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In-stent restenosis and stent compression following stenting for chronic iliofemoral venous obstruction

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ABSTRACT

Objective: In-stent restenosis (ISR) and stent compression (SC) are problems encountered after stenting for chronic iliofemoral venous obstruction that are responsible for a majority of reinterventions. However, characteristics of ISR and SC, in addition to outcomes after reintervention, have not been explored in detail and represent the focus of this study.

Methods: A retrospective analysis of contemporaneously entered electronic medical record data on 578 limbs/patients with initial unilateral iliofemoral venous stents placed from 2014 to 2018 was performed. ISR was estimated from stent and flow channel diameters measured using duplex ultrasound. SC was estimated from rated stent diameter and actual stent diameter on duplex ultrasound. Characteristics evaluated included onset of ISR/SC after stent placement and progression over time. Analysis was performed to evaluate risk factors for the development of ISR and SC. Outcomes after reintervention for ISR/SC were also appraised.

Results: A total of 578 limbs underwent stenting for stenotic lesions (nonthrombotic iliac vein lesion/post-thrombotic syndrome). ISR was noted in 27% of limbs on post-intervention day 1. The prevalence of ISR increased to 74% by 3 months and stabilized thereafter. SC was noted in 80% of limbs on day 1 and plateaued. Of the variables evaluated as potential risk factors for ISR, intravascular ultrasound determined stent inflow luminal area and shear rate were found to be significant. For SC, asymmetric stent sizing was a significant risk factor. Over a median follow-up of 24 months, 95 of 578 (16.4%) limbs underwent reintervention for ISR, SC, or a combination. The median time to reintervention was 11 months. There was no statistically significant difference in the degree of ISR/SC among patients who underwent reintervention vs those who did not ($P > .05$). However, there was a statistically significant difference in the grade of swelling ($P = .006$) and visual analog scale pain scores ($P < .0001$) between those who underwent reintervention and those who did not. Primary, primary assisted, and secondary patencies at 60 months were 70%, 98%, and 84% after reintervention for ISR and 70%, 99%, and 84% for SC, respectively.

Conclusions: Although ISR and SC are both common after stenting for chronic iliofemoral venous obstruction, neither are relentlessly progressive. Indication for reintervention must be a recurrence of symptoms with impairment of quality of life and not the percentage of ISR or degree of SC. After reintervention good outcomes can be expected both in terms of clinical improvement and stent patency. Further study of the impact of shear rate on stent flow is required to help reduce the incidence of ISR. (J Vasc Surg Venous Lymphat Disord 2021;■:1-10.)

Keywords: Lliac venous stenting; Lliofemoral venous obstruction; Post thrombotic syndrome; May Thurner syndrome; Venous stenting; Deep venous obstruction

The incidence of reintervention in the literature after iliofemoral venous stenting ranges from 11% to 20%.[1-9] The most common reason for reintervention is the recurrence of symptoms due to in-stent restenosis (ISR) and stent compression (SC).[2,5,10] Stent occlusion is rare with an incidence of around 3%.[11] Given this incidence of reintervention, it is important to identify baseline characteristics of ISR and SC in addition to determining predictors for their development. It is also vital to determine characteristics of ISR/SC in patients who undergo reintervention and evaluate outcomes after such reintervention. Such data can potentially help develop measures to reduce ISR/SC and also provide better prognostic information to patients under consideration for iliofemoral venous stenting. This study evaluates the characteristics/predictors of ISR/SC, reintervention after the development of ISR/SC, and outcomes after reintervention.

METHODS

Study design. Single-center retrospective analysis of prospectively collected data over a 4-year period from 2014 to 2018 was performed. St. Dominic Hospital institutional review board approval was obtained for

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dissemination of deidentified patient data. Patient consent was obtained for the procedure.

Setting. The center is a tertiary center for the management of venous and lymphatic disorders.

Participants. Patients who initially presented with lower extremity symptoms impairing quality of life including tiredness, heaviness, pain, swelling, hyperpigmentation, lipodermatosclerosis, and venous leg ulcers suggestive of obstructive iliofemoral venous lesions who had failed conservative measures were included. These patients underwent intravascular ultrasound (IVUS) interrogation to confirm the diagnosis and subsequent unilateral iliofemoral venous stenting after such confirmation. Patients were excluded if they had bilateral stents, stents placed in the setting of acute deep venous thrombosis after pharmacomechanical thrombectomy, or if their entire stents were not visualized during duplex ultrasound (DUS).

