An overview of in-stent restenosis in iliofemoral venous stents

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ABSTRACT

Background: Although endovenous stents have been associated with overall low morbidity, they can require reinterventions to correct stent malfunction due to in-stent restenosis (ISR). ISR has often occurred iliofemoral venous stents but has not been well described. It has been reported to develop in >70% of patients who have undergone iliofemoral venous stenting. We sought to provide an overview of ISR in iliofemoral venous stents, including the pathologic, diagnostic, and management considerations and the identification of several areas of potential research in the future.

Methods: A search of reported English-language studies was performed in PubMed and the Cochrane Library. "In-stent restenosis," "vein," "venous," "iliac," and "iliofemoral" were used as keywords. The pertinent reports included in the present review had addressed the pathology, diagnosis, and current management options for ISR.

Results: ISR refers to the narrowing of the luminal caliber of the stent owing to the development of stenosis inside the stent itself. ISR should be differentiated from stent compression. Two main types of ISR have been described: soft and hard lesions. These lesions respond differently to angioplasty. Stent inflow and shear stress are important factors in the development of ISR. The treatment options available at present include balloon angioplasty (hyperdilation or isodilation), laser ablation, atherectomy, and Z-stent placement.

Conclusions: Reintervention for ISR should be determined by the presence of residual or recurrent symptoms and not simply by a numeric value obtained from an imaging study. Overall stent occlusion due to ISR is rare, and no role exists for prophylactic angioplasty to treat asymptomatic ISR. The current treatment options for ISR are mostly durable and effective. However, more research is needed on methods to prevent the development of ISR. The role of antiplatelet and anticoagulant agents in the prevention of ISR requires further investigation, with particular attention to unique subset of patients (after thrombosis vs nonthrombotic iliac vein lesions). For high-risk, post-thrombotic patients, anticoagulation can be considered to prevent ISR. The role of triple therapy (anticoagulation and dual antiplatelet therapy) in the prevention of ISR remains unclear. (J Vasc Surg Venous Lymphat Disord 2021;■:1-12.)

Keywords: Balloon angioplasty; Hyperdilation; Iliofemoral venous stent; In-stent restenosis; Intravascular ultrasound; Isodilation; IVUS; Stent compression

Iliofemoral venous stenting has become the standard of care in the management of chronic iliofemoral venous obstruction (CIVO), and open venous reconstruction has had a more secondary role, with its use only for select patients.[1] Endovenous stenting is associated with low morbidity.[2,3] However, iliofemoral venous stents can require reintervention. Reinterventions include recanalization or thrombectomy of occluded stents, proximal or distal extension of the stents, correction of stent malfunction, including in-stent restenosis (ISR) and stent compression (SC). For some patients, more than one type of reintervention will be required.[3]

ISR has often occurred iliofemoral venous stents but has not been as well documented or described as for coronary and peripheral arterial treatment for which stenting has also been fraught with ISR. Of the patients who have undergone iliofemoral venous stenting, 5% to 20% will require reintervention, mainly for ISR or SC, or a combination of both.[1,3-8] ISR accounts for ≤83% of the reinterventions in iliofemoral venous stents.[4] It can develop in >70% of patients who undergo iliofemoral venous stenting.[5,9] Severe ISR (>50% stenosis) has been observed in 5% to 15% of limbs after iliofemoral venous stenting.[9,10] ISR mostly occurs in areas of stent overlap or at the leading edges. Similarly, malapposed stents or stents with shelving can create nonlaminar flow, which can disturb the microcirculatory homeostasis and wall shear stress, leading to platelet activation and deposition of thrombus.[11] This, in turn, can lead to the development of ISR. Patients with stent malfunction can present with recurrent or residual symptoms. In one study, ISR was present in all limbs with residual or recurrent symptoms (n = 103).[12]

From The RANE Center for Venous and Lymphatic Diseases.

Author conflict of interest: S.R. receives royalties from Veniti Inc and has U.S. patents for IVUS diagnostics and iliac vein stent design. T.S. has no conflicts of interest.

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

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2021.10.011

We sought to provide an overview of ISR in iliofemoral venous stents, including the pathologic, diagnostic, and management considerations and the identification of several areas of potential research in the future.

SEARCH STRATEGY

An electronic search was performed in July 2021 of PubMed and the Cochrane Library. Only reports for which the text was available in the English language were included for review. The references of the included studies were also searched. Conference abstracts were also reviewed. The search strategy included the keyword "in-stent restenosis" and one of the following terms: "vein," "venous," "iliac," and "iliofemoral." No time restriction was set for the date of the reports.

ISR AND SC

Both ISR and SC lead to a loss of gain of the luminal caliber that was achieved initially by angioplasty and iliofemoral venous stenting. ISR refers to narrowing of the luminal caliber of the stent owing to the development of stenosis inside the stent itself. SC refers to narrowing of the stent by extrinsic fibrous tissue or strictures. However, in many cases, ISR will develop in combination with SC.[6] ISR appears to have a more predominant role in the reduction of the flow channel caliber compared with SC.[6,12] Although ISR also occurs in stents deployed in various arterial beds (eg, coronary and peripheral arterial stents), SC appears to be unique to venous stenting.[12]

SC and ISR also differ in their response to treatment. ISR, in general, can be corrected with balloon angioplasty in most patients. In one study, complete clearance of ISR occurred in 62% of the limbs after angioplasty.[12] In contrast, SC is more resistant to treatment. Balloon angioplasty had no effect on SC correction in almost 70% of limbs, likely owing to significant recoil.[12] In one study, ISR was found more often in patients with significant SC vs those without SC (52.9% vs 21.2%; $P = .023$).[13] SC and ISR both occur most frequently in the external iliac vein (EIV).[12]

TYPES OF ISR

Two main types of ISR have been described: soft lesions and hard lesions.[3] Both lesions have certain unique characteristics and differ from each other in their response to angioplasty. The differences between the two types of ISR and some of their risk factors are listed in Table I.

