Iliofemoral Deep Vein Thrombosis Treated By Catheter Directed Thrombolysis

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Learning objectives

To discuss the clinical impact of iliofemoral deep vein thrombosis (DVT) and current medical management;

To illustrate treatment of iliofemoral DVT using a combination of catheter directed thrombolysis, mechanical thrombectomy and anticoagulation with examples from our practice;

To examine the role of imaging (including protocols and radiation burden) in the diagnosis and follow up of these patients.
Deep vein thrombosis (DVT) is usually treated with anticoagulation regardless of the extent and location of thrombus [1]. Iliofemoral DVT is recognised to have increased morbidity when compared to infrainguinal DVT, resulting in more severe post thrombotic syndrome (PTS) with increased venous claudication and ulcers, ambulatory venous hypertension, chronic venous insufficiency and recurrent DVT [2,3].

Anticoagulation therapy reduces the risk of developing pulmonary embolism (PE) but, as it only aims to restrict extension of the thrombus without eradicating it, residual thrombus remains [4]. Consequently, the risk of developing PTS has not changed significantly [5].

In patients with extensive iliofemoral DVT, acute removal of thrombus reduces the morbidity associated with PTS. Indeed, a number of recent trials have validated the efficacy and safety of catheter-directed thrombolysis (CDT) and some centres are in the process of optimising this approach [6, 7, 8, 9, 10]. The addition of CDT to the current management decreases both the incidence and severity of the symptoms of PTS via a mechanism of directly resolving the thrombus, improving the patency of occluded veins and maintaining valve function within the veins [6]. Improved quality of life and cost-effectiveness of CDT management make this an important alternative in the management of patients with extensive iliofemoral thrombosis [11].

At our centre, we utilise a protocol which selectively treats iliofemoral DVT with CDT with the use of adjuvants such as stenting, balloon angioplasty or mechanical thrombectomy as appropriate for individual cases. The initial work up and subsequent follow-up of this procedure involves the use of conventional ultrasound, CT venography and intravascular ultrasound (IVUS).
Findings and procedure details

Identification of patients for treatment

Patients who present to A&E with symptoms suggestive of DVT, Wells score >= 2 and raised D-Dimers are considered to have a clinically confirmed DVT. The DVT nurse led team then arranges further management including confirming the extent of DVT with an ultrasound scan. If iliofemoral DVT is suspected, the vascular registrar on call is contacted and a full lower limb venous duplex scan is performed by the vascular lab.

Patients with confirmed iliofemoral DVT who meet the inclusion criteria (Table 1) for the CDT is transferred to the care of the vascular team on a ward.

Patients who do not meet the criteria or meet the exclusion criteria (Table 2) are reviewed on an individual basis for CDT or mechanical thrombectomy (MT), but if considered unsuitable, proceed to the optimum medical management. Age is a relative criteria; 18-75 years is considered the optimal age, however age alone should not exclude patients from receiving CDT. All patients who are otherwise suitable should be discussed at a multidisciplinary meeting and CDT may be performed if risk / benefit analysis in favour of treatment.

Further imaging

Patients who fulfil the criteria for intervention proceed to CT Venography (CTV) and a CTPA in addition to a full vascular lab duplex scan.

CTV protocol

CTV is used to delineate the extent of thrombus extension with particular attention to the inferior vena cava (IVC). Any other factors that may be causing obstruction should also be identified.

The protocol for CT scanning is as follows:

1. 120 mls bolus administration of iodinated contrast media into the antecubital fossa
2. CTPA as per standard timing and protocol
3. Venography through the abdomen and pelvis at 120s post contrast.
CTPA is used to assess if there is any evidence of pulmonary embolus and/or right heart strain. If there is suggestion of right heart enlargement then a supplementary echocardiogram is performed. Catheter venography is performed at the time of the interventional procedure.

