Review Article

Iliofemoral deep vein thrombosis and the problem of post-thrombotic syndrome

N Denny, S Musale, H Edlin, F Serracino-Inglott & J Thachil

Abstract

Deep vein thrombosis (DVT) is an important cause of short-term mortality and long-term morbidity. Among the different presentations of DVT, thrombus in the iliofemoral veins may be considered the severest form. Although anticoagulation is the mainstay of the management of iliofemoral thrombosis, despite adequate anticoagulant treatment, complications including post-thrombotic syndrome is not uncommon. The latter is often overlooked but can cause considerable morbidity to the affected individuals. Preventing this condition remains a challenge but recent clinical trials of catheter directed thrombolysis and elasticated compression stockings provide some advance in this context. In this article, with the aid of a clinical case, we review the particular considerations to take into account when managing patients with an iliofemoral DVT.

Keypoints

Ilefoemoral; deep vein thrombosis; post-thrombotic syndrome

Key points

- Ileofemoral thrombosis is the most severe form of deep vein thrombosis with high likelihood of recurrence and the development of often disabling complication, post-thrombotic syndrome
- All patients with ileofemoral thrombosis should be discussed with a vascular specialist to consider the merits of thrombolysis
- Catheter-directed thrombolysis should be considered in centres with expertise
- The development of Post-thrombotic syndrome may be reduced or even prevented by thrombolysis

Introduction

Venous thromboembolism is the third most common form of cardiovascular illness. It contributes to significant proportion of global morbidity and mortality.[1] It presents as deep vein thrombosis (DVT), pulmonary embolism or both, the latter arising from embolization of the former. When a DVT develops, it may partially or completely occlude the venous lumen leading to symptoms such as pain or swelling. This can occur at any point along the venous system, but consideration particularly needs to be given to thrombus occurring in the proximal vessels, as complications can be life-threatening or life-changing and may be improved with newer interventions. Although anticoagulation is well established as the treatment of an acute DVT, including iliofemoral DVT, it does not necessarily cause dissolution of the clot by itself.[2] This remaining clot, which if present after an appropriate period of anticoagulation, may be termed a chronic DVT or residual venous obstruction (RVO).[3]

Case vignette part 1

A 63-year-old woman with a high body mass index of 40, type 2 diabetes and a history of colorectal cancer treated with a low anterior resection 2 years previously, presented to the acute take with a two-day history of sudden onset of left leg swelling, pain, redness and reduced mobility.

On examination, she had a grossly swollen left thigh and leg with unilateral pitting oedema of her ankle and significant generalised tenderness. The capillary refill time was less than two seconds and the dorsalis pedis pulse was palpable. She had no other focal symptoms or signs.

Investigations revealed a leucocytosis of $14.6x10^9$/L (normal $<11x10^9$/L) with a mild neutrophilia, a C-reactive protein of 45mg/L (<6mg/L) and a D-dimer of 21,550units/L. Urea and electrolytes, liver function tests and bone profile were within normal limits. A chest X-ray showed some bibasal atelectatic change but was otherwise normal. Urine dipstick showed 1+ protein and 2+ glucose. Duplex ultrasonography of her left leg showed an extensive iliofemoral DVT extending from the popliteal vein proximally. A CT thorax, abdomen and pelvis showed minimal patchy ground glass in the left lower lobe and evidence of a thrombosis extending from the left external iliac to the left popliteal vein but there was no evidence of malignancy.

What considerations are there in a patient with iliofemoral DVT?

An iliofemoral DVT is defined as thrombus involving the common femoral and/or iliac veins and may sometimes extend proximally to the inferior vena cava and/or distally to the popliteal vein.[4] It accounts

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for between 25-40% of cases of DVT.[5] Compared to more distal thrombus, iliofemoral DVT is associated with a significantly higher risk of both short-term complications such as pulmonary embolism,[6] venous ischaemia[4] and long-term complications, such as recurrent DVT[7] and the post thrombotic syndrome (PTS).[8,9]

The presenting features of an iliofemoral DVT are well recognised and, for the most part, do not differ from that of DVT in general. However, patients with iliofemoral DVT are at a much higher risk of life-threatening limb ischaemia because of venous outflow obstruction, termed phlegmasia cerulea dolens (PCD), and it is important that this is considered during initial assessment.[10] Features that support early PCD include severe pain, limb cyanosis or mottling and skin blistering, whereas sensorimotor changes, loss of pulses and gangrene suggest advanced disease.[10] This condition has amputation and mortality rates between 25-50%[10] and, if suspected, urgent involvement of vascular surgery is essential.