Table I. Differences between soft and hard ISR lesions

ISR lesions
Soft
Due to thrombus layering the stent
Can extend into stent inflow channel
Develops early after stent placement
Less echogenic on IVUS
Less tendency to recur
Less recurrence of clinical symptoms
Less resistance to balloon dilatation
Due to inflow/outflow problems that require correction
Angioplasty helpful in correction
Hard
Fibrous lesions composed of collagen; calcification possible
Usually does not extend into stent inflow channel
Develops later after stent placement
More echogenic on IVUS
More likely to recur
More recurrence of clinical symptoms
More resistance to balloon dilatation
Occurs independently of inflow and outflow problems
Laser ablation or atherectomy helpful in recalcitrant cases

ISR, In-stent restenosis; *IVUS*, intravascular ultrasound.

DIAGNOSIS OF ISR

Six modalities can be used to diagnose ISR: duplex ultrasound (DUS), contrast-enhanced ultrasound (CEUS), intravascular ultrasound (IVUS), venography (single-plane or multiplanar), computed tomography venography (CTV), and magnetic resonance venography (MRV). DUS is readily available and noninvasive. However, iliac DUS is limited by operator dependence, the patient's body habitus, the vessel depth, the presence of bowel gas, and shadowing from the surrounding organs. In our experience, the iliac vein will not be adequately visualized using DUS in ≤20% of patients because of these factors. According to a recent systematic review, IVUS is the most sensitive method for detecting CIVO.[14] It is also the most sensitive diagnostic modality for detecting stent malfunction (Fig 1, *A*).[15] ISR will have a heterogeneous appearance on IVUS, and the stent itself will appear as a "circular, striated" ring.[6] The use of IVUS has been recommended to appropriately diagnose the cause of stent malfunction such that it can be addressed by the best reintervention.[16] However, IVUS is invasive and not routinely performed after a procedure as a part of the surveillance for all patients. IVUS can be performed concurrent with venography when the vein has been accessed. Traditionally, venography has been the modality most often used in the detection of stent malfunction (Figs 1, *B*, and 2). However, the sensitivity is lower than that for IVUS, although a specific and formal head-to-head comparison of patients with ISR is lacking. Experience with CTV and MRV for stent surveillance is also limited, because these are not routinely obtained after stenting in most centers across the United States.[17] CTV is a good prescreening tool before the performance of IVUS for patients with CIVO who will undergo subsequent angioplasty and stenting.[18] Yang et al[13] recently used DUS and CTV to describe the effects of SC on ISR

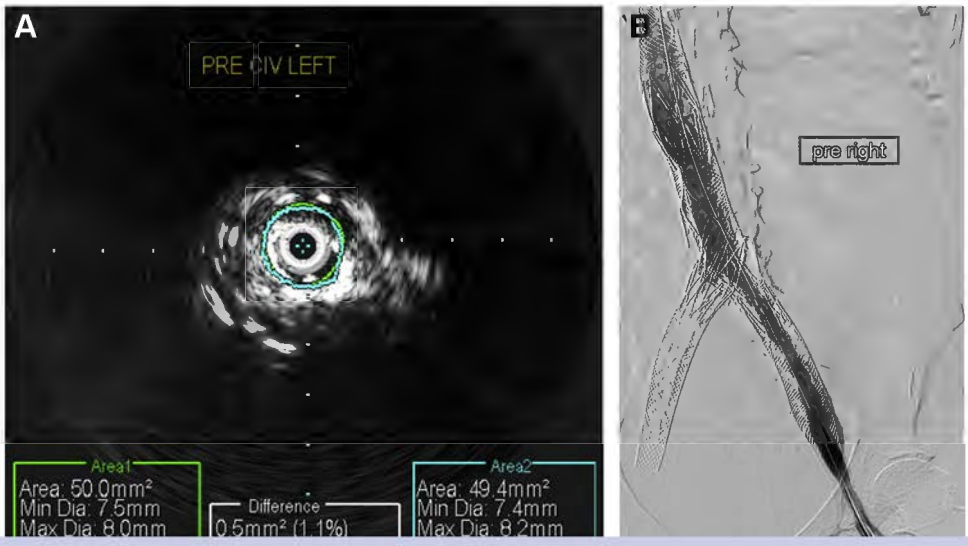

Fig 1. In-stent restenosis (ISR) in an iliofemoral venous stent. **A,** Intravascular ultrasound (IVUS) is more sensitive and displays the severity of ISR in the common iliac venous stent. **B,** Venography can show ISR but will underestimate the severity of the lesion compared with IVUS. *CIV,* Common iliac vein.

in patients who had undergone iliac vein stenting, although the two modalities were not compared to each other in their study.

Liu et al[19] compared DUS, CEUS, and CTV in the detection of iliac venous ISR. DUS and CEUS (kappa statistic, 0.449) and DUS and CTV (kappa statistic, 0.516) had weak agreement for the diagnosis of ISR, and CEUS and CTV (kappa statistic, 0.884) had better agreement. The sensitivity and specificity of DUS in the diagnosis of ISR was 63% and 88%, respectively. In contrast, CEUS showed higher sensitivity and specificity for ISR diagnosis at 91% and 97%, respectively.[19]

CALCULATION OF ISR

Using the DUS measurements, ISR can be calculated using the following formula[5]:

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

However, one technical consideration should be remembered. Because of the possibility of SC and inaccurate stent size selection (more often undersizing), the original stent diameter can be difficult to accurately ascertain in some cases. Therefore, we would recommend indexing the stent diameter for the particular segment to the optimal stent diameter for that venous segment, which has been determined using flow equations, including Poiseuille's equation and Young's scaling ratios, in healthy volunteers.[14] Thus, 16 mm for the common iliac vein, 14 mm for the EIV, and 12 mm for the common femoral vein (CFV). Thus, for undersized stents, ISR should be calculated according to the optimal size for the native vein and not on the basis of the undersized stent.