Stenting and follow-up. The technique of stenting and peri/postoperative care has been described in prior publications.[2,10-13] In essence, access is obtained in the mid-thigh femoral vein under ultrasound guidance, and an 11Fr 10 cm sheath placed. A venogram was typically performed initially (unless contraindicated) to determine flow dynamics. IVUS interrogation (Visions PV .035 digital IVUS catheter; Philips, Amsterdam, the Netherlands) was then carried out paying careful attention to minimal luminal areas in the common femoral, external iliac, and common iliac venous segments. Inflow channel luminal area, the luminal area of the vein just below the anticipated caudal end of the stent, was also computed. Criteria used for the diagnosis of iliofemoral venous obstruction involved the use of previously defined normal minimal luminal areas in the common femoral vein (CFV) (125 mm^2), external iliac vein (EIV) (150 mm^2), and common iliac vein (CIV) (200 mm^2).[13] A luminal area below these cutoff points was considered abnormal meriting stenting in the symptomatic patient. Predilation was the next step and was carried out typically using a 16 or 18 mm angioplasty balloon inflated to a pressure above nominal where equilibration occurs. Stenting was then accomplished using a Wallstent body and a Z stent top that straddles the iliocaval confluence to overcome the choke point effect. Stents usually ranged from 16 to 20 mm diameter for the Wallstent and 25 to 30 mm for the Z stent with lengths (45-90 mm for the Wallstent) dictated by the goal to cover all areas of disease with adequate overlap (2-3 cm) between stents to prevent shelving. Essentially, the stent column extended from an area of good inflow (crossing the inguinal ligament if needed) to an area of good outflow. Postdilation was then pursued usually with the same angioplasty balloon used for predilation. This was followed by completion IVUS interrogation (to ensure that adequate luminal areas have been attained) and subsequently a completion venogram.[13]

Antithrombotic therapy included prophylactic enoxaparin (30-40 mg subcutaneously) and bivalirudin 75 mg given preoperatively, therapeutic enoxaparin (1 mg/kg/dose subcutaneously 12 hourly) given postoperatively while the patient remained in the hospital, and a combination of anticoagulation (direct oral anticoagulant/warfarin), Cilostazol 50mg BID, and aspirin 81 mg for at least 6 months postprocedure as long as no contraindications for their use existed. Patients with thrombophilia or those who developed stent complications (eg, occlusion) after discontinuation of anticoagulation were maintained on longer term anticoagulation. Aspirin 81 mg was generally continued lifelong.

After intervention patients received a pair of graduated compression stockings (20-30 mm Hg) and compression wraps (20-30 mm Hg) each with the recommendation for them to be worn every day. Patients were evaluated with DUS on day 1, 2 and 4 weeks, 3 months, 6 months, 1 year after intervention, and yearly thereafter if asymptomatic without evidence of stent malfunction. Clinical evaluation was performed at these follow-up visits starting at 6 weeks. More frequent follow-up (clinical+DUS) outside of these parameters was pursued if the patient had clinical recurrence or if there were concerning findings on DUS of significant ISR (>50%) or SC (>50%) or both. Follow-up in our practice after venous stenting is lifelong.

Measurement of in-stent restenosis. ISR was estimated from stent and flow channel diameters measured using DUS. DUS was performed using the GE S8 ultrasound (GE Medical Systems, Waukesha, Wisc) with a 9 MHz linear probe for the CFV and a 1 to 5 MHz curvilinear probe for the

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective analysis of prospectively collected data
- **Key Findings:** In patients undergoing stenting for chronic iliofemoral venous obstruction, the overall incidence of in-stent restenosis (ISR) and stent compression (SC) is high. ISR peaks at 3 months and plateaus, whereas SC peaks on day 1 and steadies thereafter. Stent inflow channel luminal area and shear rate were risk factors for the development of ISR, whereas asymmetric stent sizing was a risk factor for SC.
- **Take Home Message:** Although ISR and SC are common after stenting for chronic iliofemoral venous obstruction, neither is relentlessly progressive and, overall, only 16% required reintervention. Indication for reintervention must be a recurrence of symptoms impairing quality of life and not the percentage of ISR or degree of SC.

EIV, CIV, and the inferior vena cava with the patient in a supine position. B-mode, B-flow, color flow Doppler, and pulse wave Doppler modalities were used during the scan. Evaluation of the inflow distal to the stent was first performed, followed by sequential evaluation of the CFV, EIV, CIV, and the distal inferior vena cava. The stent and flow channel diameters were then computed. ISR was obtained as a percentage using the following formula:

$$\text{ISR}(\%) = \{\frac{\text{Stent diameter} - \text{Flow channel diameter}}{\text{Stent diameter}}\} \times 100$$

Fig 1 depicts ISR on DUS. ISR was re-evaluated at each of the follow-up visits. For ISR, five segments were considered: cranial and caudal common iliac, cranial and caudal external iliac, and the common femoral segment.

Measurement of stent compression. Stent compression (SC) was evaluated by computation of the actual stent diameter from DUS and comparing it with the rated stent diameter:

$$\text{SC}(\%) = \{\frac{\text{Rated stent diameter} - \text{Actual stent diameter}}{\text{Rated stent diameter}}\} \times 100$$

As for ISR, five segments were considered for SC also: cranial and caudal common iliac, cranial and caudal external iliac, and the common femoral segment.

