 1-97 months (mean, 19 months) after initial stenting to maintain patency (in-stent restenosis >50%) or to treat unresolved or recurrent symptoms. Additional stenting of stenosis above and the below previous stent was performed in 14 and 63 limbs, respectively; balloon angioplasty of in-stent restenosis in 56 limbs, and a combination of these procedures in 13 limbs. Stents were inserted in three limbs to bridge a stenotic skip area between previously inserted stents.

The stented limbs with NIVL fared significantly better ($P < .0001$) than did those with thrombotic disease, with primary, assisted-primary, and secondary cumulative patency rates of 79%, 100%, and 100%, and 57%, 80%, and 86% at 72 months, respectively (Fig 4). The recanalized post-thrombotic limbs had the highest occlusion rates after stenting, with primary and secondary patency rates of 54% and 74% at 48 months (Appendix Fig, online only). The cumulative rate of severe in-stent restenosis (>50%) was assessed. The overall cumulative rate was 5% of limbs at 72 months and was higher in thrombotic limbs at 10% compared with 1% in NIVL limbs ($P = .0253$; Fig 5).

Factors associated with iliac vein stent thrombosis. During the observation time, 31 iliac stents occluded. All of the occluded limbs had thrombotic (secondary) obstruction. Thrombophilia test was available in 75% (454 of 610) of limbs included in the patency analysis and 38% (173 of 454) were positive. The test was positive for one or several factors in 23% (105 of 454) of post-thrombotic limbs compared with 14% (29 of 209) in NIVL limbs ($P < .001$,

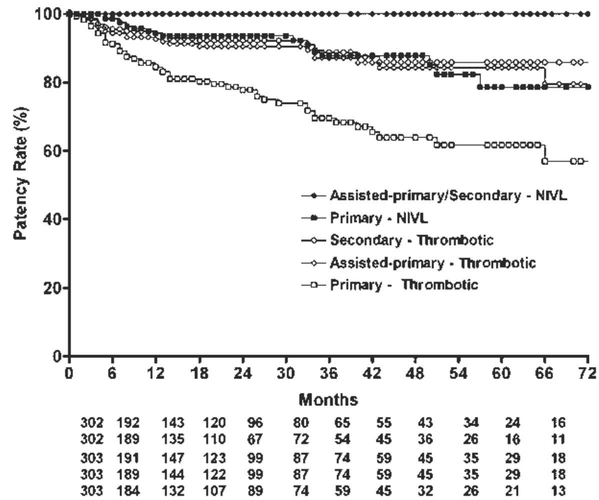

Fig 4. Cumulative primary, assisted-primary, and secondary patency rates for stented limbs with nonthrombotic iliac vein lesions *(NIVL)* and those with previous thrombosis. The lower numbers represent total limbs at risk for each time interval (all standard error of the mean <10%).

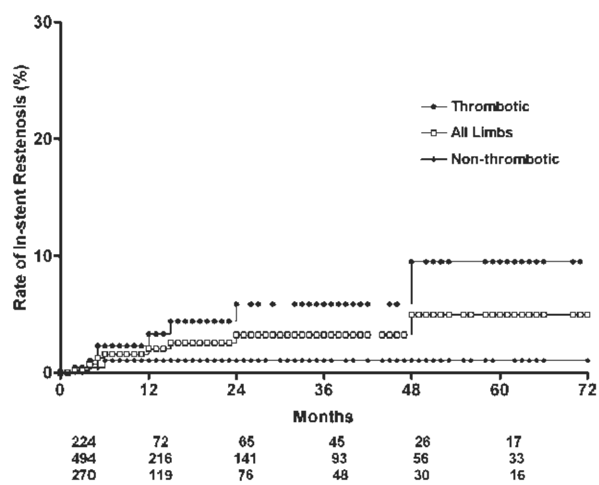

Fig 5. Cumulative rates of severe in-stent restenosis (>50% narrowing) in the entire study group for limbs stented for post-thrombotic lesions (thrombotic) and for limbs stented for obstruction caused by nonthrombotic iliac vein lesions. The lower numbers represent total limbs at risk for each time interval (all standard error of the mean <10%).

Fisher's Exact test). There was an over-representation of treated recanalized veins in the thrombosed stents (65% thrombosed vs 9% patent stents, $P < .001$).