VIRTUAL HISTOLOGIC FEATURES OF ISR

Using IVUS and color spectrometry, examination of the virtual histologic features of ISR revealed the following elements in various proportions: collagen, fatty tissue, areas of necrosis, and calcification (Supplementary Fig 1, online only).[6]

HISTOPATHOLOGIC FEATURES OF ISR

Robertson et al[20] described the histopathologic features of the tissue retrieved during directional atherectomy of iliocaval venous ISR at 1 year after stent placement. The specimen demonstrated features similar to those of arterial ISR. It is possible that different cell types and components will be present in different proportions as the ISR in venous stents matures over time. This evolution of ISR over time is not fully understood nor described at present. Early ISR likely has a predominance of fresh thrombus and late ISR, a predominance of neointima, smooth muscle cells, fibrosis, and so forth (Table II).[21]

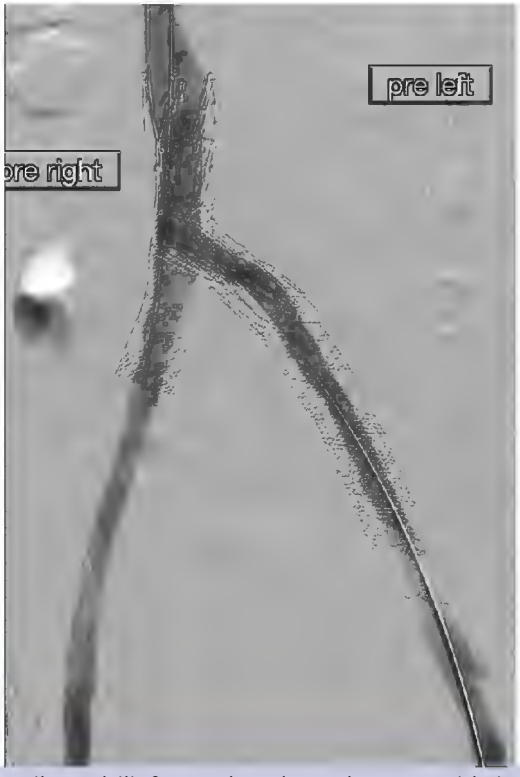

Fig 2. Bilateral iliofemoral and caval stents with in-stent restenosis (ISR) noted on single-plane venography. In general, less ISR was observed in the inferior vena cava (IVC) stents than in iliofemoral stents.

RESULTS OF REINTERVENTIONS FOR ISR

Reintervention for ISR has been associated with good and durable relief of symptoms. The cumulative improvement in pain and swelling at 18 months after reintervention was >60%. Most of the ulcers (90%) at healed at 12 months after reintervention.[3] In general, the resolution of ISR has been better with angioplasty than has the resolution for SC.[6] After reintervention for ISR, the primary, primary assisted, and secondary patency at 60 months was reported to be 70%, 98%, and 84%, respectively.[5]

NUMBER AND TIMING OF REINTERVENTIONS

In one study, most limbs (77%) had required only one reintervention, with the remainder requiring two or more reinterventions.[3] Because most limbs had required only one reintervention, the original reintervention procedure can be considered fairly durable. The median interval to reintervention was 11 to 15 months (range, 2-84 months) after initial stent placement in the different studies.[3,5]

In one study of 578 limbs, the rate of ISR had increased from 27% on postprocedure day 1 to 74% by 3 months, with a relative plateau thereafter. In contrast, SC was seen in 80% of the limbs on postprocedure day 1 and had remained steady thereafter.[5] These findings indicate the high frequency of ISR and SC after stenting in the iliofemoral venous system.

Table II. Histopathologic features of ISR in venous, arterial, and carotid artery stents and saphenous vein bypass grafts

Specimen	Stains used	Important histopathologic features
Iliocaval venous stents[21]	H&E, colloidal iron, Masson trichrome, smooth muscle actin, CD68	H&E stain: spindled and stellate cells in a myxoid material; colloidal iron stain: proteoglycan within stromal tissue; smooth muscle actin immunostain: smooth muscle differentiation in cells
Iliocaval venous stents[15]	NR	Fibrosis without thrombus
Venous stents[22]	H&E	0-2 days: fresh thrombus; 2 weeks: old thrombus (acellular and nonorganized); 4 weeks: diffuse intimal thickening
Coronary arterial stents[23]	CD68 (macrophages), and endothelial marker PECAM-1 (CD31)	Neointimal angiogenesis and macrophage infiltrates
Coronary arterial stents[24]	H&E, Masson's trichrome, and elastica van Gieson	Neointima with alpha-actin-positive and smooth muscle cells in a myxomatous extracellular matrix
Iliac arterial stents[24]	H&E, Masson's trichrome, and elastica van Gieson	Organized thrombi, mature neointima, spindle cells
Saphenous vein bypass graft with stents[25]	H&E-saffron, periodic acid-Schiff, Masson trichrome, phosphotungstic acid hematoxylin, Best's carmine, Alcian blue, von Kossa staining.	Fibrosis, atheroma, hyperplasia and thrombus
Saphenous vein bypass graft with stents[26]	H&E, oil red O	Intimal hyperplasia, atherosclerotic plaque, lipid laden macrophages, fibrous cap

H&E, Hematoxylin and eosin; *NR,* not reported; *PECAM-1,* platelet endothelial cell adhesion molecule-1.

PRIMARY, PRIMARY-ASSISTED, AND SECONDARY PATENCY

Patency is considered primary until a stent has required reintervention for any reason (eg, occlusion, ISR, SC). Primary-assisted patency is defined as the stent remaining patent after reintervention for a nonocclusive etiology. Secondary patency is defined as patency after reestablishment of flow in a thrombosed or an occluded stent.[5]

Stent occlusion is rare (0.5%-3%),[22,23] including from ISR. However, ISR can lead to residual or recurrent symptoms in patients, which will primarily necessitate reintervention on the stents.[6] Prophylactic intervention to treat asymptomatic ISR or SC has not been recommended because of the low rate of stent occlusion from ISR (<10%). The primary patency of Wallstents (Boston Scientific, Marlborough, Mass) has been 20% to 30% less than the primary-assisted and secondary patency because of the additional interventions required for adequate symptom relief after initial stenting and restoration of the luminal caliber of the stent.[4,6,24]

INDICATIONS FOR INTERVENTION

Although some investigators have advocated reintervention for patients with ≥50% ISR on imaging and the presence of symptoms, others have advocated intervention according to the symptoms alone because preoperative imaging modalities such as ultrasound can underdiagnose the true extent of stent malfunction.[3,6] Therefore, intervention determined by a binary distinction of ISR (<50% vs >50%) is not recommended.

