In 1908, McMurrich studied 107 cadavers and found 35 had adhesions in the iliac veins, the majority of which were on the left side. Subsequently in 1943, Ehrich and Krumbhaar found that 95 of 412 cadavers had obstructive lesions consisting of collagen and elastin in the left iliac veins. This was further characterised by May and Thurner in 1957 as ‘spurs’ in the left iliac veins that may predispose to venous thrombosis because of disruption of blood flow. This condition was referred to as ‘iliac vein compression’ by Cockett and Thomas in 1965. These initial studies did not attempt to differentiate between non-thrombotic iliac vein lesions (NIVLs) and thrombotic lesions. However, more recent evidence suggests that clinical outcome and recurrence rates may differ, necessitating distinction between the two lesion types.

NIVLs refer to iliac vein lumen stenosis, usually secondary to extrinsic compression, without associated thrombosis. Most commonly NIVLs are caused between arterial structures and the spine, and are associated with intrinsic vein stenosis characterised by wall fibrosis or intraluminal webs/spurs. When there is compression of the left common iliac vein by the right common iliac artery, it is commonly referred to as May–Thurner syndrome or Cockett’s syndrome.

Patients with NIVLs may develop symptoms of chronic venous insufficiency (CVI), although the true prevalence of NIVL-associated CVI is unknown. Symptoms of CVI can significantly decrease quality of life and increase healthcare costs. In patients with significant persistent symptoms despite conservative management, endovascular stent placement has been used as a safe and effective treatment option for NIVLs. To achieve treatment success, patient selection is crucial to appropriately exclude patients experiencing symptoms because of other aetiologies.

In this article, we will discuss the clinical presentation, diagnostic workup and endovascular interventions of NIVLs, along with the outcomes of NIVL treatment.

Clinical Presentation
Clinical presentation of NIVL varies, ranging from asymptomatic patients to those with symptoms of CVI. Several studies have found that a significant portion of patients with NIVL may not have appreciable symptoms. One study retrospectively reviewed 50 abdominal/pelvic CT scans of patients presenting with abdominal pain to the emergency department; there were no lower extremity symptoms or prior deep venous thrombosis (DVT). Among these subjects, 33 (66%) had >25% diameter compression, which corresponds to approximately 50% area stenosis. In a more recent study, angiography of the iliac veins was performed prospectively in 20 healthy volunteers, among whom 19 had at least two angiographic findings consistent with significant iliac vein obstruction (including contrast transluency, lumen deformity, as well as axial, transpelvic or ascending lumbar collaterals). Sixteen of these subjects had no visible or palpable signs of venous disease (CO by Clinical Etiology Anatomy Pathophysiology [CEAP] classification) and four of them...
Figure 1: Proposed Algorithm for Diagnosis and Management of Non-thrombotic Iliac Vein Lesions

<table>
<thead>
<tr>
<th>Decision Point</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination: Have non-venous causes of the patient’s symptoms been excluded?</td>
<td>Work up and treat non-venous underlying cause</td>
</tr>
<tr>
<td>Is there refractory or recalcitrant oedema, venous claudication or persistent stasis ulcer despite conservative management (e.g. compression stockings) and/or superficial venous therapy?</td>
<td>Continue conservative management</td>
</tr>
<tr>
<td>Non-invasive imaging studies: venous duplex ultrasound, CTV, MRV: Is there evidence of extrinsic compression?</td>
<td>Consider other non-venous diagnosis of exclusion, such as lymphoedema</td>
</tr>
<tr>
<td>Yes</td>
<td>Catheter-based venography and IVUS ± stent placement</td>
</tr>
</tbody>
</table>

CTV = CT venography; NUS = intravascular ultrasound; MRV = magnetic resonance venography.

were minimally symptomatic with telangiectasias/reticular veins (C1 by CEAP classification). Thus, the presence of a NIVL by imaging does not directly correlate to the presence of clinically symptomatic venous obstructive disease.

Symptomatic patients with NIVLs experience varying degrees of CVI symptoms in the lower extremities. These symptoms include – but are not limited to – lower extremity heaviness, discomfort, pain, oedema, varicose veins, telangiectasia or, in its most severe form, ulcers, in the affected lower extremity. Women with NIVLs may experience additional symptoms including chronic pelvic pain, dyspareunia, vulvar swelling/pressure, and superficial lower extremity pelvic-derived varicosities.

Given the wide range of presentation of NIVL, it has been hypothesised that NIVL is a permissive lesion, and factors such as vessel trauma or oedema are likely to precipitate further symptom manifestation. However, it remains unclear in which instances these lesions become clinically significant; a clinical conundrum, given a significant portion of the population has clinically silent compression that does not need treatment. Therefore, screening of asymptomatic patients currently remains impractical. Rather, these studies highlight the importance of appropriately selecting patients with symptoms directly attributable to iliac vein obstruction to maximise the potential benefits of endovascular treatment.