The proportional contribution of different factors to stent occlusion was analyzed (Tables I and II). The intervention side (left or right lower limb) and gender did not increase the risk of occlusion, but younger age appeared to do so. Of interest was that thrombophilia was more frequent in limbs with thrombotic disease but was not statistically associated with stent occlusion. Thrombotic etiology

Table I. Odds ratios for possible factors contributing to early (<30 days) or late occlusions of inserted stents

Factor	*Occluded, frequency, No. (%)*	*Odds ratio**	P†	*Missing values*
Operation side		1.1	.8395	
Left	22 (5.0)			
Right	9 (5.3)			
Etiology of obstruction		—	<.0001	
NIVL	0 (0.0)			
Thrombotic	31 (10.1)			
Degree of obstruction		9.0	<.0001	
Occlusion	12 (24.0)			
Non-occlusive obstruction	19 (3.4)			
Thrombophilia test		1.2	.8261	159
Negative	17 (5.5)			
Positive	7 (4.8)			
Stent extended to CFV		3.8	.0010	
Yes	12 (12.8)			
No	19 (3.7)			
Gender		1.4	.4090	
Female	21 (4.7)			
Male	10 (6.3)			
Additional procedures		1.9	.3670	
Yes	4 (5.6)			
No	27 (3.1)			

NIVL, Nonthrombotic iliac vein lesion; *CFV*, common femoral vein.
*Effect was computed as odds ratio.
†Computed by the Fisher exact test.

of the lesion and long lesions requiring several stents and extension into the common femoral vein were significantly associated with stent occlusion. The preoperative crosscut area of the stenosis, percentage stenosis on IVUS imaging, and occlusion requiring recanalization before stenting all reflect degree of stenosis and are significantly associated with thrombosis of the stent.

Factors associated with in-stent restenosis. The proportional contribution of different factors to development of severe in-stent restenosis (≥50%) was analyzed (Tables III and IV). Factors associated with restenosis are similar to those associated with stent occlusion, except that age is not associated with restenosis. The presence of thrombotic disease is the dominating factor.

Clinical outcome. All 982 limbs, regardless of stent outcome, are included in the final analysis of the clinical outcome as an intent-to-treat study. Postinterventional clinical follow-up was a mean of 24 months (range, 1 month to 8.75 years), allowing cumulative long-term analysis. Information was available in 918 of 982 limbs (93%). Before treatment, 24% of limbs were completely pain-free, and 18% had no swelling. The preoperative and postoperative mean pain and swelling scores improved substantially: 3.7 (range, 0 to 9) and 0.8 (range, 0 to 10), and 1.7 (range, 0 to 3) and 0.8 (range, 0 to 3), respectively ($P <$ .0001). The rate of limbs with severe pain (≥5 on VAS) fell from 41% to 11% after intervention, and gross swelling (grade 3) in limbs decreased from 36% to 18%. As shown in Fig 6, cumulative freedom of pain and swelling were not statistically different whether or not an additional saphenous procedure was performed (P = .8853 and P = .5708, respectively). This graph is based on complete relief of swelling and pain (grade 0 swelling and 0 level of pain) and does not reflect partial improvement. After 5 years overall, 62% and 32% remained completely free of pain and swelling, respectively. The preoperative and postoperative mean pain and swelling scores in the subsets of limbs with NIVL and thrombotic obstruction improved to the same degree in both groups. When cumulative outcome curves of complete relief were compared at 5 years, there was no significant difference in pain outcome (thrombotic and NIVL limbs, 59% and 65%, respectively, P = .7215). Limbs with thrombotic disease were, however, more frequently entirely free of swelling than NIVL limbs (39% and 24%, P = .0041).

Ulcer healing. Healing of leg ulcers was followed up in 148 of 158 limbs for a mean 23 months (range, 1 to 99 months). In 47 limbs the ulcer did not heal. In the remaining 101 limbs, the ulcer healed and recurred in only eight limbs during the follow-up period. Thus, if healing of the ulcer was achieved after this intervention, ulcer recurrence was rare within the study period. The cumulative rate of ulcer healing at 5 years was 58% overall (50% with stent alone and 57% with additional procedure, P = .9754; 62% for NIVL and 55% for thrombotic limbs, P = .2819; Fig 7).

Quality of life. The quality-of-life (QOL) questionnaire was introduced later in the study, explaining the shorter mean follow-up of 5 months (range, 1 to 79 months) and the smaller number of patients (n = 381). There was significant improvement in all QOL categories after treatment (Table V). The population of patients with no or little effect on QOL increased substantially (doubled in 3 of 5 categories). The CIVIQ score was the same in patients with thrombotic and NIVL limbs before stenting and decreased significantly in both groups of patients after the procedure. Adjunct procedures did not affect the QOL scores.

Hemodynamic outcome. To adequately assess the hemodynamic impact after successful stenting, 63 limbs with occluded stents or >50% in-stent stenosis were excluded from preintervention to postintervention hemodynamic comparison (919 limbs remaining). The hemodynamic results in the entire group and subsets of limbs with stenting combined with saphenous procedures and stenting alone are presented in Table VI. All limbs with adjunct correction of superficial reflux had a greater mean multisegment score (stent with added procedure and stenting alone, 2.3 ± 1.6 and 1.4 ± 1.7, respectively; $P <$ .0001). The prevalence of axial deep reflux was the same in both groups of limbs (18%). After stenting, the improvement of venous filling time (VFT), venous filling index (VFI_{90}), and venous volume (VV) was associated with the adjunct procedures. The mean ambulatory venous pressure (AVP), however, was improved regardless of whether an adjunct procedure was performed, although the ejection fraction and residual volume fraction remained unchanged. The hand-foot pressure differential improved in limbs having stenting alone.