Assessment of risk factors for ISR. Variables evaluated as predictors for the development of ISR included age, gender, thrombophilia, lesion type (post-thrombotic syndrome [PTS] vs nonthrombotic iliac vein lesion [NIVL]), anticoagulation status, stent inflow channel luminal area, shear rate, flow rate, platelet count, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio. When both PTS and NIVL were present, the patient was grouped in the PTS cohort. The patient was considered to be on anticoagulants if this was started in the perioperative period and continued without interruption for at least 3 months. Stent inflow channel luminal area was computed using IVUS inflow channel luminal area (smallest luminal area cranial to the femoral vein confluence and caudal to the anticipated lower end of the stent). This inflow channel luminal area was categorized as <100 mm^2 or ≥ 100 mm^2 assigning a 20% reduction from the ideal CFV luminal area as being significant.

Shear rate was computed using DUS as

$$\text{Shear rate}(s^{-1}) = \frac{4 \times \text{Time averaged velocity}}{\text{Flow radius}}$$

The maximum shear rate across the five segments was used for analysis. This was then categorized as low shear rate (≤ 125 s^{-1}) or high shear rate (>125 s^{-1}). Shear rate gives the velocity gradient across the vessel. When multiplied by viscosity it gives shear stress that has been noted to impact ISR.[14] Given differing viscosity of arterial and venous blood, and the difficulty in precisely determining the viscosity of blood in the iliac vein, it was decided to use shear rate and not shear stress.[15-18] The normal shear rates in the iliac veins are around 125 s^{-1}.[15] Flow rate or volumetric flow was computed using DUS as

$$\text{Flow rate}(\text{mm}^3/\text{s}) = \text{Inflow channel luminal area} \times \text{Time averaged velocity}$$

It is known that pelvic and lower limb arterial inflow in normal individuals at rest is roughly 1500 cm^3/min. If we make the assumption that roughly this amount returns via both the CIVs into the inferior vena cava, each individual's common iliac outflow is approximately 750 cm^3/min.

Poiseuille's equation gives us the relationship between flow, pressure gradient, and resistance:

$$\text{Flow}(F) = \frac{\text{Pressure gradient}(\Delta P)}{\text{Resistance}(R)}$$

$$F = \frac{\Delta P \pi r^4}{8 L \eta}$$

where L is the length of the vein, η is the viscosity of blood, and r is the radius of the vein.

Knowing the normal CIV outflow allows us to predict the flow in the CFV given the known values in the remainder of the equation. This turns out to be approximately 475 cm^3/min (approximately 11,000 mm^3/s assuming that flow occurs only in expiration and an expiration:inspiration ratio of 2:1). The flow rate was then averaged over the five segments and categorized as low flow rate $<11{,}000$ mm^3/s or high flow rate $\geq 11{,}000$ mm^3/s.

Inflammatory markers used included the neutrophil to lymphocyte ratio and the platelet to lymphocyte ratio, which were computed from complete blood count with differential that was obtained before intervention

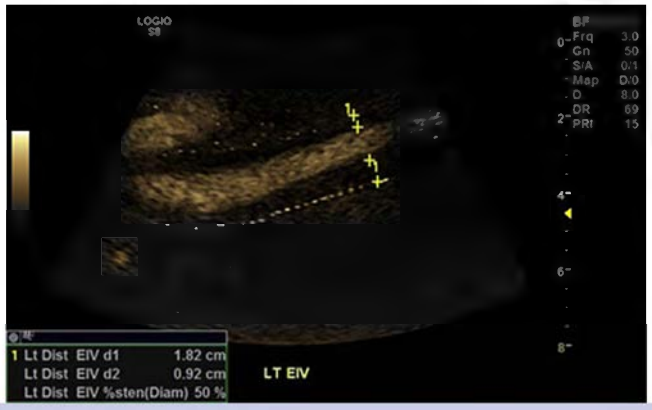

Fig 1. Duplex ultrasound (DUS) B flow mode depicting 50% in-stent restenosis (ISR) in the distal external iliac vein (*EIV*).

as part of regular preprocedure labs. The ratios were derived from absolute cell counts and not proportions. A ratio of greater than 3.65 was considered to be significant for the neutrophil to lymphocyte ratio, and a ratio above 122 was considered to be significant for the platelet to lymphocyte ratio.[19,20] Such data for ISR per se do not exist, and these ratios were derived from studies that looked at this aspect (inflammatory marker) in the setting of deep venous thrombosis.[21-24] Platelet count was also evaluated as a risk factor for the development for ISR. The cutoff was an absolute platelet count equal to or greater than 350,000 μL^{-1}, with such counts potentially representing a risk factor for ISR. Such a hypothesis was made based on the impact of absolute platelet count on deep venous thrombosis.[25,26]