As with its presentation, the risk factors for iliofemoral DVT are similar to DVT overall but in addition, there is also a recognised association with anatomical predisposition to venous stasis of the external iliac vein.[11] This may be because of congenital venous abnormalities, pelvic masses or the increasingly recognised May-Thurner syndrome, in which the right common iliac artery overlies the left common iliac vein and compresses it against the lumbar spine. May-Thurner syndrome is important to recognise as definitive treatment to include the placement of an iliac vein stent can prevent recurrence.[12]

How should this patient be managed initially?

In the first instance, as with other patients with less extensive DVT, patients with iliofemoral DVT require appropriately dosed anticoagulation therapy to minimise clot propagation and reduce the risk of embolism.[4,13] In most instances, this will be low molecular weight heparin (LMWH), although if an interventional strategy such as catheter directed thrombolysis (CDT) is likely and imminent, an infusion of unfractionated heparin (UFH) may be considered due to its shorter half-life and reversibility. CDT can still be carried out 12-24 hours following administration of treatment dose LMWH in patients with normal renal function and therefore, if in doubt, patients with iliofemoral DVT should receive LMWH.

Clot removal and reduction strategies are varied and include systemic thrombolysis, surgical thrombectomy and a range of endovascular techniques that involve localised delivery of a thrombolytic, termed catheter-directed thrombolysis (CDT). When percutaneous mechanical thrombectomy is also carried out, this is termed pharmaco-mechanical catheter directed thrombolysis (PCDT).[14] The main role of these interventions, aside from a more rapid resolution of DVT related symptoms or treatment of PCD, is to reduce the long-term consequences of iliofemoral DVT, such as PTS and recurrence.[15]

Post-thrombotic syndrome

PTS is a clinical syndrome characterised by pain, swelling and ulceration in a limb previously affected by a DVT. It may develop anywhere between 3 and 24 months post an acute DVT and its severity can be measured using the Villalta score.[16] Patients with iliofemoral DVT are recognised as being at particularly high risk of these complications with 30-80% developing PTS and a 10% risk of recurrent DVT. This represents a with a 2-3-fold increase in the risk of PTS compared to distal DVT[9,17] and 2-fold increase in the risk of recurrence compared to more distal DVT.[7] A recent Cochrane review by Watson et al. in 2016 found that both systemic and catheter directed thrombolysis in the context of iliofemoral DVT increased venous patency and reduced the risk of PTS at 2 years by a third.[18] As a result, present guidelines from the American Heart Association (19), National Institute of Clinical Excellence[20] and Canadian InterEPID[4] all recommend the use of CDT or PCDT in select patients with iliofemoral DVT for these very reasons.

Thrombolytic therapy – which method?

Systemic thrombolysis, typically with streptokinase, has been extensively trialled for acute extensive DVT and both increases the rate of complete clot lysis and reduces the risk of PTS.[18] However, it is also associated with a 3-4-fold increase in the risk of major bleeding[15] and is not generally recommended, particularly if other techniques are available. The evidence for surgical thrombectomy is more limited, consisting of a small randomised trial[21] and a meta-analysis of observational studies.[22] These studies also demonstrated an improvement in vein patency and reduction in PTS compared to standard treatment but, due to the invasive nature of the procedure and potential surgical complications, it is rarely carried out. Nevertheless, it should be considered in cases where a patient may benefit from clot reduction but has high bleeding risk or where the limb is threatened and there may not be enough time for lytic agents to work. In contrast to surgical thrombectomy, CDT is percutaneous and can be carried out under local anaesthetic. Consequently, although direct head to head trials of systemic thrombolysis or surgical

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thrombectomy versus CDT are lacking, guidelines[4,19] support its use over these other techniques due to its lower bleeding rate, minimally invasive nature and trend towards superior results.

Although, a body of observational and single centre study evidence supports thrombolysis and in particular CDT or PCDT for acute iliofemoral DVT, there are a limited number of high quality multicentre randomised controlled trials (RCT) comparing validated outcomes with prolonged follow up in this area. So far, the Catheter-directed Venous Thrombolysis (CaVenT) study is the only multicentre RCT to compare the long-term outcome between CDT and standard care in the context of iliofemoral DVT.[23] At 2 years, with a follow up of 90%, there was a 14.4% absolute risk reduction in the frequency of PTS and a 28% absolute risk reduction at 5 years with a number needed to treat of 4 patients to prevent 1 case of PTS. However, there was a 3% absolute risk increase in major bleeding but there was no intracranial bleeding or permanent disability as a result.[23] Nevertheless, these complications can be life threatening and consequently these patients should be managed in dedicated vascular or high dependency unit beds.