Table II. Variables tested for effect on patency

Variable	*Patent (n = 576)**	*Occluded* (n = 31)*	*Effect†*	P‡	*Missing values*
Before stenting					
Stenosis on IVUS, %	74.6 ± 19.8	87.2 ± 19.2	−3.24	.0013	69
Area by IVUS, cm^2	0.50 ± 0.34	0.21 ± 0.39	3.58	.0004	186
Patient age, y	54.0 ± 13.7	45.1 ± 14.8	3.51	.0005	
Stents, No.	1.7 ± 0.9	2.5 ± 0.9	−4.97	<.0001	11

IVUS, Intravascular ultrasound.
*Values are presented as mean ± standard deviation.
†Effect was computed as *T* statistic.
‡Computed two independent samples *t* test.

Table III. Odds ratios for possible factors contributing to the development of severe in-stent recurrent stenosis (≥50%) in inserted stents

Factor	*Restenosis ≥50%, frequency, No. (%)*	*Odds ratio**	P†	*Missing values*
Operation side		1.3	.3908	
Left	30 (7.3)			
Right	15 (9.4)			
Etiology of obstruction		26.7	<.0001	
NIVL	2 (1.0)			
Thrombotic	43 (15.5)			
Degree of obstruction		8.3	<.0001	
Occlusion	14 (34.2)			
Non-occlusive obstruction	31 (5.9)			
Thrombophilia test		1.2	.7026	151
Negative	23 (7.9)			
Positive	12 (9.3)			
Stent extended to CFV		5.5	<.0001	
Yes	19 (23.5)			
No	26 (5.3)			
Gender		1.6	.2093	
Female	30 (7.0)			
Male	15 (10.5)			
Additional procedures		1.8	.2521	
Yes	6 (5.0)			
No	39 (8.7)			

NIVL, nonthrombotic iliac vein lesion; *CFV,* common femoral vein.
*Effect was computed as odds ratio.
†Computed by the Fisher exact test.

Limbs with obstruction and no superficial or deep reflux were compared with those stented in the presence of reflux, which was left untreated (Table VII). This comparison shows the true hemodynamic influence by stenting alone in limbs with and without reflux. Except for decrease of the hand-foot pressure differential in both groups, only ambulatory pressure was decreased in the nonrefluxing group after stenting.

Hemodynamics and etiology of obstruction. Comparison of the thrombotic with NIVL limbs revealed a greater multisegments score (2.2 ± 1.9 and 1.1 ± 1.3; $P <$ .0001) and higher rate of deep axial reflux (32% and 6 %; $P < .0001$). The hemodynamic results in the two stented subgroups of primary and secondary etiology are given in Table VIII. Limbs with adjunct procedures to control reflux were excluded. After intervention, the hand-foot pressure differential improved in both sets of limbs. The ambulatory venous pressure, ejection fraction, and residual volume fraction improved in the NIVL limbs, indicating a global improvement of the hemodynamics and more efficient calf muscle pump. The hemodynamic effect of stenting was minimal in the thrombotic limbs, and residual volume fraction remained unchanged despite a decrease in ejection fraction.

Hemodynamics and axial reflux. Axial reflux due to primary (39 limbs) and thrombotic disease (138 limbs) was present in 177 of 982 limbs (18%). Except for improvement of the hand-foot pressure differential after stenting, all other parameters remained unchanged in this group of limbs after stenting. No enhancement of the retrograde reflux was observed as measured by VFT or VFI_{90}, neither in limbs with primary nor secondary axial reflux.

Hemodynamics and clinical symptoms. Before stenting, ambulatory venous pressure was higher (42 ± 19% and 58 ± 21% drop), VFT shorter (10 ± 6 seconds and 16 ± 15 seconds), and VFI_{90} greater (5.1 ± 2.5 mL/s and 3.3 ± 1.5 mL/s) in nonhealing limbs compared with healing limbs. Other hemodynamic results were the same in both groups. After stenting, all parameters remained unchanged in both limb groups when limbs with the adjunct procedures were excluded. As stated above, the cumulative rate for ulcer healing was the same whether or not an adjunct procedure was performed.

There was no difference in cumulative freedom of pain and swelling whether or not additional saphenous procedure was performed. When limbs with an adjunct procedure were excluded from the calculations, all except the hand-foot pressure differential remained unchanged. This pressure decreased significantly in both groups of limbs, with complete pain and swelling relief (1.2 ± 1.3 to 0.7 ± 1.0 [P = .0087] and 1.6 ± 1.7 to 0.8 ± 1.4 [P = .0147], respectively).

