British Medical Bulletin, 2016, **117**:107–120
doi: 10.1093/bmb/ldw006
Advance Access Publication Date: 17 February 2016

Contemporary management of acute and chronic deep venous thrombosis

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Accepted 3 January 2016

Abstract

Introduction: This review aims to provide an update on the management of deep vein thrombosis (DVT).

Sources of data: A systematic search of PubMed, Google Scholar and Cochrane databases was carried out.

Areas of agreement: Direct oral anticoagulants (DOACs) are as effective and easier to use than vitamin K antagonists for the treatment of DVT. Catheter-directed thrombolysis can reduce post thrombotic syndrome in patients with iliofemoral DVT. Compression bandaging can help heal a venous ulcer.

Areas of controversy: Compression hosiery to prevent post thrombotic syndrome. Long-term evidence to show clinical benefit of using endovenous therapies to restore deep vein patency.

Growing points: Developing imaging methods to identify patients who would benefit from venous thrombolysis. The evolution of dedicated venous stents.

Areas timely for developing research: Understanding the mechanisms that lead to stent occlusion and investigation into the appropriate treatments that could prevent in-stent thrombosis is required.

Key words: DVT, endovenous, catheter-directed lysis, thrombolysis, venous stent, post-thrombotic syndrome

Introduction

Deep venous thrombosis (DVT) is a common condition estimated to affect around 100 000 patients each year in the UK.[1] It can lead to death through pulmonary embolism and rarely limb loss through phlegmasia cerulea dolens. The chronic sequelae of DVT, known as post-thrombotic syndrome (PTS), includes persistent pain, swelling or ulceration that occurs in around half of patients within 2 years of a DVT.[2] PTS is associated with significant morbidity and, together with venous thromboembolism, carries a financial burden to the NHS costing an estimated £1 billion per year to treat.[1]

Vessel wall injury, stasis and blood hypercoagulability are considered important instigators of venous thrombosis, with more recent evidence suggesting that 'sterile' inflammation has a pivotal role in this pathology.[3] Mechanical (stretch or surgery) or chemical (cytokine storm from sepsis) activation of the endothelium leads to local up-regulation of procoagulant proteins, surface adhesion molecules and cytokine production that results in the accumulation of neutrophils and platelets, forming the nidus for thrombus formation. The neutrophils at the site of thrombus formation create a scaffold for thrombus propagation through the release of DNA (neutrophil extracellular traps, NETs) which, together with the cross-linked fibrin, capture red cells to form the main body of the thrombus.[4] The neutrophils also release damage-associated molecular patterns (DAMPs) that act as danger signals to promote further inflammation[5] including the infiltration of mononuclear phagocytes that orchestrate thrombus resolution.[3] This involves a slow process of tissue organization that aims to recanalize the vein.[6]

Although traditional anticoagulation and compression hosiery remain the cornerstone of treatment, the management options for deep venous disease are expanding. In the acute setting, the new direct oral anticoagulants (DOACs) appear to be a more attractive alternative to vitamin K antagonists (VKA), while percutaneous interventional procedures have shown promise in reducing long-term complications with minimal risks of bleeding. In the chronic post-thrombotic limb, also, there has been a greater impetus to treat symptomatic patients using invasive treatments that are designed to reduce the morbidity caused by PTS.

This review aims to provide a brief overview of the management options that are now available to patients with both acute and chronic venous disease, with particular emphasis on the minimally invasive endovenous interventions that are being increasingly used.

Acute DVT

Medical management

Parenteral anticoagulation, with low molecular weight heparin, followed by a VKA has been the mainstay of medical treatment for patients presenting with an acute DVT. This regimen is designed to prevent thrombus propagation and reduce the risk of embolization, allowing the thrombus to resolve naturally. The use of VKAs such as warfarin can be cumbersome for patients, however, as it requires frequent laboratory monitoring to ensure that an adequate level of anticoagulation is achieved (using the international normalized ration, INR). The level of anticoagulation can be difficult to predict and it is estimated that only 50% of patients taking a VKA at any one time are within 0.5 INRs of the expected therapeutic range.[7] As a result, there is a risk of recurrent thrombosis or bleeding in patients with sub-therapeutic or high INRs. In addition, the many food and drug interactions with VKAs can limit their efficacy. DOACs have been developed to overcome some of these problems.[8] They do not require laboratory monitoring, have no food interactions and appear to have few drug interactions. Non-inferiority studies comparing their use to current standard treatment of LMWH, followed by a VKA, have shown that they have similar rates VTE recurrence and bleeding,[9–11] with the risk of intracranial haemorrhage appearing to be lower with DOACs compared with VKA in particular. The direct factor Xa inhibitors, Rivaroxaban (Bayer AG) and Apixaban (Pfizer/Bristol-Myers Squibb), and the direct thrombin inhibitor, Dabigatran (Boehringer

Ingelheim), are currently licenced and approved by NICE for use in the UK for venous thromboembolism (VTE, NICE technology appraisals TA 267, 327 and 341).