**Anticoagulation**

All patients with a confirmed DVT are commenced on anticoagulation in the form of subcutaneous LMWH Dalteparin (Fragmin) until CDT / MT is commenced. LMWH is discontinued the night before / the morning of the treatment and an IV heparin infusion at a dose of 100 U/kg is started. LMWH is to be reintroduced in combination with warfarin or newer agents (with a target INR of 2.0 - 3.0) 1 hour after completion of the procedure. This is guided by the haematologists who manage the patients jointly with the vascular team.

Post procedure transition to oral anti-coagulants is covered throughout with LMWH to prevent re-thrombosis. Post procedure anti-coagulation is monitored through the thrombosis clinic and continued for a minimum of 3 months.

**IVC filter placement**

Selective use of IVC filters is indicated in the presence of:

1) Unstable IVC clot as detected on CTV
2) Symptomatic pulmonary embolus
3) Right heart strain

Patients with none of the above features are preceded to CDT without IVC filter placement.

During the procedure for filter placement, passage through the thrombosed limb needs to be avoided. At placement, adequate space is needed for inflation of thrombectomy catheter balloons to prevent dislodging the filter (i.e. the filter should be placed as high as is practicable). Right femoral and right internal jugular venous approaches are the most suitable. All filters should be retrieved at the earliest possible opportunity once the period of risk has passed and on completion of successful treatment.

**Catheter Directed Thrombolysis**
Preparation: Timing and Clotting

CDT is planned as a semi-elective procedure at the beginning of the week to avoid the risk of lysis continuing over the weekend. Patients do not need to be kept nil by mouth as for arterial lysis cases. At the start of the CDT, an intravenous bolus dose of unfractionated heparin (UFH), 5000 U is given if not already on an IV heparin infusion. Following the procedure, continuous intravenous UFH infusion at 15 U/kg per hour is commenced via the sheath. The UFH dose is adjusted to keep activated partial thromboplastin time at 1.2 to 1.7 times prolongation (i.e., 40-60 seconds) during CDT.

Venous Access

An appropriate vein is selected for puncture under US guidance and local anaesthetic and a 5 or 6 Fr introducer sheath inserted. This is usually at the ipsilateral femoral or popliteal vein depending on the extent of thrombosis. Ideally, access is preferred below the level of the thrombus to facilitate venographic assessment of the progress of lysis. However, if this is not practical, thrombosed veins can be accessed directly if necessary and thrombolysis initiated. The ipsilateral posterior tibial vein can also be selected for catheterization for thrombolysis if there is extensive calf vein thrombosis that also requires treatment.

CT Venographic Assessment of the Thrombus

A venogram is then performed to determine the location and extent of the thrombus. A wire transversal test is performed to ensure the thrombus can be passed. If it is not possible to pass a guidewire into the thrombus, this might indicate chronicity of the thrombus and a decision may be taken not to proceed with lysis depending on an individual patient basis. In these cases, mechanical thrombectomy may be considered more appropriate.

If a wire transverses through the thrombus then further venographic assessment of the venous system distal to the clot is performed.

Thrombolysis

A multi-side-hole infusion catheter is then introduced over a guide wire and embedded within the main body of the thrombus. Alteplase is prepared (Table 3) and administered using a syringe driver, usually at a dose of 0.5 mg/hour. In general, a maximal dose of 20 mg/24 hours should not be exceeded. Thrombolysis with the Alteplase is started
proximally (from the IVC / iliac veins rather than popliteal veins). Check venograms are scheduled at convenient intervals throughout the working day (usually at the beginning and end) to monitor progress of lysis and to enable repositioning of the catheter as required.

**Continuation and Monitoring of the CDT**

When catheter-directed infusion of Alteplase and intravenous UFH are established, treatment continues on a ward. Blood pressure, pulse and the puncture site are assessed several times a day. Activated partial thromboplastin time is monitored twice daily for the adjustment of heparin dose. Patients are encouraged to use the muscle pump of the leg while in bed, and there are no food and drink restrictions. The progress of thrombolysis can be graded by a scoring system (Table 4 & 5). If there is limited radiographic evidence or progress of CDT after 48 hours and a decision is made to continue CDT, this should not continue beyond a maximum of 96 hours.