Assessment of risk factors for SC. Age, gender, lesion type (PTS vs NIVL), iliofemoral venous stenosis over 50%, asymmetric stent sizing, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio were evaluated as potential risk factors for the development of SC. Iliofemoral venous stenosis over 50% was determined using normal IVUS luminal area cutoffs outlined above: CFV (125 mm^2), EIV (150 mm^2), and CIV (200 mm^2). The stent sizing variable was grouped into those with symmetric stent sizing (stent size ≤20% relative to the IVUS inflow channel luminal area) and those with asymmetric stent sizing (stent size >20% relative to the IVUS inflow channel luminal area). Correspondingly, symmetric stent sizing involved using the Wallstent size of 16 mm for the inflow channel luminal area (ILA) <125 mm^2; 18 mm Wallstents for ILA 125 to 200 mm^2, and 20 mm Wallstents for ILA >200 mm^2. When larger stents were used, they were categorized as asymmetrically sized. Stent sizes below 16 mm were not used keeping in line with the need for an adequate luminal caliber to help resolve venous hypertension.[13]

Reintervention. Patients presenting with recurrent symptoms impairing quality of life underwent repeat IVUS interrogation and stent angioplasty with/without laser ablation of ISR. Laser ablation was used in patients with severe ISR not responsive to balloon angioplasty alone and was performed using a 2.3 mm Spectranetics laser catheter (Spectranetics Corp, Colorado Springs, Colo) supported by an 8.5Fr 63 cm Swartz Braided Transseptal Guiding Introducer (Abbott Labs, Abbott Park, Ill) that allowed four-quadrant and circumferential ablation of ISR. After reintervention clinical improvement was assessed using pre- and post-grade of swelling (GOS: 0-3) and visual analog scale (VAS: 0-10) pain scores. Stent outcomes including primary, primary assisted, and secondary patencies were also evaluated after reintervention.

Statistical analysis. All statistical analysis was performed using Prism version 9 (GraphPad, San Diego, Calif)/SPSS statistics version 24 (IBM Corp, Armonk, NY). Repeated-measures analysis of variance (ANOVA) and Tukey's post-test were used to compare ISR/SC at different follow-up time points. Multiple regression analysis was used to evaluate risk factors for the development of ISR/SC. Outcomes after reintervention for ISR/SC were also appraised. The Kaplan-Meier analysis was used to assess stent patency after intervention, whereas the paired *t*-test was used to examine pre- and post-intervention outcomes. Primary patency continued till the stent required a procedure for stenosis or occlusion. Primary assisted patency was defined as continued maintenance of patency in a nonthrombosed stent, whereas secondary patency was defined as patency after the restoration of flow in a thrombosed stent. A *P* value of ≤.05 was considered significant.

RESULTS

A total of 578 limbs/patients underwent stenting for stenotic lesions (NIVL/PTS). The median age was 59 years. There was a preponderance of women (395:183). Left laterality was more common (365:213). With regard to Clinical, Etiological, Anatomical, and Pathophysiological classification (CEAP) clinical class, of the 554 limbs for which data were available, there were 2 (0.36%) C0 patients, 0 C1 patients, 3 (0.54%) C2 patients, 1506 (27.2%) C3 patient, 299 (542%) C4 patients, 29 (5.3%) C5 patients, and 71 (12.9%) C6 patients. Patients with CEAP classes of 0 and 2 underwent intervention secondary to disabling venous claudication (leg pain/tightness that develops with ambulation/exercise). The median follow-up was 24 months. Given the short length of the Wallstent, the median number of stents placed per patient was 2, with a median stent length of 80 mm. Taking into account the required overlap between stents and the foreshortening that occurs with angioplasty the actual length of the stent column is less than the combined

Table I. Incidence/prevalence of in-stent restenosis (ISR) at various follow-up time points

	CFV	Caudal EIV	Cranial EIV	Caudal CIV	Cranial CIV
Day 1					
Incidence (n)	9	15	16	10	9
Total limbs (n)	103	103	103	103	103
Incidence %	9	15	16	10	9
3 months					
Prevalence (n)	19	42	49	41	35
Total limbs (n)	103	103	103	103	103
Prevalence %	19	42	49	41	35
6 months					
Prevalence (n)	36	50	58	50	48
Total limbs (n)	103	103	103	103	103
Prevalence %	36	50	58	50	48
12 months					
Prevalence (n)	27	34	49	37	31
Total limbs (n)	103	103	103	103	103
Prevalence %	27	33	48	36	30

CFV, Common femoral vein; *CIV*, common iliac vein; *EIV*, external iliac vein.

lengths of the stents. A total of 18 of the 24 (75%) limbs/patients undergoing recanalization underwent placement of caval stents (24 mm × 45 mm Wallstents) as well giving additional stent length into the cava.

Characteristics of ISR. Overall, 27% of limbs had any degree of ISR on day 1. By 3 months, 74% of limbs had developed ISR that remained stable (74%) at 6 months, but went up to 78% at 12 months (Table I). The severity of the ISR by segment is also considered in Table I. Data were available for 103 limbs at all time points and were used for the repeated-measures ANOVA/Tukey's post-test analysis. This analysis revealed a significant difference between day 1 and month 3 ($P = .0001$), without a significant difference in prevalence of ISR between 3, 6, and 12 months suggestive of stabilization of ISR around 3 months (Fig 2). At 60 months after intervention, only 51% of patients had ISR over 50% in any segment (Fig 3).