The symptoms of stent malfunction can be residual or recurrent chronic venous insufficiency symptoms after the performance of intervention and can include swelling, pain, venous dermatitis, and slow-healing or recurrent ulceration.[3,5] Such symptoms might not improve with conservative therapy alone and could require reintervention. The philosophy behind symptom-driven reintervention is similar to that advocated for intervention for native iliac vein stenosis. The VIDIO (venogram vs intravascular ultrasound for diagnosing iliac vein obstruction) trial considered ≥50% stenosis to be clinically significant enough to warrant intervention in native iliac vein stenosis.[25,26] However, it is important to remember that iliac vein pathology is permissive.[27] Thus, the condition is widely prevalent but silent in the general population, as shown by Kibbe et al.[28] A second insult such as trauma, surgery, or infection is required to precipitate the symptoms in a permissive condition such as chronic venous insufficiency.[27] Hence, the symptoms must be carefully considered, without just considering the numeric degree of ISR or iliac venous stenosis from a preoperative imaging study. A recent study by Jayaraj et al[29] showed that the initial clinical presentation, clinical and quality of life improvement, and reintervention after stenting were all independent of the degree of venous stenosis noted initially on IVUS. In a study of 578 limbs, no significant difference was found in the proportion of ISR among patients with reintervention vs those without ($P > .05$).[5] The median stenosis found on IVUS from symptomatic ISR or SC in one series was <40% and not >50%.[6]

FACTORS ASSOCIATED WITH REINTERVENTION FOR ISR

Post-thrombotic lesions vs nonthrombotic iliac vein lesions. In one study, an equal proportion of post-thrombotic limbs (13%; 76 of 577) and nonthrombotic iliac vein lesions (NIVLs; 12%; 61 of 508) had required reintervention (P = NS).[3] However, ISR has developed more frequently in post-thrombotic limbs than in limbs with NIVLs and patients with thrombophilia.[9]

Stent inflow and shear stress. A stent inflow area <125 mm^2 (hazard ratio [HR], 1.88; $P = .02$) and shear rate >100 s^{-1} (HR, 6.7; $P < .0001$) appear to significantly affect the development of ISR.[5] The former is the area of the native vein, usually proximal to the femoral vein–profunda vein confluence and just distal to the expected distal end of the stent. The latter is a measure of velocity gradient and can be calculated using the following formula[5]:

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

Low and oscillatory endothelial shear stress has a well-known role in the development of arterial atherosclerosis and has also been implicated in the development of ISR.[30] The implantation of stents alters the flow and shear stress in the vessels and modifies the vessel's reaction to endothelial injury.[31] High shear stress reduces the development of ISR.[32] In addition, circumferential stress generated by the stretching of the stenosed venous wall by the stent could have a role in the development of ISR.[30] Ideally, the stent should be matched to the inflow, in addition to aiming for restoration of the optimal luminal caliber.[5] If the stent is much larger than the inflow (inflow–stent size mismatch), the venous system will attempt to compensate by layering the stent with thrombus such that size homogeneity between the stent and inflow will be restored and laminar flow reestablished. However, this compensatory process can overshoot and lead to the development of aggressive ISR.

MORBIDITY AND MORTALITY ASSOCIATED WITH REINTERVENTION FOR ISR

Reinterventions for ISR are associated with minimal morbidity. Some of the infrequent complications that can occur after reintervention for ISR include access site hematomas (6%),[6] back pain (25%),[6] deep vein thrombosis (1%),[6] stent occlusion (2.5%),[6] cut-down for a retained balloon (1.7%),[33] retroperitoneal hematoma

(1.7%),[33] and arteriovenous fistulas. No mortality with the procedures has been reported.[3]

ISR IN INFERIOR VENA CAVA STENTS

In some cases, the stents will need to be extended into the inferior vena cava (IVC) to correct outflow stenosis. In other cases, IVC stenosis or occlusion can be encountered in isolation and will require endovenous stenting to establish in-line flow. However, the rate of ISR and the subsequent need for reintervention in IVC stents has been noted to be lower than that for iliofemoral stents in small case series.[3,34] In one study of 83 patients with Budd-Chiari syndrome, only 1 patient had developed ISR in the IVC stents.[35] In two other studies, 1 of 9 patients (11%) and 1 of 13 patients (7.7%) developed restenosis.[36,37] This might be related to the larger caliber of the stents and the more dynamic flow rate in the IVC. Typically, 24-mm Wallstents (Fig 2) will be used in the IVC with or without Z-stents (Cook Medical, Bloomington, Ind).

ISR IN DEDICATED VENOUS STENTS

Four dedicated nitinol stents became available for revascularization of CIVO in the past 2.5 years in the United States. The trials for these stents included VIRTUS (an evaluation of the Vici venous stent system in patients with chronic iliofemoral venous outflow obstruction), VIVO clinical study, VERNACULAR (BARD the VENOVO venous stent study for treatment of iliofemoral occlusive disease), and ABRE (clinical study of the Abre venous self-expanding stent system). However, the VICI (Boston Scientific Corp, Marlborough, Mass) and Venovo (BD Interventional, Wokingham, UK) stents were recalled earlier in 2021 because of issues with stent embolization (<1%; VICI) and the deployment delivery system (>250 reports; Venovo). The short-term primary patency for these stents in various trials was not inferior to that of the Wallstent (Boston Scientific). However, the rate of reintervention to treat ISR is unknown at present owing to the relatively short duration of follow-up.[38] With the newer dedicated nitinol stents, longer lengths are available, and they have exhibited less foreshortening. Therefore, on average, fewer nitinol stents will be required per patient compared with Wallstents, which have demonstrated more foreshortening. This could have an effect on the incidence of ISR. In coronary studies, a higher number of stents was associated with a greater incidence of ISR.[39] ISR in a Venovo stent (BD Interventional) in a patient who had presented with recurrent symptoms is shown in Fig 3.