DISCUSSION

Stenting of the venous outflow obstruction of the lower extremities can be performed with low risk, long-term high patency rate, and a low rate of in-stent restenosis. It resulted in major symptom relief in patients with chronic venous disease, which was not consistently reflected in any substan-

Table IV. Variables tested for effect on development of severe in-stent restenosis (≥50%) in inserted stents

Variable	*Restenosis <50%* (n = 525)*	*Restenosis ≥50%* (n = 45)*	*Effect†*	P‡	*Missing values*
Before stenting					
Stenosis on IVUS	73.9 ± 19.5	86.3 ± 18.9	−3.78	.0002	62
Area by IVUS, cm^2	0.51 ± 0.34	0.33 ± 0.47	1.98	.0563	167
Patient age, y	54.0 ± 13.7	51.4 ± 15.5	1.23	.2182	
Stents, No.	1.64 ± 0.82	2.51 ± 0.94	−6.78	<.001	11

IVUS, Intravascular ultrasound.
*Values are written as mean ± standard deviation.
†Computed as *T* statistic.
‡Computed 2 independent samples *t* test.

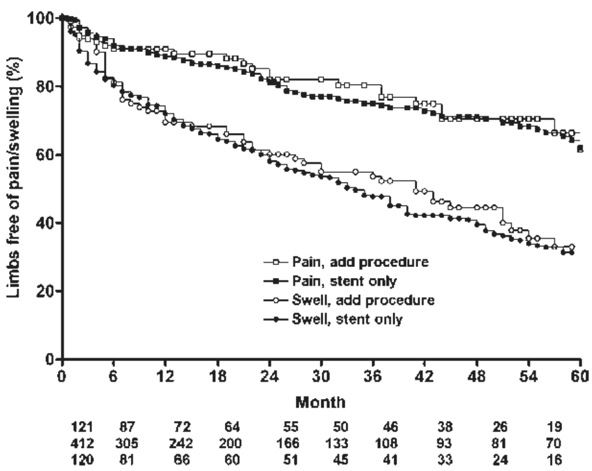

Fig 6. Cumulative sustained complete relief of pain and swelling after femoroiliocaval stenting in patients who had stent placement alone and in those with additional procedures. These curves do not reflect partial improvement only. Only limbs that had preoperative pain or swelling are shown. The lower numbers represent limbs at risk for each time interval (standard error of the mean <10%).

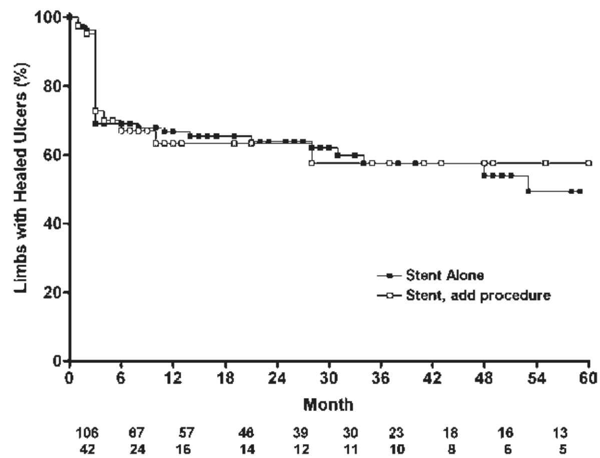

Fig 7. Cumulative rate of limbs with healed ulcers in patients having stent placement alone and in those with additional procedures. Limbs with ulcers that never healed were marked as unhealed and censored at 3 months. The lower numbers represent limbs at risk for each time interval (standard error of the mean <10%).

tial hemodynamic improvement by conventional measurements. The beneficial clinical outcome occurred regardless of the presence of remaining reflux, adjunct saphenous procedures, or etiology of obstruction.

Although the literature has numerous small case reports, only a few larger series with acceptable short-term to mid-term follow-up have been published. Most of these reports mix limbs stented for chronic obstruction with those stented after clot removal.[30,31] A recent retrospective analysis of 50 stented patients was reported.[32] Nearly half the patients had lysis before stenting, and more than 90% had thrombotic obstruction. Cumulative primary, assisted-primary, and secondary patency rates at 48 months were 58%, 71%, and 83%, respectively. Hartung et al[33] reported results of iliocaval stenting in 44 patients with chronic obstruction of primary, secondary, and congenital etiologies in 32, 10, and 2 limbs, respectively. Stenting was not preceded by thrombolysis. Overall cumulative primary, assisted-primary, and secondary patency rates at 36 to 60 months were 73%, 88%, and 90%, respectively, with intention to treat. Their results are comparable with those found in the present study.

Primary and secondary patency rates were obviously mainly related to the presence and severity of thrombotic disease. Further analysis of possible contributing factors confirmed that tight, long lesions of thrombotic etiology requiring multiple stents reaching caudad into the common femoral vein were of greatest risk to occlude. Even though the thrombotic state was such a high risk factor, the presence of thrombophilia in itself was not significantly associated with occlusion. The operation side and gender did not influence stent outcome, but younger age appeared to do so. Knipp et al[32] found that gender, recent trauma, and age younger than 40 years were predictive of decreased primary patency. The different finding may be explained by selection of patients, because half of the patients enrolled in that study had acute DVT. Only 10% of the limbs presented without current or previous DVT, possibly too few to detect the thrombotic state as being predictive.