Approach to Diagnostic Workup

Diagnostic workup for a patient suspected to have a NIVL should begin with thorough history and physical examination to look for other aetiologies of the patient’s symptoms, including but not limited to medications (e.g. calcium channel blockers), congestive heart failure, lymphoedema, liver disease and endocrine dysfunction. Once other nonvascular aetiologies have been excluded and NIVL is suspected to be a major contributor to the patient’s symptoms, further evaluation for diagnosis and characterisation of NIVL may be pursued (Figure 1). Given that CVI more frequently affects women, female patients should routinely be assessed for chronic pelvic pain symptoms.

The severity of symptoms can be scored using the revised Venous Clinical Severity Score (VCSS). This can be supplemented by the CEAP system, although this assessment lacks precision and simply reports the most severe physical manifestation of venous disease, not taking into account functional limitations. At this time, there is no disease severity scoring metric that is specific to NIVL. Regardless of the classification system used, a baseline disease severity should be documented to allow assessment of clinical progression or improvement after treatment.

Imaging studies aid in diagnosis and treatment planning. Initial non-invasive workup should include a venous duplex ultrasound, which may directly visualise compression or obstruction of the iliac vein as well as exclude venous thrombosis and post-thrombotic changes. Venous insufficiency or reflux should be assessed with augmentation techniques. Ultrasound evaluation of the iliac vein may be limited by technical factors (including operator experience, body habitus, or overlying bowel gas) and may fail to directly visualise the pathology within the iliac vein. In these cases, indirect findings of a clinically significant iliac vein lesion may be utilised. These include pre-stenotic vein dilatation, absent respiratory phasicity, internal iliac vein flow reversal and poor response to augmentation. In addition to duplex ultrasound, axial imaging may aid in non-invasive diagnosis. CT or magnetic resonance venography (MRV) can identify extrinsic compression, as well as concurrent thrombosis or presence of collateral veins. Limitations of cross-sectional imaging includes variable sensitivity depending on the hydration status of the patient, ionizing radiation with the use of CT, and necessity for local expertise with MRV. Catheter-based venography and intravascular ultrasound (IVUS) are the primary interventional imaging modalities for diagnosis and treatment of NIVLs. With IVUS, high resolution circumferential sonographic imaging with high frequency probes leads to improved accuracy of diagnosing venous lesions, such as webs or spurs. Additionally, IVUS is critical to improved accuracy of luminal measurements for treatment planning and stent size selection, as well as assessment following stent placement.

Endovascular Management

Asymptomatic patients with NIVLs discovered incidentally are not candidates for endovascular intervention. In these patients, counselling on risks of developing symptoms of CVI including DVT may be indicated, though has not been prospectively validated. Conservative management should always be pursued first in patients with symptoms of CVI, including regular use of compression stockings. Endovascular management should be considered in patients with moderate to severe symptoms and those who are refractory to conservative management. For patients with superficial venous pathology that is thought to be a significant contributing cause to their symptoms, superficial treatment should be considered prior to iliac vein stent placement.

The primary objective of intervention for an obstructive venous lesion is to establish adequate inflow and outflow. Studies have found that angioplasty without stent placement for NIVL is generally not sufficient because of lesion recoil, therefore stent placement is the primary endovascular treatment modality for NIVL. The interventional procedure involves a series of general technical steps. First, ultrasound-guided venous access is obtained below the level of disease, typically in the ipsilateral common femoral, cranial great saphenous, or femoral vein with placement of a vascular sheath. Initial venography is performed to assess the lesion and the degree of compression/obstruction, presence of pre-stenotic dilation and venous collaterals. IVUS is then used to further assess the obstructive venous lesion and obtain measurements to determine the size of the stent. The size of the stent is chosen based on the size of the adjacent normal segment. In our practice, we use a normal ipsilateral external iliac vein; care must be taken to not measure pre-stenotic dilation as a reference segment as this can lead to incorrect stent sizing. A self-
expanding stent is then deployed, extending into the external iliac vein, generally with a goal to extend the stent around the natural curve of the external iliac vein such that adequate stent anchoring in normal anatomy occurs, to minimise the risk of stent migration. Wallstent (Boston Scientific) is a type of elgiloy stent, which has now been approved for treatment of iliofemoral venous obstruction. Additionally, self-expanding nitinol stents such as ViCi (Boston Scientific), Venovo (Becton Dickinson/Bard), Abre (Medtronic), and Zilver Vena (Cook Medical) have also been approved for this application in the United States. In Europe, Sinus Venous (Optimed) and BlueFlow (Plus Medica) are additional options.36