For the sinus venous stent (OptiMed GmbH, Ettlingen, Germany), a dedicated venous stent available in Europe, ISR occurred in 11.5% of patients (23 of 200), with stent occlusion noted in 12.5% of patients (25 of 200).[40] In another study, the primary patency of the sinus Obliquus hybrid nitinol stent (OptiMed GmbH) was 83% at 10 months. One patient had required reintervention for ISR (1 of 24; 4.2%).[41]

MANAGEMENT OF ISR

Medications

Anticoagulant and antiplatelet agents. At present, the role of antiplatelet and anticoagulant agents in the prevention of ISR in venous stents remains unclear. Some studies have shown no benefit from these agents and others have advocated for the use of these agents to prevent ISR. In a systematic review of 14 studies,

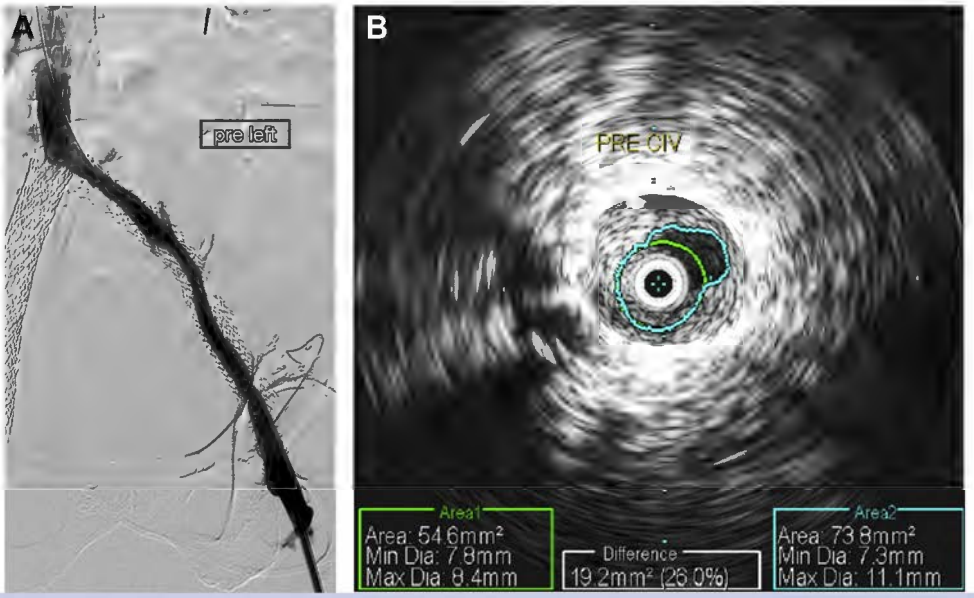

Fig 3. In-stent restenosis (ISR) in a dedicated venous stent (Venovo stent) seen by venography **(A)** and intravascular ultrasound (IVUS; **B)**. Note that venography underestimates the severity of ISR. *CIV,* Common iliac vein.

antithrombotic therapy did not affect the incidence of restenosis after venous stenting.[42] In 86% of the studies included in that review, all the patients had received anticoagulant agents, with antiplatelet agents administered to patients in only 33% of the studies.[42] A more recently reported systematic review concluded that the data at present are insufficient to address the role of anticoagulation therapy after stenting.[43] In another study, the duration of anticoagulation did not appear to affect stent patency.[44] In contrast, Jalaie et al,[45] in their review of various studies, found that anticoagulation therapy had a role in maintaining stent patency. However, no clear consensus was reached on the duration or type of anticoagulation.[45] Langwieser et al[46] described their experience with rivaroxaban (20 mg daily) and clopidogrel (75 mg daily or every other day depending on the results of the platelet aggregation assay) in a small series of nine patients and reported no restenosis after a short median follow-up of 14 months.

In a retrospective study by Pappas et al,[47] the effect of anticoagulation was studied in 377 patients with NIVLs after stenting. Three months of anticoagulation therapy with rivaroxaban was compared with no anticoagulation therapy after the procedure. No significant difference was found in stent patency at 30 months in the two groups (99% vs 98.5%; $P \leq .44$). The investigators recommended postprocedural anticoagulation therapy for NIVL patients if insertion site thromboses or thrombus layering were found on the follow-up ultrasound scans.[47] Matson et al[48] evaluated triple therapy (dual antiplatelet with anticoagulation therapy) in a small subset of five patients with severe post-thrombotic syndrome, a history of multiple venous interventions and/or recanalizations, and recurrent stent thrombosis. The primary stent patency was 80% and the assisted primary patency at 3 months was 100% using dual antiplatelet therapy with anticoagulation therapy.[48]

Anticoagulation is likely beneficial for patients with high-risk post-thrombotic lesions.[49] More data are needed from robust studies of anticoagulation and antiplatelet agents before a final recommendation on their use can be made in the prevention of ISR.

Steroid therapy. Animal and human studies have shown that inflammation plays an important role in the development of ISR after stenting.[50-53] Therefore, anti-inflammatory agents such as steroids could have a role in reducing ISR after stenting.

Beraprost sodium. In small animal experiments, beraprost sodium (a prostaglandin I_2 analogue) was found to have an inhibitory effect on platelet accumulation and smooth muscle cell propagation, reducing the incidence of ISR in Gianturco Z-stents (Cook Medical) that had been implanted into iliac veins.[54] The use of beraprost in the venous system represents a potential area for future research.

Cilostazol. Cilostazol, a platelet phosphodiesterase III inhibitor with antiplatelet properties, appears to prevent ISR in coronary, carotid, and femoropopliteal stents.[55-59] However, the role for cilostazol in the prevention of ISR in venous stents is unknown at present.

Colchicine. Colchicine, primarily used in the treatment of gout because of its anti-inflammatory properties, has been studied on a limited basis in coronary stents, in which it appeared to prevent ISR development.[60] The role for colchicine in the prevention of ISR in venous stents is undefined at present.