In this study, the cumulative in-stent restenosis rate remained low in the long-term: 5% at 72 months. Risk

Table V. Comparison of values before and after the procedure of quality of life assessment using the disease-specific Chronic Venous Insufficiency Quality of Life Questionnaire in 381 patients

	Total score (mean ± SD)		Patients with no or little affect on QOL, %		Patients with very much or extreme affect on QOL, %	
Value	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
Leg pain (none = 1, max score 5)	3.5 ± 1.1	2.6 ± 1.2*	19%	46%	55%	26%
Work-related leg problem (not bothered = 1, max score, 5)	3.5 ± 1.1	2.7 ± 1.3*	18%	44%	54%	30%
Sleep disturbance due to leg problems (never = 1, max score, 5)	3.2 ± 1.3	2.5 ± 1.3*	33%	57%	43%	25%
Effect on social activities (none = 8, max score, 40)	25.1 ± 8.4	21.4 ± 9.0*	17%	34%	25%	16%
Effect on morale (none = 9, max score, 45)	26.0 ± 9.8	22.1 ± 9.7*	25%	41%	19%	12%

SD, Standard deviation; *QOL,* quality of life.
**P* < .001, paired nonparametric Wilcoxon rank test.

Table VI. Hemodynamic characteristics of limbs before and after intervention*

Characteristic	*Pre*	*Post*	P
All limbs, n = 426			
AVP drop, %	62 ± 20	66 ± 21†	.0015
VFT, s	32 ± 35	36 ± 32†	.0120
Hand-foot pressure differential, mm Hg	1.2 ± 1.3	0.8 ± 1.2†	.0005
Hyperemia pressure increase, mm Hg	5.6 ± 3.9	6.3 ± 4.1	.0540
VFI_{90}, mL/s	2.5 ± 2.0	2.3 ± 1.0†	.0038
VV, ml	87 ± 40	84 ± 39†	.0193
EF, %	57 ± 22	57 ± 24	.7814
RVF, %	34 ± 23	32 ± 25	.0693
Limbs with stenting and reflux procedure, n = 108			
AVP drop, %	59 ± 21	65 ± 22†	.0106
VFT, s	23 ± 25	34 ± 32†	.0024
Hand-foot pressure differential, mm Hg	0.8 ± 0.7	0.7 ± 0.9	.6622
Hyperemia pressure increase, mm Hg	5.6 ± 4.1	6.0 ± 3.9	.4730
VFI_{90}, mL/s	3.5 ± 2.3	2.6 ± 2.2†	.0001
VV, mL	103 ± 42	92 ± 38†	.0029
EF, %	53 ± 20	56 ± 21	.2686
RVF, %	39 ± 25	35 ± 27	.1320
Limbs with stenting alone, n = 318			
AVP drop, %	64 ± 20‡	68 ± 20†	.0490
VFT, s	34 ± 30‡	37 ± 32	.1887
Hand-foot pressure differential, mm Hg	1.3 ± 1.4‡	0.8 ± 1.2†	.0003
Hyperemia pressure increase, mm Hg	5.7 ± 3.8	6.4 ± 4.1	.0670
VFI_{90}, mL/s	2.2 ± 1.8‡	2.2 ± 2.0	.7296
VV, mL	82 ± 37‡	81 ± 39	.3312
EF, %	58 ± 23‡	57 ± 24	.7511
RVF, %	33 ± 22	31 ± 24	.2022

AVP, Ambulatory venous pressure; *VFT,* venous filling time; *VFI_{90},* venous filling index; *VV,* venous volume; *EF,* ejection fraction; *RVF,* residual volume fraction.
*Data are expressed as mean ± SD. Only limbs with prestent and and poststent values are included.
†Statistical significance comparing limbs preintervention to postintervention (paired nonparametric Wilcoxon rank test).
‡Statistical significance, comparing groups of limbs of different interventions preprocedure (unpaired nonparametric Wilcoxon rank test).

factors for in-stent restenosis have been shown to be similar to those for stent occlusion, but it has not been conclusively proven that progressive in-stent restenosis results in occlusion.[14] Stent occlusion appears to be caused by a recurrent thrombotic event rather than slowly evolving narrowing of the stent. The cumulative rate of in-stent restenosis in this study was higher in thrombotic limbs (10%) than in nonthrombotic limbs (1%). Hartung et al[33] reported a 13% restenosis rate, but these authors appear to have included stenosis at the lower stent-vein border area, which is not considered true in-stent restenosis. The mechanism of development of in-stent restenosis is not yet known.