**Avoidance of Other Antithrombotic Agents**

During the interventional procedure, the concomitant use of other antithrombotic agents is avoided because of increased risk of bleeding. This includes antiplatelet agents (e.g. acetylsalicylic acid, NSAIDs and glycoprotein IIb/IIIa inhibitors) and anticoagulants (e.g. LMWH, warfarin). Because of a possible increase in risk of anaphylactic reactions, the concomitant use of angiotensin converting enzyme inhibitors is also avoided.

**Removal of Catheters and Continuation of Anticoagulation**

The infusion catheters are removed immediately after the end of CDT. Haemostasis is obtained by initial manual compression of the puncture site followed by 2 hours of compression bandaging while the patient is immobilised. Thigh length class 2 compression stockings are put on over the compression bandages and Flowtron boots put on the patients immediately following the end of the procedure. Low molecular weight heparin is given subcutaneously within 1 hour of removal of catheters. This can be done in the IR suite. Anticoagulation is then established and continued as described earlier.

**Indications for MT**

All patients who do not fulfil the criteria for CTL are considered for MT. MT is useful for isolated, segmental thrombus to either attempt complete treatment in one session or to reduce overall length of time that CDT is carried out. MT is preferentially performed at the
start of the procedure rather than as an adjunct after failed CDT. In some circumstances, if felt clinically appropriate, MT can be considered if there is no improvement in clot burden with CDT alone after 48 hours.

If patients are still deemed unsuitable for intervention, best medical therapy through the haematology thrombosis clinic is considered.

**Indications for Stenting**

Following completion of CDT and/or MT, balloon dilatation and stent placement is considered in patients in whom there is:

1. Residual stenosis
2. Residual chronic clot that has not lysed
3. Residual occlusion

This is assessed using completion venography and/or IVUS. If appropriate then balloon dilatation and stent placement takes place during the same procedure. Heparin bolus administration and rigorous flushing of the sheath must be carried out during stent insertion. Alternatively patients may be discharged on anti-coagulation with a planned elective admission following clinic review for stent placement in more complex cases (e.g. IVC obstruction, chronic lesions).

**Stent Placement**

Stent placement takes place after completion of the initial CDT/MT procedure in appropriate patients. LMWH is not to be discontinued prior to the placement of the stent and a bolus of 2000 to 5000 U of IV heparin is given at the time of the procedure.

Stent procedures can be performed in the interventional suite under local anaesthetic and conscious sedation unless the dilatation is very painful in which case the patient may need to be scheduled for general anaesthesia. This is usually the case for a majority of patients with chronic occlusions.

For stenting, a 9 Fr sheath is required. This may be exchanged and inserted through the original access for MT or CDT if being performed immediately and access to a large enough vein has been obtained. Otherwise ipsilateral percutaneous femoral vein access is obtained. Use of a stiff guidewire and predilatation with serial dilators facilitates sheath placement in cases of perivenous fibrosis. Repeat venography may be needed to ensure passage of the guidewire in the correct vessel and not via collaterals, which may run
in parallel. If a perforation is detected (by free lateral movement of the guidewire tip or contrast extravasation) then the procedure is terminated and re-attempted at a 3-4 week interval.

Successful passage into the vena cava beyond the diseased segment is confirmed by venography and/or IVUS. Serial progressive dilations to 16 mm for the distal cava and common iliac veins, to 14 mm for the external iliac vein, and 12 mm for the common femoral vein are performed prior to stent placement. A stent of appropriate size to match the nominal diameter of the diseased venous segment is then used. Extension of the stent into the distal vena cava for 2 to 3 cm or even longer as well as distally below the inguinal ligament is considered in all cases to reduce the risk of delayed stenosis. Stent overlap needs to be between 3-4 cm. Skip areas of less than 4 cm in length between stents should be avoided even if the segment is patent/disease free.

**Discharge and Follow up**

All patients are discharged with thigh length class 2 compression stockings. These may be changed to knee length stockings to aid compliance at 6 weeks follow up if clinically appropriate.