Characteristics of SC. Overall, 80% of limbs had some SC on day 1. SC was noted in 81% of limbs at 3 months, 79% of limbs at 6 months, and 84% of limbs at 12 months (Table II). The severity of the SC by segment is also considered in Table I. Data for SC were available for 80 limbs at all time points and were used for the repeated-measures ANOVA/Tukey's post-test analysis. This analysis found no significant difference in SC between day 1, months 3, 6, and 12, indicating that SC occurred right after stent placement and remained stable subsequently (Fig 4).

Risk factors for ISR. Multiple regression analysis demonstrated stent inflow channel luminal area (hazard ratio [HR], 1.88, $P = .02$) and shear rate (HR, 6.70, $P < .0001$) to be significant risk factors for the development of ISR on day 1. Shear rate was again a significant risk factor at month 3 (HR, 4.53, $P < .0001$) (Table III).

Risk factors for SC. Asymmetric stenting was (HR, 2.65, $P = .004$) found to be a statistically significant predictor on day 1 (Table IV).

Reintervention. Over a median follow-up of 24 months, a total of 109 of 578 (18.9%) limbs underwent reintervention. Of these, reinterventions for ISR alone was performed in 45 (7.8%) limbs, SC alone in 1 (0.2%) limb, ISR and SC in 49 (8.5%) limbs, and stent occlusion in 14 (2.4%) limbs. The median time to reintervention was 11 months. A total of 32 limbs underwent stent extension at the time of reintervention. The median number of added stents was 1. The degree of ISR or SC alone did not determine reintervention as demonstrated by the finding that median % ISR (40% vs 39%, $P = .23$) or median % SC (25% vs 33%, $P > .05$) did not differ in patients who underwent reintervention vs those who did not. Clinical severity of recurrent symptoms was what determined reintervention in patients. There was a statistically significant difference in the GOS ($P = .006$) and VAS pain scores ($P < .0001$) between those who underwent reintervention (GOS 2 and VAS pain score 5) vs those who did not undergo reintervention (GOS 1; VAS 1). After reintervention, the VAS pain score changed from 5 to 3 and GOS from 2 to 1 at 12 months ($P < .05$). Primary, primary assisted, and secondary patencies at 60 months were 70%, 98%, and 84% after reintervention for ISR (Fig 5) and 70%, 99%, and 84% after reintervention for SC, respectively (Fig 6). There were no repeat reinterventions.

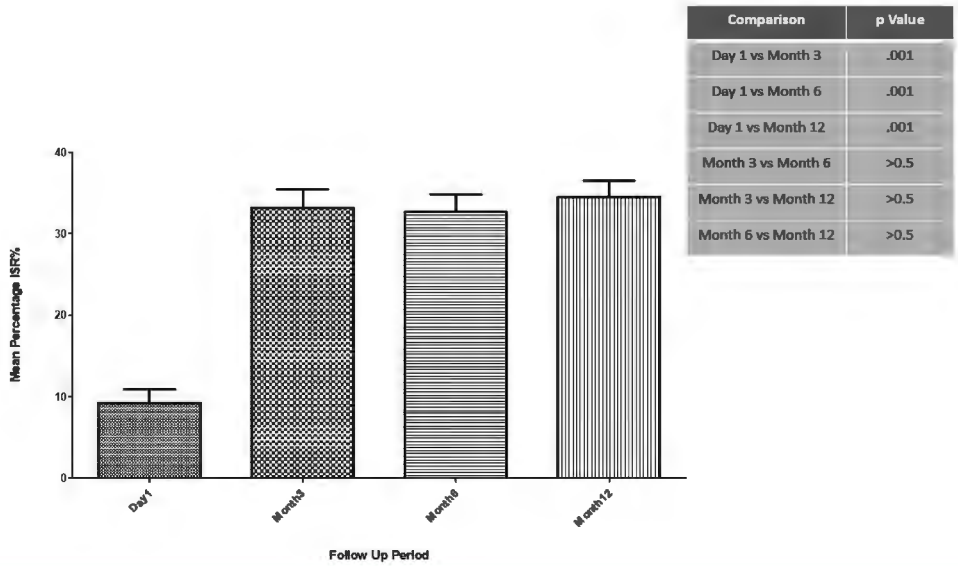

Fig 2. Repeated-measures analysis of variance (ANOVA)/Tukey's post-test analysis for comparison of percentage in-stent restenosis (*ISR*) on day 1, month 3, month 6, and month 12.

DISCUSSION

ISR and SC represent the most common complications of iliofemoral venous stenting followed by stent occlusion.[1,2,11] The incidence of severe ISR (≥50%) has been noted to be 5% to 13%.[2,27,28] Overall, reintervention rate after femoroiliocaval stenting in this study of less than 20% is similar to what has been previously reported.[2,5,10,29]

The universality of in-stent restenosis and stent compression. By 3 months, 74% of the patients who underwent femoroiliocaval stenting had some degree of ISR. The prevalence then plateaus. Maximal ISR was in the CIV or EIV segments. In addition, only 51% of patients had 50% or more ISR at 5 years after intervention. This is suggestive of ISR not being a relentlessly progressive condition leading to stent occlusion. The latter is a more acutely occurring condition.[11] With regard to SC, the incidence is highest on day 1 without a significant increase subsequently. Maximal SC was variable across the CFV, EIV, and CIV segments depending on the follow-up time point. Overall, SC alone was rare, and a combination of ISR and SC was far more common.