The DOACs are not without drawbacks. They cannot be used in patients with severe renal impairment (creatinine clearance <15 ml/min); they are more expensive than VKA per tablet; they are not yet recommended for treatment of cancer-associated VTE and are not known to be safe in pregnancy or breastfeeding. A recent meta-analysis also suggests that there could be an increased risk of gastrointestinal bleeding associated with the use of dabigatran and rivaroxaban in the elderly.[12] Perhaps their biggest problem is the lack of specific reversible agents. Antidotes are currently in development.[13,14] DOACs are, however, likely to be increasingly used in the future as they are easier to use in the community as they need no monitoring and enable an 'all-oral' approach to treatment.[15]

Thrombolysis

The mechanisms that lead to development of PTS after DVT are not completely understood. It has been suggested that early removal of thrombus after the index event can prevent a sustained high venous pressure and preserve or limit damage to venous valves, which is thought to contribute to PTS.[16,17] Since the first report of transcatheter thrombolysis in the early 1990s,[18] there have been a number of studies that have shown benefit for this therapy. A recent Cochrane Review analysed 17 controlled trials that randomised a total of 1103 people with acute DVT (within 21 days of onset of symptoms) to receive thrombolysis or anticoagulant treatment.[19] Fewer people developed PTS in the lysis group at 6 months (number needed to treat 5) compared with anticoagulation alone.

Thrombolysis for DVT is now generally performed with a catheter positioned directly in the thrombus as opposed to systemic lytic therapy using a cannula inserted in a vein away from the thrombus.[20–22] This is thought to reduce the total amount of thrombolytic agent required to remove the thrombus and minimize haemorrhagic risk, though direct evidence for this is limited.[19,23] Catheter-directed thrombolysis (CDT) starts with an ultrasound-guided venous puncture usually in the popliteal vein and uses fluoroscopic imaging to position the catheter appropriately. A check venogram is usually carried out 12–24 h after initiation of lysis to assess the degree of thrombus dissolution (Fig. 1). The decision can then be taken whether to continue with CDT or to use alternative endovenous treatments aimed at rapidly re-establishing vein lumen patency (discussed below).

There is currently no standardization for the concentration of lytic agent (or type) that should be used or the infusion volume and rate, both of which are likely to impact on the success and complications associated with lysis. We use a maximum dose of 1 mg tissue plasminogen activator (tPA) diluted in normal saline and administered at a volume of 10 ml/h. All patients should be counselled about the risks of bleeding prior to starting treatment (around 1.5- to 2-fold increased risk of major bleeding compared with anticoagulation[24]) and are usually placed on a high dependency unit while undergoing therapy. Some have, however, advocated use of monitoring on a general vascular ward.[21]

Adjunctive treatments to thrombolysis

Contemporary surgical management of acute DVT includes the use of pharmacomechanical adjuncts (PMAs), venoplasty, and endovenous stents together with CDT. These are employed to help remove thrombus and restore vein patency when CDT alone has not been wholly effective. PMAs include rotational, rheolytic and ultrasound-enhanced devices, which are designed to minimize both the time of CDT and the amount of lytic required.[25] Rotational devices include the Amplatz thrombectomy device (Microvena) and Trerotola device (Arrow International), which use a rotating helix to macerate the thrombus, while rheolytic devices such as the Angio-Jet device (Possis) generate a pressure gradient to form a high pressure jet that can fragment the thrombus, which is then aspirated. Ultrasound-enhanced devices, such as the EKOS Endowave (EKOS) partially fragment the thrombus with high-frequency,