Statins. Statins could have a potential role in delaying or preventing the development of ISR in venous stents. They have been studied in coronary stents in combination with an angiotensin receptor blocker.[61] Inhibition of smooth muscle cell migration was noted in vitro when a statin was used in combination with an angiotensin receptor blocker.[62] Statins have also been shown to prevent ISR in peripheral arterial stents.[63]

Endovascular interventions

Isodilation and hyperdilation. For both ISR and SC, balloon angioplasty using high-pressure balloons (14-16 atm usually) has been the most common method of correction (Supplementary Fig 2, online only). Isodilation refers to the dilation of a stent up to its rated diameter using an angioplasty balloon. Thus, a 16-mm iliac venous stent can undergo angioplasty up to 16 mm using a target caliber balloon (16-mm caliber and usually 4-6 cm in length). However, isodilation might not be enough to correct ISR and SC in some patients. For these patients, hyperdilation or overdilation will be a more suitable technique.[6] Hyper- or overdilation refers to the dilation of the stent beyond its rated diameter using an angioplasty balloon. Thus, a 16-mm iliac venous stent can undergo angioplasty up to 18 or 20 mm with a target caliber balloon (an 18- or 20-mm balloon that is usually 4-6 cm in length and inflated to 14-16 atm). The Wallstent (Boston Scientific) can be ballooned up to 2 to 4 mm beyond its rated diameter without adverse sequelae.[6] Hyperdilation is not recommended for nitinol stents because they will fracture if dilated beyond their rated diameter. The technique of hyperdilation, therefore, is suited only for Wallstents.

Two important technical considerations with hyperdilation must be remembered. First, freshly implanted Wallstents should not be hyperdilated because that will cause the new stent to foreshorten significantly, sometimes to ≥40% to 50% of its total length. Also, no adequate platform around the stent will be present other than at the venous wall. Hyperdilation with freshly implanted stents can lead to iatrogenic perforation of the venous wall. Generally, sustained inflation with an angioplasty balloon for a few minutes will be enough to seal the perforation. Additionally, anticoagulation therapy might need to be withheld for a few days. If

extravasation persists in the setting of hemodynamic disturbances, stenting across the perforation should be considered to exclude it. Finally, open repair of the venous injury could be required if endovascular methods have failed to control it.

At several weeks after stent implantation, the hyperdilation technique can be used more safely and effectively to relieve ISR or SC with less foreshortening. By several weeks after implantation, an additional support layer will also have formed around the vein. Thus, the risk of an iatrogenic venous perforation will be lower. However, it is important to be vigilant about the possibility of lesions becoming uncovered by foreshortening, which could compromise the long-term patency of the stents.[6] Hyperdilation can require stent extension if such lesions become uncovered. Also, aggressive hyperdilation can cause separation of overlapping stents. Such separation is especially likely to occur when the overlap between the stents is <30 mm. Additional bridging stents might need to be placed to cover the gap caused by stent separation from hyperdilation.[6]

Hyperdilation will result in better clearance of ISR than will isodilation ($P = .0001$). Overall, hyperdilation resulted in greater significant improvement in supine foot venous pressure, visual analog scale scores for pain, and venous clinical severity score compared with isodilation. Additionally, more ulcers had healed with hyperdilation than with isodilation (67% vs 23%; $P = .008$).[6]

Technical aspects of angioplasty balloon complications during isodilation and hyperdilation. ISR and SC can sometimes be very resistant to balloon dilatation, which can create three problems. The first issue is balloon slippage proximal or distal to the lesion. The solution is to recenter the balloon and repeat the inflation until the lesion has resolved.[6] The second problem that can arise is balloon rupture. In most cases, it will be inconsequential. However, rarely, the balloon could remain inflated with retained contrast despite the rupture and not empty completely while inside the stent, becoming trapped above a severe stenosis. This is because when the balloon ruptures, it can "intussuscept" on itself, leading to trapping of the contrast between the walls of the balloon. This can be addressed using two methods. The first solution is to obtain another access point, place an angioplasty "buddy balloon" next to the ruptured balloon and inflate it to deflate the ruptured balloon completely to allow the ruptured balloon to brought out through the sheath.[6] The second solution for a ruptured balloon near the inguinal ligament is to perform percutaneous ultrasound-guided aspiration of retained contrast from the ruptured balloon to help deflate it completely. Finally, an open cut-down could be needed over the femoral or common femoral veins with a venotomy to retrieve the retained balloon. The third unique case we have encountered is complete detachment of the balloon from the shaft system during its passage across a very tight stenosis in a stent. An alternate access site was quickly obtained via the right internal jugular vein, and the detached balloon was snared and removed through the right internal jugular vein access site before it had a chance to embolize to the heart.

Laser ablation of ISR. Another useful technique for the correction of ISR is laser ablation. In ~20% of patients, balloon angioplasty alone will result in inadequate correction of the ISR.[64] In a series of 18 patients with recalcitrant ISR in iliofemoral venous stents that was not satisfactorily corrected by balloon angioplasty, laser ablation of the ISR was performed using a 2.3-mm Spectranetics laser (Spectranetics Corp, Colorado Springs, Colo) and an 8.5F angled support sheath. Laser ablation was performed in a longitudinal four-quadrant and circumferential manner with significant post-procedural improvement in the venous clinical severity score ($P = .0005$) and visual analog scale score ($P = .0005$). Primary and primary assisted patency at 10 months was 87% and 100%, respectively, with no stent occlusion reported.[64] However, 33% of the limbs had required reintervention after undergoing laser ablation, with a median reintervention time of 11 months.[64]

Atherectomy of ISR. Robertson et al[20] described the use of directional atherectomy to treat iliocaval venous ISR that had developed 1 year after placement of Veniti Vici stents (Boston Scientific). Several passes were performed with the HawkOne directional atherectomy device (Medtronic, Minneapolis, Minn) to remove the ISR tissue, followed by angioplasty, with good radiographic and clinical results.[20]

The development of heavy calcifications within ISR in venous stents has also been described. Schmidt et al[65] described the case pf a patient in whom stent occlusion and heavily calcified ISR was encountered. A temporary IVC filter was placed and removed at completion of the procedure for embolic protection. After ultrasound-accelerated catheter-directed thrombolysis was performed, the ISR was debulked using an 8F Rotarex catheter (Straub Medical AG, Vilter-Wangs, Switzerland). After rotational excisional atherectomy, they also performed balloon angioplasty and relined the venous stent with good results.[65]

However, based on only two reports, it is difficult, at present, to make recommendations regarding the device options or sizing for atherectomy. It is important to note that the use of an atherectomy device for the treatment of ISR in iliofemoral venous stents is off label. Risks such as stent fracture or entanglement with stent interstices should be remembered.