 Historically, lesions with >50% area stenosis (corresponding to approximately 30% diameter stenosis) were considered candidates for stent placement.35,37 More recent evidence suggests otherwise. In the prospective, single-arm VIDIO trial, 68 patients were included with CEAP C4–6 who had a stent placement, 48 of whom had NIVL (20 had post-thrombotic lesions).30 The study found no correlation between area of stenosis and outcome, and an area receiver operating characteristic curve analysis demonstrated clinical improvement when a higher threshold of >61% diameter stenosis was used in NIVL.38 Based on this prospective trial, we suggest consideration of stent placement in patients with lesions that have >61% diameter stenosis relative to an average reference diameter in a normal venous segment (in our practice, this is frequently the external iliac vein). After placement of a stent, repeat venography and IVUS confirm appropriate stent position/apposition and the presence of unimpeded flow (Figure 3). Collaterals, if initially present, can be reassessed for resolution at this step, suggestive of a therapeutic outcome. Currently, there is no consensus on the use of anticoagulation or anti-platelet agents after stent placement.38 We do not routinely prescribe anticoagulation after NIVL stent placement.

In women with NIVL and coexistent ovarian vein reflux with symptoms of chronic pelvic pain, treatment should be directed according to the dominant symptomatic feature. For such patients who primarily present with pelvic pain and minimal lower extremity symptoms, we suggest ovarian vein embolisation prior to stent placement for NIVL. Patients who have a dominant feature of lower extremity symptoms, including venous claudication, we suggest consideration of initial stent placement. The patient should be reassessed at follow-up, with staged stent placement for NIVL or ovarian vein embolisation if symptoms are refractory or only minimally improved.

Outcomes and Complications
Stent placement has been shown to improve pain and swelling, ulcer healing and quality of life in NIVL patients.5,39,40 Oedema relief was reported in nearly 90% of the patients.39 Ulcer healing was reported in more than 80% patients, with one study reporting even better healing in patients with NIVL compared to post-thrombotic iliac vein lesions with 5-year healing rates of 87% and 66%, respectively.41,42

Multiple studies have reported excellent patency rates for endovascular treatment of NIVLs.5,43,44 A meta-analysis reported primary patency of 94.1% at 1 year and 88.9% at 3 years. Assisted primary-secondary patency rates were 100% at 3 years.45 In the recent prospective, multicentre trial VIRTUS, self-expanding nitinol stents were placed successfully in 170 symptomatic patients with >50% stenosis. At 1 year, the primary patency rate was 98.4% in the NIVL limb, compared with 79.8% in the post-thrombotic limb.38 In this study, which included patients with VCSS of ≥2 or CEAP ≥C3, 64% of patients (including both NIVL and post-thrombotic limbs) demonstrated at least a 3-point reduction in VCSS in 1 year, with 5-point average reduction specifically in the NIVL limb.38 The majority (58%) of the patients (including both NIVL and post-thrombotic limbs) reported improvement in quality of life in 1 year with at least a 9-point reduction in the Chronic Venous Insufficiency Quality of Life Questionnaire-20, with 14-point average reduction specifically in the NIVL limb.36

The rate of development of in-stent restenotic material is lower in NIVL treatment compared with post-thrombotic lesion treatment. One study reported cumulative rate of material accumulation resulting in >50% stenosis to occur approximately in 1% of stents placed for NIVL lesions, compared to 10% for post-thrombotic lesions.39

The most common complication after endovascular treatment of NIVL is access-site-related complications including bleeding, haematomas or arteriovenous fistulas; the risk of the latter is further reduced by use of...
ultrasound guidance. Another common complication includes, but is not limited to, back pain from stents, which is often self-limited. One specific complication of iliac vein stent placement is contralateral common iliac vein thrombosis from its exclusion in the case of stent extension into the inferior vena cava, though this is uncommon. Rare complications such as stent fracture, malposition, migration or erosion have also been reported.

**Future Directions**

At this time, there is no consensus or guideline to suggest use of any specific stent for treatment of NIVL for instance, those designed specifically for treatment of May–Thurner syndrome versus standard stents), although this would warrant further investigation. Additional areas for investigation include refinement of our understanding of what constellation of symptoms constitute a clinically relevant NIVL, identification of validated diagnostic criteria for NIVL given the presence of specific symptoms and procedural endpoints and outcomes measurements to demonstrate clinical improvement following treatment.

**Conclusion**

Appropriate initial patient selection is key to a successful outcome in the endovascular treatment of NIVL. Further studies are needed to determine which lesional or clinical features lead to a NIVL becoming clinically symptomatic, given that a significant number of NIVLs are clinically silent and do not merit treatment. Studies have demonstrated that stent placement is safe and effective with largely positive outcomes when performed at experienced centres in patients where it is clinically indicated.