The present study spans a 9-year period and includes all patients during this period of time, including the initial "learning curve." Increasing experience throughout the time period has led to subsequent modification, which has improved outcome. Stent procedures performed early in the series sometimes needed later correction, explaining why some of the secondary procedures were performed. Skipped areas between inserted stents were abandoned

Table VII. Hemodynamic characteristics of limbs with and without reflux before and after stenting*

Characteristic	*Pre*	*Post*	P
Limbs with reflux and stenting alone, n = 178			
AVP drop, %	61 ± 22	63 ± 21	.6826
VFT, s	26 ± 25	27 ± 27	.1801
Hand-foot pressure differential, mm Hg	1.4 ± 1.9	0.9 ± 1.5†	.0038
Hyperemia pressure increase, mm Hg	5.8 ± 3.9	6.8 ± 4.4	.0581
VFI_{90}, mL/s	2.8 ± 1.9	2.7 ± 2.2	.4681
VV, mL	88 ± 39	87 ± 41	.6210
EF, %	54 ± 23	51 ± 26	.3766
RVF, %	36 ± 23	34 ± 27	.2391
Limbs with no reflux and stenting alone, n = 105			
AVP drop, %	70 ± 15‡	75 ± 14†	.0030
VFT, s	47 ± 32‡	50 ± 33	.6220
Hand-foot pressure differential, mm Hg	1.4 ± 1.5	0.8 ± 1.1†	.0157
Hyperemia pressure increase, mm Hg	5.2 ± 3.6	5.4 ± 3.3	.7137
VFI_{90}, mL/s	1.2. ± 0.9‡	1.2 ± 1.0	.9258
VV, mL	72 ± 32‡	69 ± 33	.3666
EF, %	62 ± 23‡	62 ± 23	.9123
RVF, %	30 ± 20	28 ± 20	.9136

AVP, Ambulatory venous pressure.
*No adjunct procedures were performed. Only limbs with prestent and poststent values are included (mean ± SD).
†Statistical significant comparing limbs presenting with poststenting (paired nonparametric Wilcoxon rank test).
‡Statistical significance, comparing the two groups of limbs presenting (unpaired nonparametric Wilcoxon rank test).

Table VIII. Hemodynamic characteristics of subgroups of limbs with nonthrombotic iliac vein lesions (n = 149) and thrombotic obstruction (n = 93) before and after intervention*

Characteristic	*Pre*	*Post*	P
AVP, drop, %			
NIVL	70 ± 18	76 ± 12†	.0006
Thrombotic	59 ± 20‡	60 ± 22	.9356
VFT, s			
NIVL	37 ± 29	38 ± 28	.3970
Thrombotic	31 ± 30	36 ± 35	.2067
Hand-foot pressure differential, mmHg			
NIVL	1.2 ± 1.4	0.8 ± 1.1†	.0044
Thrombotic	1.4 ± 1.8	0.9 ± 1.3†	.0091
Hyperemia pressure increase, mmHg			
NIVL	5.9 ± 4.0	6.2 ± 3.8	.4899
Thrombotic	5.3 ± 3.7	6.5 ± 4.4	.0529
VFI_{90}, mL/s			
NIVL	1.8 ± 1.4	1.8 ± 1.4	.6395
Thrombotic	2.7 ± 2.0‡	2.5 ± 2.2	.9606
VV, ml			
NIVL	88 ± 39	81 ± 42†	.0066
Thrombotic	76 ± 40‡	84 ± 38	.1710
EF, %			
NIVL	56 ± 22	61 ± 23†	.0195
Thrombotic	57 ± 23	49 ± 25†	.0103
RVF, %			
NIVL	34 ± 22	27 ± 21†	.0063
Thrombotic	34 ± 22	38 ± 29	.3365

AVP, Ambulatory venous pressure; *NIVL,* nonthrombotic iliac vein lesion; *VFT,* venous filling time; *VFI_{90},* venous filling index; *VV,* venous volume; *EF,* ejection fraction; *RVF,* residual volume fraction.
*Data expressed as mean ± SD. Limbs with adjunct procedures to control superficial reflux are excluded.
†Statistical significance, comparing limbs pre-to post-intervention (paired nonparametric Wilcoxon rank test).
‡Statistical significance, comparing groups of limbs of different etiology (unpaired nonparametric Wilcoxon rank test).

early because they were prone to restenosis. In the first 25 patients, care was taken to avoid extension of the stent into the IVC by placing it slightly beyond the stenosis, even when the narrowing was at the iliocaval junction. About 40% of these stents developed proximal restenosis due to caudad migration when a braided Wallstent was used.[15] After this experience, all braided stents were inserted well into the IVC, thus preventing caudad migration. This is the explanation for the secondary cephalad stent extension.