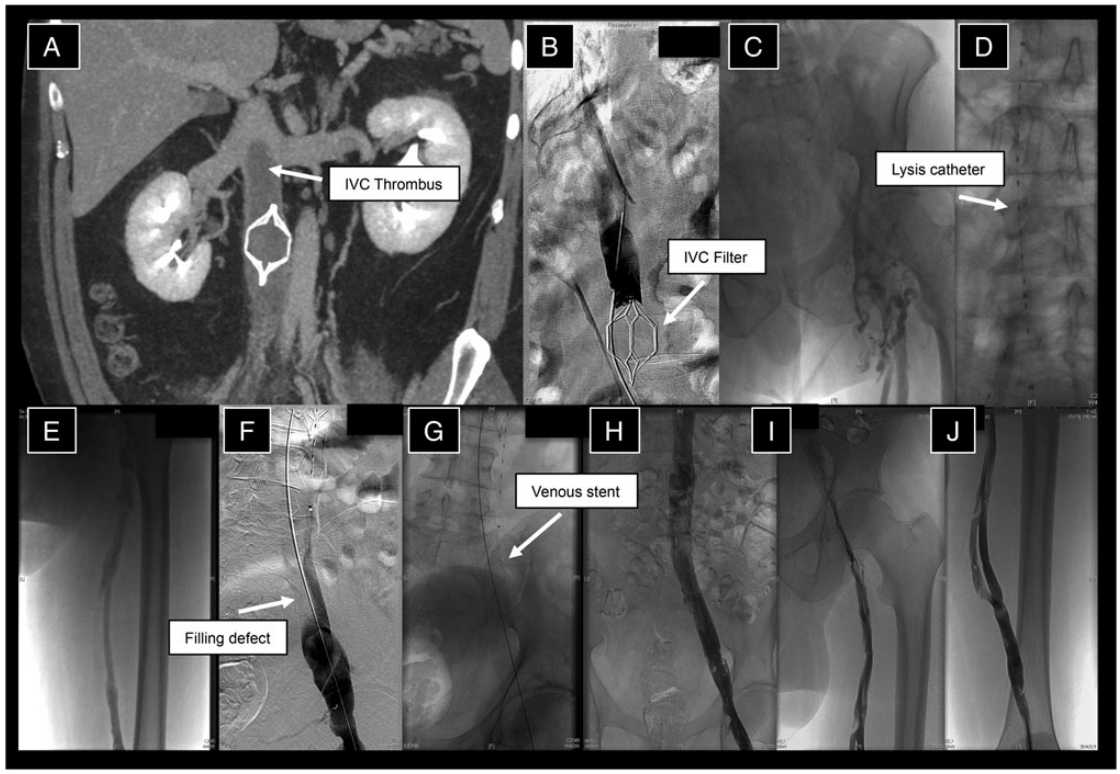

Fig. 1 Thrombolysis for acute iliocaval DVT. Computed tomography with contrast showing a DVT around a previously inserted permenant IVC filter (**A**). Digital subtraction venography shows absent venous flow in the IVC, iliac and femoral veins up to the level of the filter (**B** and **C**). An EKOS lysis catheter was used to enhance catheter-directed thrombolysis (**D**). A repeat venogram performed 24 h later demonstrated flow in the popliteal, femoral and external iliac veins (**E** and **F**). A venous stent was inserted for a residual filling defect in the common iliac vein (**G**). Repeat venography demonstrated restoration of blood flow in the deep venous system (**H–J**). This was associated with resolution of patient symptoms.

low-energy ultrasound, which can enhance lytic therapy *in vitro*.[26] A recent randomized trial has, however, failed to show benefit of this technique in man.[27] There is a paucity of robust long-term data demonstrating the effectiveness of PMT devices for the treatment of DVT and no direct comparison of one device versus another. Until patient benefit has been clearly demonstrated in large clinical trials, the added costs will limit their use.

Venoplasty and stenting have a role in treating a subset of patients with an underlying stenosis (May-Thurner's or Cockett's syndrome) or those with residual thrombosis.[28,29] Balloon venoplasty is used to macerate thrombus, predilate the vein prior to stenting and post-dilate an inserted stent. The principles for treating venous disease are different to the approach when treating arterial pathology. There is high elastic recoil in the veins, which generally always requires placement of a stent. The first generation of dedicated venous stents has excellent short-term patency results, and this appears to correlate with a reduction in symptoms.[30,31] There are, however, no reliable methods to demonstrate a functional stenosis and identify those in whom a stent would be most beneficial. In three recent randomized trials, comparing medical and surgical therapy, PMAs, venoplasty and stenting were used at the discretion of the treating physician.[32–34] The selective use of these techniques could improve patient outcomes.