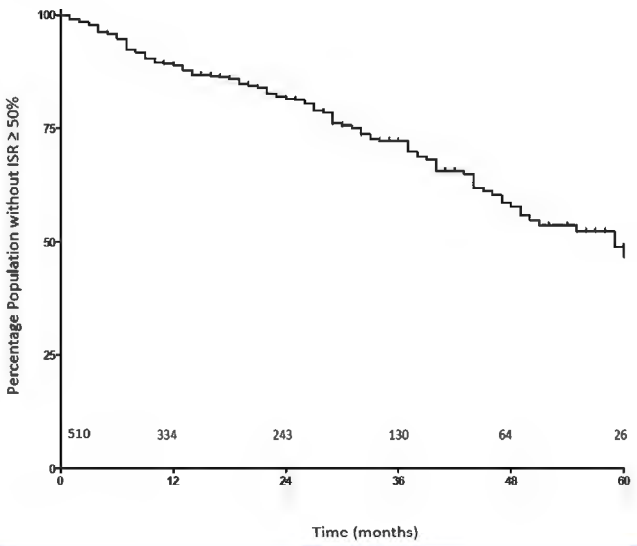

Fig 3. Plot demonstrating stented limbs that exceed 50% in-stent restenosis (*ISR*) over time. All limbs had less than 50% ISR at the starting point. (Standard error of the mean was <10%.)

Predictors for the development of in-stent restenosis and stent compression. Of the several variables evaluated as predictors for ISR, IVUS inflow channel luminal area and shear rate were found to be risk factors for the development of ISR. Of these, IVUS inflow channel luminal area less than 125 mm^2 had an HR of 1.88 ($P = .02$). Shear rate, which represents velocity gradient across the vessel segment, greater than 100 s^{-1} had an HR of 6.70 ($P < .0001$) on day 1 and 4.53 ($P < .0001$) at month 3. These findings are suggestive of a higher velocity gradient reducing the risk for ISR. The placement of a stent changes this gradient and hence the shear rate. This change is possibly the result of the interplay between relief of venous stenosis with its impact on both radius and velocity and the creation of a new "vein wall" likely generating more friction and altering the laminar flow that existed previously. The final shear rate represents the outcome of this complex interaction and is a risk factor for ISR. Any increase in shear rate will reduce the risk of ISR development. The goal of stenting has to be to increase the luminal radius and at the same time to increase velocity to provide a net increase in shear

Table II. Incidence/prevalence of stent compression (SC) at various follow-up time points

	CFV	Caudal EIV	Cranial EIV	Caudal CIV	Cranial CIV
Day 1					
Incidence (n)	53	55	47	38	35
Total limbs (n)	80	80	80	80	80
Incidence %	66	68	58	48	43
3 months					
Prevalence (n)	47	45	54	34	39
Total limbs (n)	80	80	80	80	80
Prevalence %	59	57	67	43	49
6 months					
Prevalence (n)	54	56	50	44	41
Total limbs (n)	80	80	80	80	80
Prevalence %	67	70	63	55	52
12 months					
Prevalence (n)	54	51	48	51	47
Total limbs (n)	80	80	80	80	80
Prevalence %	68	64	60	64	59

CFV, Common femoral vein; *CIV*, common iliac vein; *EIV*, external iliac vein.

rate. If the luminal radius increases at the cost of reduced velocity, the shear rate will drop and set the stent up for ISR development. This can occur with the use of excessively large venous stents. Use of too small a stent may increase shear rate but at the cost of persistent venous hypertension and persistent/residual symptoms. In this regard, the authors do not recommend placement of a stent smaller than 14 mm in the CFV with 2 mm addition for the CIV stent.[30] Having said this, stenting must be individualized to the patient. With regard to SC, asymmetric stent sizing was found to be a statistically significant predictor. This is likely due to stent recoil, with larger sizes at greater risk than smaller ones. Despite this finding, it is important to keep the aforementioned principles in mind while determining appropriate stent sizes. Reinterventions for SC alone were few, and in those with combined ISR and SC, ISR was the bigger problem highlighting the decreased significance of SC.