All patients who undergo CDT/MT or stent placement are followed up by haematology and additionally DVT clinic every other week. The anti-coagulation program for each patient is guided by haematology input. Haematology investigations for any underlying cause for the development of DVT are conducted and used to guide the on-going management of anti-thrombotic therapy.

All patients with evidence of PE are referred to the pulmonary hypertension clinic for outpatient follow up. All patients are discussed on completion of CDT/MT at the venous MDT.

Patients who have successful lysis and who do not require additional stent have post procedure duplex assessment performed at 6 weeks, 3 months, 6 months and 12 months to monitor the treated segments.

All patients who undergo an additional stent procedure have a duplex performed at 2 weeks, 6 weeks, 3 months, 6 months, and 12 months to assess stent patency and evidence of restenosis. If there are any concerns regarding the stent and imaging is unclear then the patients may require CTV/MRV/venography in addition to duplex assessment.
Patients in whom a stenosis / re-occlusion or suspicion of stenosis are identified undergo venography and appropriate re-intervention (balloon dilatation or additional stent procedure) at the next available elective opportunity.
Table 1: Inclusion criteria.

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<table>
<thead>
<tr>
<th>Contraindications to thrombolytic therapy (e.g. bleeding diathesis)</th>
<th>Less than 14 d post surgery /post trauma (may be included after 14 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications for systemic thrombolytic therapy (e.g. plegmasia cerulea dolens/ isolated vena cava thrombosis / existing PE)</td>
<td>History of subarachnoid / intracerebral bleeding</td>
</tr>
<tr>
<td><strong>Severe anaemia (Hb less than 8 g/dL)</strong></td>
<td>Disease with life expectancy less than 24m</td>
</tr>
<tr>
<td><strong>Thrombocytopenia (platelets 80 to 109/dL)</strong></td>
<td>Drug abuse or mental disease that may interfere with the treatment and follow-up</td>
</tr>
<tr>
<td><strong>Severe renal failure (EGFR less than 30)</strong></td>
<td>Previous ipsilateral proximal DVT</td>
</tr>
<tr>
<td><strong>Severe hypertension (&gt;=160 mm Hg or diastolic blood pressure above 100 mm Hg)</strong></td>
<td>Malignant disease requiring chemotherapy</td>
</tr>
<tr>
<td><strong>Pregnancy and thrombosis &lt;= 7 d postpartum</strong></td>
<td>Any thrombolytic therapy within 7 d before presentation</td>
</tr>
</tbody>
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**Table 2:** Exclusion criteria.

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<table>
<thead>
<tr>
<th>Dilution of Alteplase</th>
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</thead>
<tbody>
<tr>
<td>Alteplase is provided in a 1mg/ml concentration.</td>
</tr>
<tr>
<td>2.5ml (2.5mg) Alteplase is added to 47.5ml normal saline to make up a 50cc volume (0.5 mg Alteplase / 10ml saline). The infusion is run at 10 cc/ hr to deliver 0.5mg tPA/hour.</td>
</tr>
</tbody>
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**Table 3:** Dilution of alteplase.

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<table>
<thead>
<tr>
<th>Thrombus score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Vein is patent and completely free of thrombus.</td>
</tr>
<tr>
<td>1</td>
<td>Vein is partially occluded</td>
</tr>
<tr>
<td>2</td>
<td>Vein is completely occluded i.e. vein lumen totally filled with thrombotic material</td>
</tr>
</tbody>
</table>

* A total thrombus score is calculated before, during, and at the completion of CDT by adding the scores for the following seven vein segments: inferior vena cava, common iliac vein, external iliac vein, common femoral vein, proximal and distal segments of femoral vein, and popliteal vein. Total score ranges from 0-14 |

**Table 4:** Thrombus score.

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**Lysis Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III</td>
<td>100% lysis with no residual clots</td>
</tr>
<tr>
<td>Grade II</td>
<td>50%-99% lysis</td>
</tr>
<tr>
<td>Grade I</td>
<td>Less than 50% lysis</td>
</tr>
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Lysis grade is then calculated by dividing the **difference** of the total **pre- and post** lysis thrombus scores by the **pre lysis score**.