Z-stent placement. In a few patients with recurrent ISR and SC leading to recurrent stent occlusion, Gianturco Z-stents have successfully been placed to relieve the extrinsic and intrinsic stenosis in the iliofemoral venous stents (Supplementary Fig 3, online only). For most of these patients, recurrent ISR and SC remained refractory

to balloon angioplasty, leading to recurrent occlusion. The Gianturco Z-stent was used successfully in these patients to restore stent patency without further incidence of stent occlusion.

Optimal stent sizing. To adequately decompress peripheral venous hypertension, restoration of the venous luminal caliber to its normal value is recommended. Based on the findings from healthy volunteers without signs and symptoms of venous disease, the following values were calculated from flow equations: IVC ≥20 mm, common iliac vein ≥16 mm, EIV ≥14 mm, and CFV ≥12 mm.[66] The use of small stent sizes will create iatrogenic stenosis and result in inadequate symptom relief. If ISR develops in an undersized stent, it will compromise the lumen further and subsequently affect the clinical outcomes. At the other extreme, excessive oversizing of the stents can accelerate the development of ISR or SC. Therefore, particular attention should be given to optimal stent sizing.[67,68]

Slight oversizing. With Wallstents, slight oversizing (1-2 mm) can be used such that future problems such as ISR and SC can be accommodated. Inevitably, most stents will develop some degree of ISR or SC, or both. The use of slightly larger stents will allow for the performance of future balloon dilatation with larger balloons and more aggressively should significant ISR and SC be encountered.[3,6] However, excessive oversizing should be avoided. Oversizing is also not recommended with nitinol stents.

Removal of IVC filters when feasible. IVC filters are known to increase the rate of lower extremity deep vein thrombosis compared with those without an IVC filter (10% vs 3%; $P = .03$). Although patency was not affected, IVC filters were found to increase the reintervention rate for ISR after iliofemoral stenting compared with a control group (16% vs 4%; $P = .006$). If no longer indicated, IVC filter retrieval should be attempted in every patient to reduce the reintervention rate for symptomatic ISR after iliofemoral venous stenting.[69]

Stenting across the inguinal ligament. The use of longer stents and the extension of stents below the inguinal ligament have been shown to be associated with ISR in the iliofemoral venous system.[70] In one study, severe restenosis (>50%) was noted in 40 limbs with stents that had terminated below the inguinal ligament vs 9 limbs in which the stents had ended above the inguinal ligament ($P < .001$). The increase in ISR was most rapid in the first 6 months.[9] However, more postthrombotic limbs had also had stents that had extended below the inguinal ligament.[9] In another study, the overall rate of focal ISR at the site of the inguinal ligament for stents crossing it was low (7% limbs), and patency was not affected by placing stents across the inguinal ligament.[71] In a study by Ye et al,[70] long stents with extension distal to the inguinal ligament had developed ISR more frequently (hazard ratio, 1.77-6.5; $P = .0146$).

Potential role of drug-eluting balloons and stents. One area of future investigation in the iliofemoral venous system could be the use of drug-eluting balloons and drug-eluting stents to prevent neointimal hyperplasia and the development of ISR. The drugs used in the arterial system for this purpose include sirolimus, paclitaxel, zotarolimus, everolimus, and dexamethasone.[72] However, as reported by Jayaraj et al,[5] the dose of the medication delivered via balloons or stents must be carefully computed owing to the larger surface area of venous stents in contrast to arterial or coronary stents.

Bilateral stenting. Staged, rather than simultaneous, bilateral stenting is now recommended because of the long-term improvement in the nonstented contralateral limb in most patients (95%) owing to off-loading by the pelvic collateral vessels. In at least two studies, only ~5% contralateral limbs had required stenting in the long term after the ipsilateral limb had been stented.[4,73] However, if bilateral stenting is required, the reported data have suggested that the technique of bilateral stenting used will have an effect on the reintervention rates. In one study, three techniques of iliocaval confluence reconstruction were evaluated, including the double barrel technique, an inverted Y-stenting technique performed through fenestration of a previously placed stent across the iliocaval confluence, and an apposition technique in which a small unstented area is left between the stents near the confluence. The reintervention rates were lowest for the double barrel technique (8%), followed by the apposition technique (32%) and inverted Y-stenting technique (37%).[74] In another study of the double barrel technique, the frequency of reintervention for ISR was 16.7%.[75]

Hybrid interventions

Closure of arteriovenous fistulas. In some patients with CIVO and poor inflow, a hybrid procedure can be performed such that iliofemoral venous stenting is combined with endophlebectomy and creation of an arteriovenous fistula (AVF) to improve inflow. The timing of the closure of the AVF has remained a subject of debate. Generally, it has been recommended to close the AVF 6 to 12 weeks later. At least one study has been reported of accelerated restenosis in the CFV segment that might have been attributable to the arterialized flow from the AVF that necessitated closure of the AVF with a plug and further extension of the stent distally into the inflow vessel.[76] Formation of an AVF is also possible as an access site complication during iliofemoral venous stenting. Consideration should also be given to closure of these AVFs because of the possibility of accelerated restenosis and exacerbation of venous hypertension in the limb. However, in some cases, this might be at the expense of

potentially compromised inflow that could, rarely, lead to stent occlusion.

Brachytherapy

A potential role might exist for brachytherapy for patients with recurrent ISR in the venous system that should be identified as an area of future research. Brachytherapy has been successfully used in several arterial beds to prevent intimal hyperplasia, including the coronary system.[77] In the central venous system in hemodialysis patients, both success and progression to complete occlusion have been reported after brachytherapy.[78,79] Gamma radiation with a dose of 12 to 20 Gy was used for most patients; however, beta radiation has also been used in some studies. In addition, some studies have reported an increase in the incidence of edge restenosis after brachytherapy, possibly owing to a "geographic miss" from radiation.[80,81]

STENT SURVEILLANCE

Our stent surveillance protocol has included DUS on postoperative day 1, at 2 to 4 weeks and 3 to 6 months, followed by annual intervals.[82,83] Data on other imaging modalities in the follow-up of ISR, such as CTV and MRV, are sparse. Because venography and IVUS are more invasive, their use has been recommended for the confirmation of ISR if the patient's symptoms are severe enough to warrant further investigation and subsequent intervention.