Reintervention. The median time to reintervention was 11 months. ISR alone or in combination with SC was responsible for the majority of reinterventions in

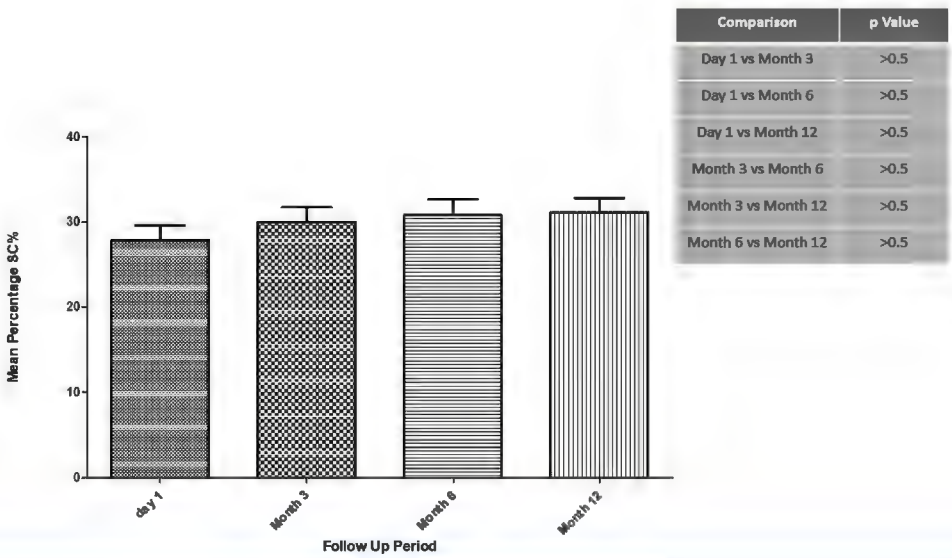

Fig 4. Repeated-measures analysis of variance (ANOVA)/Tukey's post-test analysis for comparison of percentage stent compression (SC) on day 1, month 3, month 6, and month 12.

Table III. Risk factors for development of in-stent restenosis (ISR) on day 1 and month 3 (multiple regression analysis)

Variable	Day 1 HR(*P*)	Month 3 HR(*P*)
Age	1.687 (.052)	0.705 (.375)
Gender	1.041 (.869)	0.900 (.782)
Coexistent thrombophilia	1.104 (.729)	1.130 (.751)
NIVL/PTS	1.501 (.110)	0.444 (.862)
Anticoagulation status	1.248 (.409)	1.373 (.374)
Shear Rate	**6.702 (.000)**	**4.527 (.000)**
Flow rate	1.143 (.560)	1.345 (.388)
Inflow area	**1.877 (.017)**	0.886 (.785)
Asymmetric stenting	0.610 (.165)	1.667 (.545)
NLR	1.019 (.936)	1.136 (.705)
PLR	0.790 (.309)	1.554 (.192)
Platelet count	0.816 (.645)	2.88 (.076)

HR, Hazard ratio; *NIVL*, nonthrombotic iliac vein lesion; *NLR*, neutrophil lymphocyte ratio; *PLR*, platelet lymphocyte ratio; *PTS*, post-thrombotic syndrome.
Boldface *P* values represent statistical significance.

Table IV. Risk factors for development of stent compression (SC) on day 1 (multiple regression analysis)

Variable	Day 1 HR(*P*)
Age	0.772 (.277)
Gender	0.920 (.713)
Asymmetric stenting	**2.651 (.004)**
MTS/PTS	1.204 (.405)
Stenosis over 50%	0.529 (.388)
NLR	0.721 (.115)
PLR	1.075 (.729)
Platelet count	1.004 (.993)

HR, Hazard ratio; *MTS*, May Thurner syndrome; *NLR*, neutrophil lymphocyte ratio; *PLR*, platelet lymphocyte ratio; *PTS*, post-thrombotic syndrome.
Boldface *P* value represent significant.

our cohort in keeping with prior findings.[5] Degree of ISR alone was not an indication for reintervention, as evidenced by the absence of a statistically significant difference in median ISR among those who underwent reintervention vs those who did not. The same degree of ISR may not necessarily result in similar symptoms in different patients. In addition, worse symptoms may occur in a patient with less ISR than in another with greater ISR. This highlights the futility of using a cutoff value of ISR for reintervention. By extension, this also holds true for setting a predetermined cutoff threshold for percentage stenosis for initial stenting because the same degree of stenosis may cause varying degrees of venous hypertension and consequently differing clinical manifestations. Recurrence of symptoms should be the guiding factor for reintervention after venous stenting as reflected by the significant difference in the GOS (2) and VAS pain score (5) among those who underwent reintervention vs those who did not undergo reintervention (GOS 1; VAS 1). Good outcomes can be expected after reintervention, as evidenced by improvement in the GOS and VAS pain score after reintervention at 12 months. Reintervention when offered to patients with recurrence of symptoms impairing quality of life results in clinical improvement with good stent patency. Prior studies have used venograms to evaluate ISR/SC; this study differs in that IVUS was exclusively used to determine the presence of ISR and/or SC and to evaluate treatment response in patients undergoing reintervention.