Two further prospective trials comparing CDT to standard treatment with compression and anticoagulation in the treatment of acute iliofemoral DVT are currently underway and due to report. The Catheter Versus Anticoagulation (CAVA) trial is a multi-center study in which patients are randomized to ultrasound-enhanced CDT and standard therapy or standard therapy alone. This trial is currently recruiting and has a primary endpoint of PTS at 12 months. The Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial has recently reported its preliminary data and detailed results are due to be published this year. This study aims to compare medical management with standard anticoagulation and knee high 30-40mmHg graduated elasticated compression stockings (ECS) to PCDT and medical managment to determine the effect of PCDT on rates of PTS at 6 and 24 months. All patients 16 to 75 years old with symptomatic iliac and/or femoral DVT were eligible for inclusion but patients with significant bleeding risk, recent surgery, active cancer, pregnant, critically unwell or symptom duration longer than 14 days were excluded. Unlike, the CaVenT study, the ATTRACT trial failed to demonstrate a significant difference in the rates of PTS between intervention and control arms at either time point. Moreover, PCDT was associated with a significantly higher major bleeding risk of 1.7% compared to 0.4%, although none of these bleeding complications were intracranial or fatal. Nevertheless, the ATTRACT trial did show a significant reduction in the severity of PTS particularly in the context of iliofemoral DVT as opposed to femoro-popliteal DVT and also a reduction in symptoms during the acute thrombotic period. As a result, CDT or PCDT remain effective interventions in patients with acute iliofemoral DVT and a low bleeding risk and continue to be recommended in this context.

The role of IVC filters

A dilemma which often arises in the management of ileofemoral thrombosis is the place for inferior vena cava (IVC) filters. Should they be considered prior to patients receiving thrombolytic therapy for DVT? In general, the anecdotal reports of pulmonary embolism (PE) complicating systemic thrombolysis for ileofemoral DVT have been attributed to the fact that these patients are very high risk for PE even without thrombolysis. Indeed, a significant proportion may already have silent PE on presentation. As a result, the British Society of our patient had an extensive symptomatic iliofemoral DVT and no factors that would put her at increased risk of bleeding, we would refer her to the local vascular and endovascular specialists for consideration of CDT. An algorithm for the management of ileofemoral thrombosis is given in figure 1.

Case vignette part 2

Since the patient presented elsewhere, she was initially treated with weight-based treatment-dose low molecular weight heparin, divided into twice daily injections with anti-Xa monitoring to ensure adequate anticoagulation, and after 5 days was converted to treatment dose apixaban for 6 months. She also received 5 days of amoxicillin for a presumed lower respiratory tract infection. She was advised about the risks of post-thrombotic syndrome and to monitor for further pain, redness or swelling. She was discharged approximately 10 days following her original presentation and her leg pain and swelling had improved significantly. She was advised to attend her GP within 2 weeks for follow up and the GP was asked to prescribe elasticated compression stockings on the discharge summary.

Reducing risk of post-thrombotic syndrome

Inadequate anticoagulation reduces clot breakdown and so increases the risk of PTS. When warfarin was used, patients that only spent 50% of their time with an International Normalised Ratio (INR) of 2-3 were significantly more likely to develop PTS with an odds ratio of 2.7 compared to patients receiving effective anticoagulation.[24]