Even though the number of stents, length of stented area, and extension of the stent underneath the inguinal ligament into the common femoral vein are associated with stent occlusion and development of severe in-stent restenosis, the absolute numbers are low, and the stent length should not be limited for those reasons. Stents placed in the artery below the inguinal ligament often fracture and occlude. Fractures of venous stents placed in this position have never been reported, were not observed during this study, and are not related to venous stent occlusion at this site. Stent occlusions will be seen more frequently if the venous lesions are incompletely covered.

Careful IVUS investigations have taught us that the internal-external iliac vein confluence is stenotic in more than half of obstructed limbs with NIVL due to compression of the external iliac vein by the internal iliac artery diving into the pelvis.[10] Secondary stenting procedures for restenosis below the stent were due to a primarily overlooked compression lesion at this site or a predilection of this site for restenosis.

In the treatment of thrombotic obstruction, adequate inflow and outflow are crucial for long-term patency. The lower end of the stent is often placed just above the profunda-femoral veins confluence in these limbs to ensure sufficient inflow. IVUS imaging has been shown to be superior to venogram in the assessment of the degree and extension of iliofemoral occlusive lesions[27,34] and should be an integral part of the stenting technique.

Venous stenting after ultrasound-guided venous access is performed with minimal risk.[30,33,35,36] The overall rate of thrombotic events was 4.5%, similar to 5% reported by Hartung et al.[33] Thrombosis of the stented iliac veins occurred in 3% of all limbs and only in limbs treated for thrombotic obstruction. Stenting of primary iliac compression lesions with the present technique had very favorable long-term result, with no occlusions.

The extension of the stent into the IVC has raised concerns about relative obstruction to the venous outflow of the contralateral limb and subsequent thrombosis. The thrombosis rate was low (1%), however, and three-fourths of patients were stented for thrombotic obstruction. Probably because of acute onset of significant symptoms, the patients sought immediate treatment, and the success rate of thrombolysis or mechanical thrombectomy was high (82%). Thus, contralateral iliac vein thrombosis related to the IVC stent extension was generally benign and infrequent.

Chronic venous disease rarely threatens the survival of the limb or the patient, so the goal is to improve symptoms and the quality of life. The use of the VAS to measure the amount of pain has been properly validated and is useful.[28] The evaluation of swelling is semi-quantitative and less precise. Nevertheless, mean pain score and degree of swelling decreased significantly after stenting, and the proportion of patients with severe pain and swelling was significantly reduced. Complete relief of pain and swelling and healing of an ulcer are clear end points. Cumulative freedom from pain was better sustained than absence of swelling in the long term. The cumulative ulcer recurrence-free rate was 58% at 5 years. Long-term cumulative relief of pain and ulcer healing was the same in stented limbs with NIVL and thrombotic obstruction. The long-term complete relief of swelling was less in the NIVL limbs. The reason for this observation is unknown.

These end points capture different expressions of the chronic venous disease but do not provide information on the functional impact on the patient. For this purpose, generic and disease-specific questionnaires have been developed to assess the burden of disease on the individual patient as perceived by the patient. It has previously been shown that both primary chronic venous disease with "simple" varicose veins and disease with development of post-thrombotic stigmata significantly reduce QOL.[37-39] Specifically, previous iliofemoral DVT may cause clinically pertinent iliac outflow obstruction resulting in a marked compromise of QOL.[7]

All five problem categories of the CIVIQ form used in this study improved significantly after stenting of both NIVL and thrombotic outflow obstructions. Chronic venous disease, regardless of etiology, affects QOL adversely, and stenting in patients with chronic venous outflow obstruction frequently markedly improved QOL. Significant improvement of Venous Clinical Severity and Venous Disability Scores has previously been reported by Hartung et al.[33]

The hemodynamic changes using conventional methods were relatively minor compared with the clinical improvement. A few observations are noteworthy. Better results for reflux-related variables (VFT, VFI_{90}, and VV) after treatment were observed only when adjunct saphenous procedures were combined with the stenting. In no subset of patients was a deterioration of venous reflux observed. An increase of reflux in a small group of post-thrombotic limbs after stenting has been reported.[40] Axial deep reflux present before stenting did not, however, worsen the global reflux measurably after stenting in this study. The contention that the stenting of the proximal venous outflow obstruction would result in the loss of protection or buffering of retrograde reflux was not supported by these observations.

Significant decrease of the mean hand-foot pressure differential in stented limbs occurred with and without remaining reflux and no adjunct procedures, and ambulatory venous pressure improved in most subsets of limbs. Although numerically small, these changes were statistically significant and indicated that the outflow obstruction was alleviated and the global hemodynamics improved after stenting.[16] Before stenting, limbs with thrombotic obstruction clearly had more extensive venous disease with more severe obstruction and reflux more frequently involving multiple systems and levels than limbs with NIVL. Despite this observation, stenting improved clinical symptoms and QOL substantially and similarly in both groups of patients. The positive clinical outcome was achieved with an improvement of the calf muscle pump function in the NIVL limbs, whereas the thrombotic limbs had no measurable hemodynamic improvement in these indicators. The hemodynamic response in patients who became completely free of pain and swelling or whose ulcers healed was no different than in those with residual pain or swelling or nonhealing ulcers. The lack of improvement of conventional hemodynamic test results underscores the poor understanding of the pathophysiology and the inability to accurately test hemodynamically significant venous obstruction.