The first contemporary randomized control trial (RCT) to report their results for CDT was the single-centre TORPEDO study.[32] One hundred and

eighty-three patients with symptomatic DVT were randomized to receive endovascular treatment plus anticoagulation or anticoagulation alone. Recurrent thrombosis and PTS developed in significantly fewer patients in the interventional group (4.5 vs. 16% and 6.8 vs. 29.6%, respectively) at 30 months. A subsequent study, the CaVenT trial, had a multicentre design with 209 patients enrolled.[35] PTS was significantly lower in the lysis group compared with control at 2 years (41.1 vs. 55.6%). The modest reduction in PTS, though significant, may have been the result of the inclusion of 'proximal' DVT patients without an affected iliac segment, while use of venous stenting was limited. Results from the larger ATTRACT trial, a multicentre study carried out in the USA with 694 patients are awaited,[34] but this trial also includes patients with femoral DVT not extending into the iliac veins (who we may treat with anticoagulation alone). The term 'proximal' DVT is probably out dated and should be changed to one that more accurately represents the anatomical location of the thrombus that would help guide intervention. The lower extremity thrombosis (LET) classification is a tool that has been proposed for stratification of thrombus into Classes I–IV based on the vessels that are affected by DVT.[36,37] Based on this system, we advocate treatment in patients with Class III (iliofemoral thrombosis) or Class IV (caval thrombosis) disease. Future studies would benefit from more standardized inclusion criteria, a consensus of how best to measure the degree and rate of clot dissolution, and ensure that PTS is measured using a validated scoring system, the Villalta Score, alongside other objective measures of post-thrombotic complications.[38]

Selecting patients for treatment

NICE guideline CG144 currently recommends that thrombolysis is considered for patients with symptomatic ileofemoral DVT if they have symptoms of <14 days, good functional status, life expectancy >1 year and low bleeding risk. Strict selection criteria are required to identify patients who are suitable for endovascular venous intervention. It is therefore likely that appropriate surgical treatments are often underused. Recent studies show only around 15% of DVT patients eligible for intervention received appropriate treatment in a UK centre.[39] One reason for this is perhaps the variability in presentation, signs and symptoms of DVT patients, the lack of awareness of potential interventions, and a paucity of local resources and expertise.

Lytic therapy is only effective in fibrin-rich thrombi, which are thought to be fresh, and tPAs will not help dissolve the collagen that accumulates in an organized thrombus. Some patients are likely to resolve their thrombi faster than others; therefore, thrombus 'age' may have little bearing on thrombus structure and fibrin/collagen content. This could explain why patients respond differently to lysis. We, and others, are developing imaging methods to characterize the structure of thrombi *in vivo*. Magnetic resonance T_1 mapping, in particular, has potential to help identify thrombi suitable for lysis, and we are currently looking to translate this and other MR sequences into the clinic.[40–42] In the meantime, to help stratify patients who may benefit from intervention and removal of thrombus, we have developed the BLAST tool to better identify patients who are suitable for DVT lysis (Table 1). These factors should all be considered: Bleeding risk, Life expectancy, Anatomy, Severity and Time of symptoms of the DVT before treatment is offered.

Chronic venous disease

Post-thrombotic syndrome

The measures discussed so far are designed to prevent or limit the incidence and severity of PTS. This should remain a treatment goal for all patients presenting with acute DVT together with minimizing the risk of embolic events. Historically, however, enthusiasm for these treatments was tempered by the perceived complication rate, and therefore, the incidence of PTS remains high. Estimations of PTS range from 20 to 50% of DVT patients at 2 years, suggesting that up to 50 000 new patients suffer some form of these chronic problems each year in the UK.[1,2] Long-term severity of PTS is greatest in patients with an iliofemoral DVT, high body mass index, recurrent

Table 1 BLAST Tool for the identification of patients suitable for venous thrombolysis