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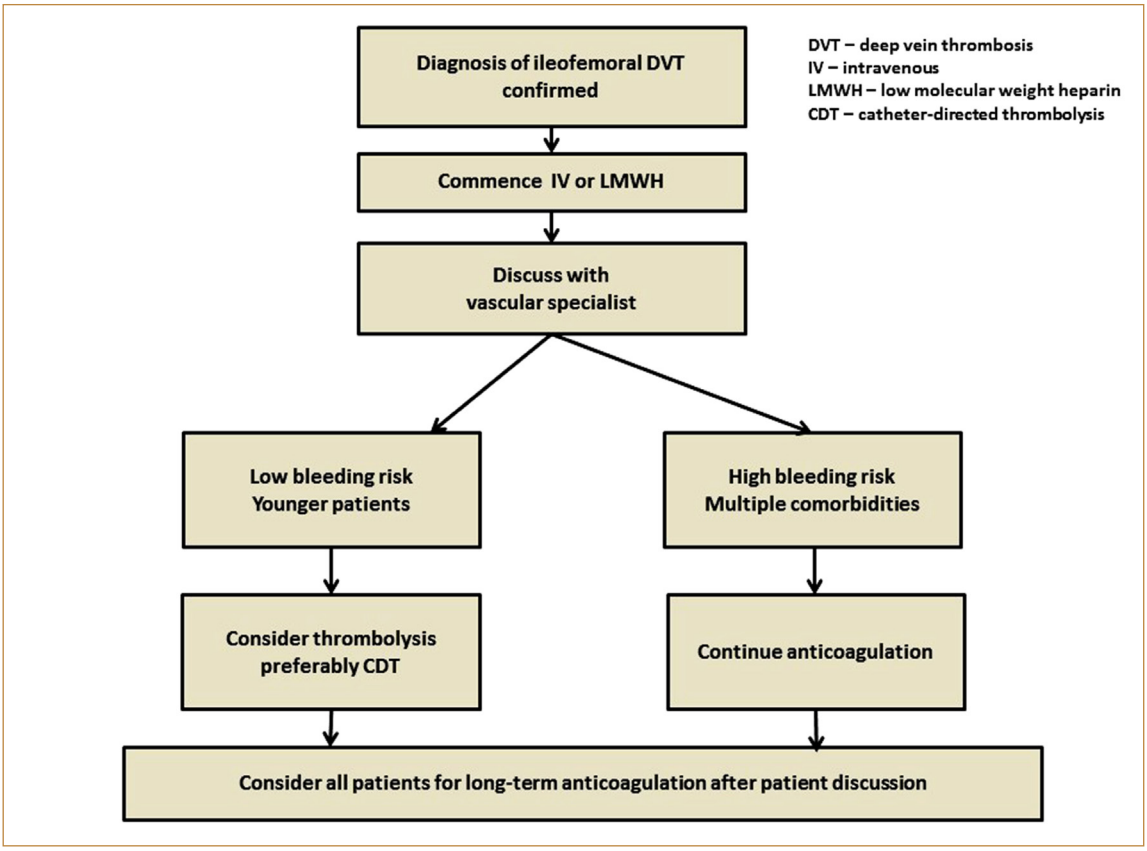


Figure 1.

Thrombosis is a pro-inflammatory process and it is hypothesised that inadequate control of the inflammatory process may cause vessel wall damage and contribute to PTS. LMWHs have anti-inflammatory properties and, for this reason, it has been suggested that they are more effective than VKAs for PTS prevention.[25] Consequently, several prospective randomised trials have compared LMWH and warfarin for the reduction of PTS and residual vein thrombus.[26] Although heterogenous in outcomes measured and duration of follow up, a meta-analysis of 5 of the studies reporting recanalization and clot lysis demonstrated a significant risk reduction in favour of LMWHs.[26] Moreover, in the studies examined, patients treated with LMWHs also had a considerable reduction in the rate of ulceration and fewer self-reported PTS symptoms. However, in these studies follow up was limited to between 3 and 6 months, which may be too short a time frame for many cases of PTS to develop. Therefore, whilst a prolonged course of LMWH is not routinely recommended for the treatment of DVT solely to prevent PTS, in cases where there is extensive thrombus and CDT has not been carried out, such as our patient, it may be worth considering.

Given the potential inflammatory nature of PTS, many other venoactive and anti-inflammatory drugs including NSAIDs, defibrotide and statins have been trialled. Interestingly, rosuvastatin at a dose of 10mg in combination with LMWH, significantly reduced PTS at 3 months compared to LMWH alone[27] and many other studies have also pointed towards a reduced incidence of DVT or recurrent DVT with statin use. Nevertheless, such trials are limited by short follow up and heterogenous outcome measurements and further well-designed trials are needed before firm recommendations can be made.

Wearing elasticated compression stockings (ECS) has long been suggested for the prevention of PTS based on observational studies and 2 open label trials in which patients with a first DVT were randomised to wear 30-40mmHg ECS for 2 years in addition to anticoagulation or to anticoagulation alone.[28,29] Both trials demonstrated approximately a 50% reduction in the rates of PTS in patients wearing ECS. However, the more recently published SOX trial has led to this orthodoxy being reversed. This multicentre randomised placebo controlled trial enrolled over 800 patients and, in contrast to previous studies, no difference was demonstrated in PTS rates between placebo ECS and 30-40mmHg ECS groups.[30] ECS may still have a role in the treatment of established PTS and there are further trials, such as the IDEAL DVT trial, to reassess the role for ECS in PTS

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prevention but at present NICE and other guideline groups do not recommend the routine use of ECS for this indication.[20] Consequently, we would not suggest that our patient wear ECS for PTS prevention.

Conclusion

In summary, the clinical management of acute and chronic DVT is becoming increasingly complex as research informs treatment decisions in various circumstances. An acute iliofemoral DVT is a particular subtype of DVT that should be managed aggressively, where possible with CDT, in order to minimise the risk of future morbidity, such PTS and recurrence.

Competing interest

none

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