AUTHOR CONTRIBUTIONS

Conception and design: PN, SR
Analysis and interpretation: PN, SR
Data collection: PN, SR, CH
Writing the article: PN
Critical revision of the article: PN, SR, JO
Final approval of the article: PN, JO, SR
Statistical analysis: JO, PN, CH
Obtained funding: Not applicabale
Overall responsibility: PN

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Additional material for this article may be found online at www.jvascsurg.org.

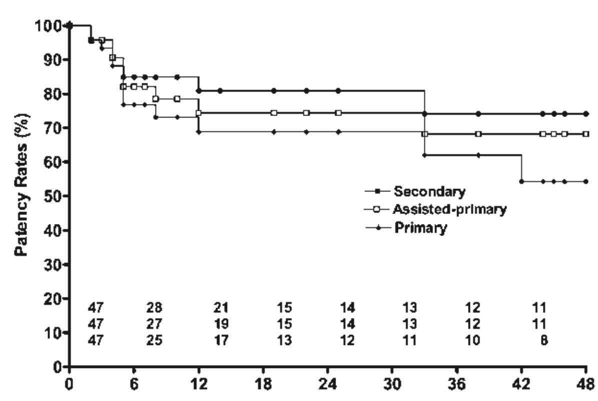
Appendix Table EI (online only). Detailed description of hemodynamic and lymphatic studies

Study	*Description*
Ascending and transfemoral venography[21,22]:	Injection of contrast medium into the common femoral or femoral vein was made to delineate the distribution and nature of femoroiliocaval morphologic changes, including occlusion, stenosis, and presence of collateral circulation, as well as to assess patency of inserted iliofemoral stents. Ascending venogram with injection of contrast medium into a dorsal foot vein was occasionally used to evaluate stent patency but not the degree of in-stent restenosis.
Duplex Doppler study with standardized compression[23,24]:	Duration of reflux >0.5 seconds was considered significant. The pattern of reflux was reported in two ways: 1. In a deep axial fashion, mimicking Kistner's classification, giving 1 to 4 points as the reflux involved in the common femoral, femoral, popliteal, and distal posterior tibial veins, consecutively; and 2. In a multisegment score, with 1 point each awarded to the femoral, profunda, popliteal, posterior tibial, above and below knee great saphenous, and small saphenous veins (maximum score = 7), whether or not axial reflux was present.[21-23] Deep reflux reaching below the popliteal vein (ie, Kistner classes 3 and 4) was considered axial.
Ambulatory venous pressure measurement:	The pressure was recorded in the dorsal vein with the patient standing erect and motionless and holding onto a frame, during 10 toe-stands, and throughout the period of pressure recovery to baseline level. The ambulatory venous pressure (AVP) was measured as the percentage drop of baseline pressure at rest to the level at the end of the exercise and reflects global venous hemodynamics. The time required for the pressure to return to base level was the venous filling time (VFT in seconds), reflecting mainly venous reflux.
Arm-foot pressure differential and hyperemia-induced pressure increase[25]:	The pressure differential between a needle placed in the dorsal foot vein and a hand vein, both on levels with the right atrium of the heart, was measured (normal, <4 mm Hg). After reactive hyperemia induced by ischemia using a cuff, the rise of the dorsal vein pressure was measured (normal, <8 mm Hg). An individual or combined abnormal test defines grade 2 to 4 of outflow obstruction.
Air plethysmography:	Details of air plethysmography using APG-1000 (ACI Medical Inc., Sun Valley, Calif) have been described by Christopolous et al.[26] Venous filling index (VFI_{90}, mL/s), measured at 90% of total increase of calf volume when shifting from the supine to the erect position, has been shown to be a useful parameter to reflect global venous reflux.[23] In addition, venous volume (VV, mL), ejection fraction, and residual volume fraction of the calf were measured. The ejection fraction and residual volume fraction are postulated to reflect mainly calf muscle pump function.

Appendix Table EII (online only). Type of adjunct procedures to venous stenting performed to control superficial venous reflux

Type of procedure	*No.*
GSV laser ablation*	52
GSV stripping*	68
GSV radiofrequency closure*	55
SSV stripping	7
Stab avulsions	15
Total number of interventions	197

GSV, great saphenous vein; *SSV,* small saphenous vein.
*GSV procedures combined with SSV stripping in 7 limbs, stab avulsion in 75 limbs.



Appendix Fig (online only). Cumulative primary, assisted-primary, and secondary patency rates in a subset of limbs stented after recanalization of post-thrombotic occlusion. The lower numbers represent total limbs at risk for each time interval (all standard error of the mean <10%).