**Table 5:** Lysis grade.

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Fig. 1: Case 1. Patient assessment. 25 year old male presenting with acute right lower limb pain and swelling. US duplex scan demonstrates extensive iliofemoral thrombosis extending into below-knee veins. Red arrow: no flow within the R CFV, which contains thrombus and is non-compressible. Green arrow: patent R FCA.

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Fig. 2: (a) CTPA demonstrates bilateral proximal pulmonary emboli. (b) CT venogram demonstrates extensive right-sided deep venous thrombosis extending from the lower aspect of the IVC. (c) From the right common iliac vein to the right femoral vein. (d) The left common iliac, external iliac and common femoral veins are patent with no evidence of thrombus. Patient did not have any contraindications for venous thrombolysis. Red arrow: bilateral pulmonary emboli. Green arrows: thrombus in IVC (image B), thrombus in IVC and right common iliac vein (image C), thrombus in right CFV (image D).

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**Fig. 3:** Case 1 (contd): management. Right lower limb venous thrombolysis. Ultrasound guided right popliteal vein puncture. 5-French sheath. Venograms demonstrate extensive thrombus from the right popliteal vein to the right common iliac vein and distal IVC. (a) Guidewire access to right common iliac vein origin. (b) Cragg-McNamara catheter (20 cm infusion length) placed from right CFV to common iliac vein (arrow). Actilyse 5 mg and 5000 units heparin bolus. Heparin and tPA infusion commenced via sheath and catheter respectively (2.5 mg Actilyse and 47.5 ml normal saline running at 5 ml/hour via each catheter. Heparin infusion (25,000 units 50 ml normal saline) running at 1 ml/hour in each leg via sheath side-arm).

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Fig. 4: (a) Right venogram 20 hours later shows significant reduction of clot burden and improved flow with patency of the SFV and CFV. (b) The EIV is also patent, but there is a 50-75% stenosis present. Right CIV is patent and with a normal caliber. Red arrow: residual stenosis in the right iliac vein. (c) A 14x 80mm EV3 stent was inserted from the CIV to the EIV and angioplastied to 12mm (arrow). (d) Final venography showed a successful angiographic result.

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Fig. 5: Case 1 (contd): management of recurrent intra-stent thrombus. Patient returned one month later. (a) Right venogram performed via 5F sheath placed in popliteal vein demonstrates a contrast filling defect in the proximal right EIV-CIV stent that is extending to the IVC. (b) This was treated via venoplasty with a 16 x 40mm high pressure balloon. (c) The final venogram showed improved appearances within the stent.

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Fig. 6: Follow up venogram performed 3 months later demonstrates widely patent right femoral, iliac and lower IVC.

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Fig. 7: Case 2: May-Thurner deformity treated with stenting. 27 year old male presenting with acute shortness of breath and left leg swelling. (a) CTPA demonstrates bilateral peripheral pulmonary emboli. (b) CT abdomen and pelvis shows left common femoral vein. No pelvic masses identified.

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**Fig. 8:** Venogram and venous thrombolysis performed via popliteal vein puncture. Ultrasound guided left popliteal vein micropuncture. 5-French sheath. (a) Venograms demonstrate thrombus extending from the popliteal vein to the common femoral vein. (b) No iliac venous thrombosis is present. (c) The thrombosed femoral vein was crossed with a hydrophilic guidewire and a Cragg McNamara (10 cm infusion length) catheter placed from the common femoral vein distally (arrow). Actilyse 5 mg and 5000 units heparin bolus. TPA and heparin infusion commenced.