Strategies to counter in-stent restenosis and stent compression. ISR appears to be impacted by flow mechanisms including inflow channel luminal area and shear rate. In light of this individually tailoring the stent to a size that allows for appropriate inflow match at the same time enabling mitigation of venous hypertension may help reduce the ISR. At times this may not be possible especially in patients with severe PTS changes in the lower extremity and a degree of ISR is to be expected. Once ISR develops, balloon angioplasty alone may be adequate. Laser ablation with/without repeat angioplasty is helpful in recalcitrant situations when a "hard ISR lesion" is encountered.[5] This lesion also has a higher recurrence than the more common "soft ISR lesion." There are some pathologic data to suggest that these hard lesions could represent neointimal hyperplasia.[31] Large caliber drug eluting balloons may have a role to play in this setting by preventing repeat buildup of ISR provided it is possible to keep the side effects down vis-à-vis drug dose delivered. The same goes for the possibility of drug eluting venous stents. The key limitation will be

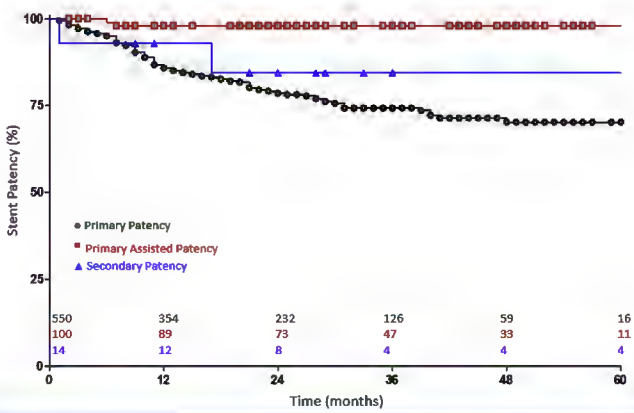

Fig 5. Stent patencies after reintervention for in-stent restenosis (ISR). (Standard error of the mean was <10%.)

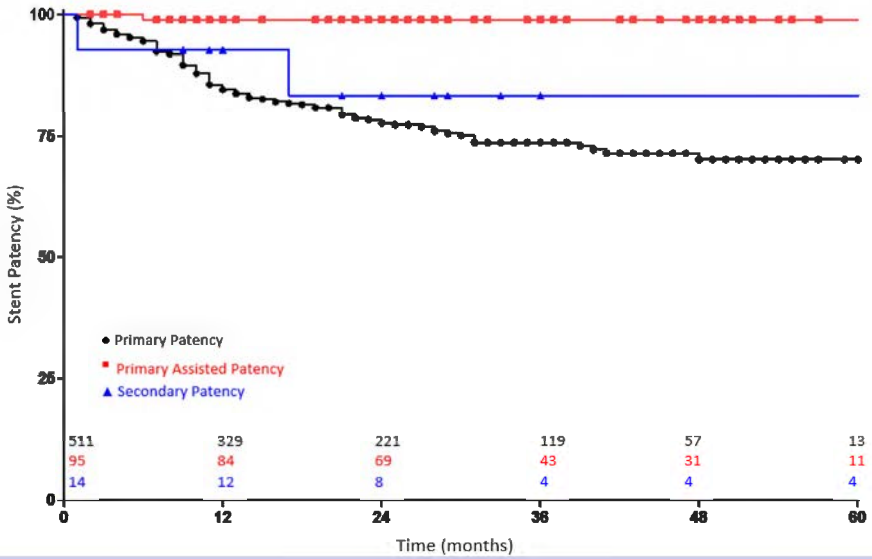

Fig 6. Stent patencies after reintervention for stent compression (SC). (Standard error of the mean was <10%.)

the drug dose that will be required given the much larger caliber of the venous stents compared with arterial.

For SC, avoidance of asymmetric stents may help reduce its incidence. An overwhelming majority of stents deployed crossed the inguinal ligament and so was not possible to assess the impact of this on SC.

In essence, although ISR and SC are universal, they are seldom progressive to the point of requiring reintervention. In fact, only 16% of limbs required reintervention for ISR and/or SC.

Limitations. These include the inherent retrospective nature of the study and the inability to adequately visualize all the iliofemoral segments in every patient at each visit. The latter was due to depth of the vessel, bowel gas, or shadowing from other adjacent structures and was primarily responsible for the decreased number of limbs at the various follow-up time points. Only those patients whose entire stent could be visualized were included in the analysis. Loss to follow-up over time after stenting also represents a problem. The impact of crossing the inguinal ligament on ISR/SC could also not be assessed because an overwhelming majority of stents were extended below the inguinal ligament into an area of good inflow. There were no definitive ways to counter these limitations which have a bearing on the results of the study.

CONCLUSIONS

Although ISR and SC are both common after stenting for CIVO, neither are relentlessly progressive. Indication for reintervention must be a recurrence of symptoms with impairment of quality of life and not a percentage of ISR or degree of SC. After reintervention good outcomes can be expected both in terms of clinical improvement and stent patency. Further study of the impact of shear rate on stent flow is required to help reduce the incidence of ISR.

AUTHOR CONTRIBUTIONS

Conception and design: AJ
Analysis and interpretation: AJ, RF, SR, JS
Data collection: RF
Writing the article: AJ, RF
Critical revision of the article: AJ, SR, JS
Final approval of the article: AJ, RF, SR, JS
Statistical analysis: RF, JS
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Overall responsibility: AJ

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