STUDY LIMITATIONS

The main limitation of the present review was the lack of diverse and robust data available on the subject. Several studies have been reported of ISR of iliofemoral venous stents, some with clinical data and others more theoretical or speculative in their approach. In many cases, we had to rely on a few key references in certain areas, in particular for interventional management, to support our conclusions. Therefore, extrapolation of these conclusions to generalized patient care should be performed with caution.

CONCLUSIONS

ISR occurs often in iliofemoral venous stents. Reintervention for ISR should be determined by the presence of residual or recurrent symptoms and not simply using a numeric value obtained from an imaging study. The treatment options available at present for ISR are mostly durable and effective. However, more research is required on methods to prevent the development of ISR. Several potential areas for future research have also been identified in our review, including unusual drug therapies. The role of antiplatelet and anticoagulant agents in the prevention of ISR requires further investigation, with particular attention to a unique subset of patients (post-thrombotic vs NIVLs). In high-risk, post-thrombotic patients, anticoagulation therapy could be considered to prevent ISR. The role of triple therapy (anticoagulation and dual antiplatelet therapy) in the prevention of ISR remains unclear.

AUTHOR CONTRIBUTIONS

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

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Submitted Aug 6, 2021; accepted Oct 13, 2021.

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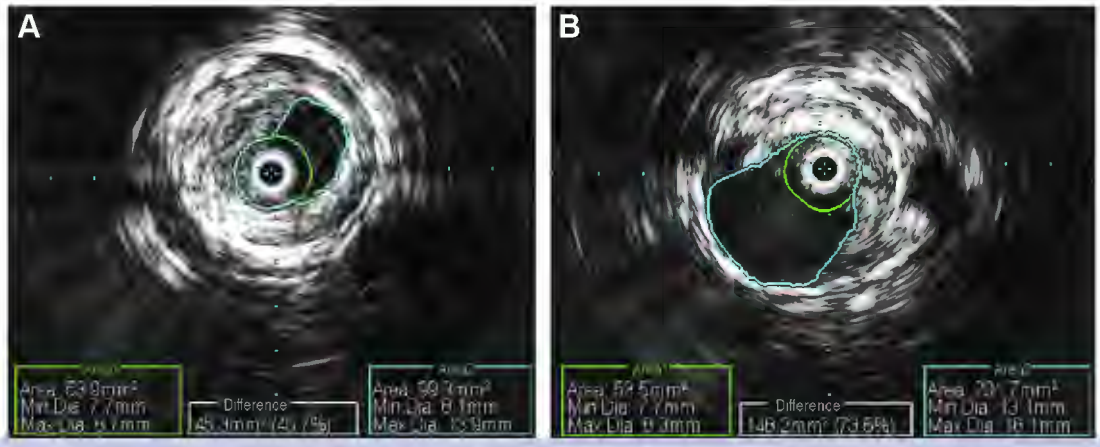
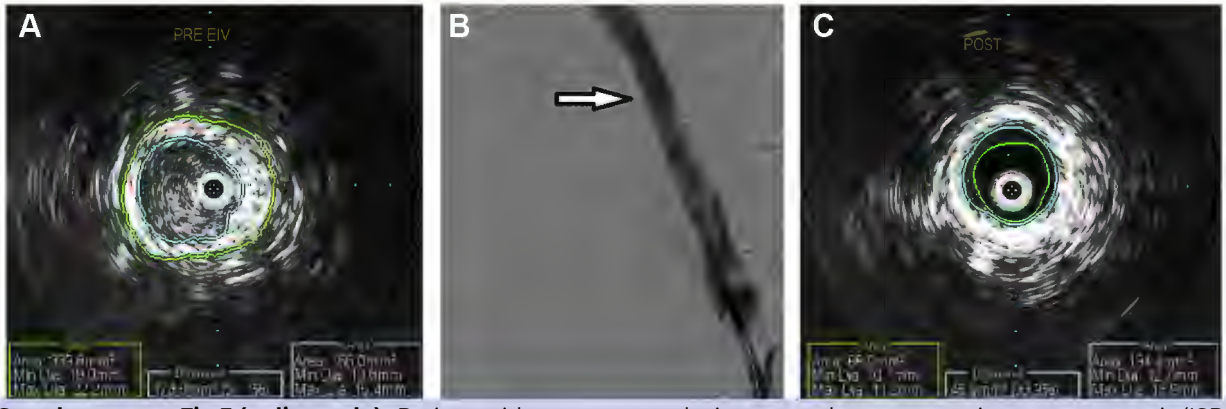
APPENDIX (ONLINE ONLY)

Supplementary Fig 1 (online only). Virtual histologic features of in-stent restenosis (ISR) obtained with a Visions PV 0.014P RX catheter (Volcano, San Diego, Calif). *Dark green* indicates collagen; *light green,* fibrofatty tissue; *red,* necrosis; and *white,* calcifications.



Supplementary Fig 2 (online only). In-stent restenosis (ISR) in an iliofemoral venous stent. **A,** Intravascular ultrasound (IVUS) showing the stent as a *bright circular ring* and ISR appears heterogeneous. **B,** Partial clearance of ISR after balloon angioplasty with a large-caliber, high-pressure balloon. Note that the cross-sectional area had doubled after the performance of angioplasty. The patient reported good relief of recurrent symptoms after angioplasty. *Dia,* Diameter; *Max,* maximal; *Min,* minimal.



Supplementary Fig 3 (online only). Patient with recurrent occlusion secondary to severe in-stent restenosis (ISR) that was not responsive to balloon angioplasty. **A,** Intravascular ultrasound (IVUS) showing severe ISR and stent compression in the external iliac venous stent. **B,** Placement of Z-stent (*white arrow*) within the Wallstent (Boston Scientific) in the external iliac vein (*EIV*) showing patency on venography. **C,** Patent Wallstent and Z-stent at follow-up IVUS with no further stent occlusion at 1 year of follow-up.