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Fig. 9: Check venogram approximately 24 hours post-thrombolysis. (a) Residual thrombus within the proximal femoral vein, close to the sheath in situ within the popliteal vein. (b) Distal femoral, common femoral and iliac veins are patent. (c) There is a May-Thurner type venographic appearance to the distal common iliac on the left. May-Thurner's type deformity was confirmed on INTRAVENOUS US. (d) 16 x 140 mm venous stent placed across the common iliac vein and dilated with a high pressure 16mm balloon. Subsequent INTRAVENOUS US shows residual stenosis. (e) Further 16 x 60 mm Wallstent placed within the EV3 stent across the iliac narrowing for added support and venoplastied. Satisfactory subsequent appearances on INTRAVENOUS US. Thrombolysis was continued for further 24 hours to reduce clot burden in proximal femoral vein.

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Fig. 10: Venograms performed on following days show patent popliteal and femoral veins with little residual clot, and widely patent iliac veins with rapid contrast flow.

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**Fig. 11:** Case 3: patient with relative contraindication to venous thrombolysis treated with primary mechanical thrombectomy. 40 year old female with known endometrial cancer admitted with right DVT. CT scan (a and b) shows pelvic collection suspicious of recurrent tumour and extensive right ileofemoral DVT with close proximity of the iliac vein to the pelvic collection. Red arrows: pelvic collection. Green arrows: thrombus in the right common iliac vein.

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Fig. 12: Given increased risk of haemorrhage from direct thrombolysis due to pelvic malignancy, following discussions with the patient and vascular surgeons, a decision was made to perform primary mechanical thrombectomy. US guided right popliteal vein puncture, 9-French sheath. Venogram demonstrates soft extensive thrombus from the proximal femoral to the common iliac vein (a and b). The IVC is patent. The extensive thrombus was easily crossed with a guide wire. Mechanical thrombectomy of the common iliac and subsequently femoral segments performed with 20 mg Actilyse. Subsequent venograms demonstrate successful recanalisation of the veins (c and d). 16 x 140 mm and 16 x 100 mm venous stents deployed from common iliac to just above the femoral head (e). High pressure balloon angioplasty to 16 mm. Residual stenosis in the pelvis at the level of the surgical clips resistant to balloon treatment (f). Stenosis confirmed on
intravascular ultrasound. 16 mm Wallstent deployed across this site for added support. Repeat angioplasty to 16 mm. Satisfactory appearances on final venogram.

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Fig. 13: Case 4: bilateral ileofemoral DVTs. 32 year old female presenting with bilateral leg swelling. CT venogram demonstrates extensive DVT involving the infra-renal IVC and extending into the left CIV and right SFV (a and b).

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**Fig. 14:** Ileofemoral venogram and thrombolysis. Bilateral popliteal vein punctures. Bilateral venograms via popliteal veins confirm CT findings (a-right, b-left). Bilateral Cragg McNamara thrombolysis infusion catheters (50 cm infusion length) inserted to the level of the infrarenal IVC. 2.5 mg Actilyse bolus via each catheter.

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**Fig. 15:** Daily check venograms were performed. Following 4 days of thrombolysis, there is a significant thrombus burden improvement in both legs. (a) The left leg venogram shows a persisting contrast filling defect in the CIV. (b) The right venogram shows a partial contrast filling defect along the SFV, EIV and CIV.

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**Fig. 16:** Bilateral self expanding stents placed across the iliac veins extending into the IVC origin (a and b).

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**Fig. 17:** CT scan performed a day later shows satisfactory position of the stents with patent and largely clot free bilateral ileofemoral veins.

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Conclusion

Direct venous thrombolysis offers an alternative in managing significant iliofemoral thrombosis and, unlike anticoagulation, reduces the morbidity associated with PTS. Good imaging protocols are important to achieve diagnostic images from CT venograms and minimise radiation dose. A multidisciplinary team approach is essential in the long term care of these patients in order to:

Identify suitable patients;

Ensure safe protocols are in place for directing therapy;

Enable management to be tailored appropriately to individual cases, many of which are complex and involve a young patient population;

Establish pathways for maintaining good follow-up;

Identify patients who require additional treatment and/or re-interventions.
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