B	Bleeding risk	Patients in whom lysis is considered should be evaluated for potential haemorrhage. Active or recent bleeding, recent major surgery, trauma, pregnancy and lesions with the potential to bleed (e.g. cancers) are all potential contraindications to lysis.
L	Life expectancy	Aggressive therapy to prevent PTS in patients with a very short life expectancy is less likely to be beneficial. Patients with significant co-morbidities, for example those with respiratory problems may find difficulty lying prone. Our cut-off point is usually a year; however, this is a soft indication and patients are considered on a case-by-case basis.
A	Anatomy of DVT	The anatomical extent of DVT should be considered before lysis. Patients with acute thrombus located in the cava or iliac vessels should primarily be considered for lytic treatment. Patients with popliteal or calf DVT should be anticoagulated.
S	Severity of DVT	Patients with clinically severe thrombosis that is life, limb or organ threatening should be considered for emergency treatment. When pain and swelling are severe enough to prevent walking and activities of daily living, lytic treatment should also be considered. In these situations, patients must be made aware of the risks and benefits of surgery to make an appropriately informed decision.
T	Timing	Timing since symptoms of DVT can be subjective, but inclusion criteria for many trials in this area range from 14 to 21 days. We recommend lysis to be considered in patients with thrombi 'aged' 14 days or less and on a case-by-case basis if the thrombus is older.

DVT, old age and female sex[43] and is associated with a severely impaired quality of life.[44] Importantly, DVT is not exclusively a disease affecting the elderly with an annual incidence of VTE in the 15–44 years age group of 1.49 per 1000.[45] There are significant direct and indirect health costs associated with thrombotic disease, with an estimated 2 million workdays lost in the USA each year in patients with severe PTS.[46] In one small study, ~90% of patients with iliofemoral DVT were unable to work because of leg symptoms 10 or more years after the episode of thrombosis.[47]

Conservative treatments

Apart from the traditional treatment of leg elevation and bed rest, compression therapy is a non-invasive method of reducing venous hypertension with the aim of preventing PTS. Therapies include elastic stockings, bandages and intermittent pneumatic devices designed to compress the superficial and deep veins. A recent multicentre RCT examining 401 patients has shown that progressive compression with maximal pressure at the calf is more effective than traditional compression stockings with higher pressure at the ankle, in improving symptoms in patients with chronic venous insufficiency.[48] However, despite a number of small studies and individual clinical reports suggesting that elastic compression stockings (ECS) can improve patient symptoms and prevent PTS, the SOX trial, a multicentre, randomized, placebo-controlled trial to establish whether ECS can prevent PTS after proximal DVT, has suggested otherwise.[49] The cumulative incidence of PTS in this trial was 14.2% in patients wearing ECS compared with 12.7% in controls. Although this was the largest and only placebo-controlled study examining a role for ECS, its findings have caused controversy, and ECS are still recommended by many. The low compliance rate (56% used compression for 3 or more days a week) has been suggested as one reason why there were no observed differences between groups, and this may because compression hosiery is difficult to apply, can be uncomfortable for some patients and requires replacement every few months.

Less controversial is the use of compression bandaging to improve ulcer healing. Four-layer compression bandaging with at least 40 mmHg pressure over a week is effective at improving ulcer healing,[50] and although there are a number of other methods to ensure adequate compression (two layer, three layer, paste bandages, high compression stockings, Unna

boot), this still remains the gold standard for treating patients with leg ulceration. Surgical correction of superficial venous reflux does not confer benefit to ulcer healing in addition to compression bandaging, but reduces the recurrence of ulcers at 4 years.[51] Patients with healed ulcers should therefore be evaluated for superficial venous disease and treated accordingly.

An array of commercially available dressings such as alginate, foam dressings, hydrocolloid dressings, silver-donating dressings are some of the ulcer dressings that are sometimes used in the community, though few have shown significant benefit.[52,53] Topical cadexomr iodine in addition to compression and zinc oxide impregnates paste bandages appear to be the exception, although some patients complain of local side effects, particularly with zinc.[54,55]

Medical treatments

Current standard treatment remains use of anticoagulatants to prevent recurrence. Venoactive drugs such as naftazone and calcium dobesilate are rarely used in the UK, but more commonly prescribed in other countries. They are designed to decrease capillary permeability and/or improve venous tone. A Cochrane Review concluded that in patients without ulceration there is a lack of sufficient evidence to justify their use.[56] Horse chestnut extract (HCSE) may, however, be effective at reducing oedema, pain and itching.[56] Other medications that reduce oedema have been used in trials and include micronized purified flavonoid fraction (MPFF),[57] calcium dobesilate[58] and red vine leaf extract.[59] A recent clinical practice guideline from the European Society of Vascular Surgery recommended that venotonic drugs should be considered in patients with pain and swelling caused by chronic venous disease.[60]

Surgical intervention

A number of pathophysiological outcomes can occur following DVT. The thrombus can completely resolve with minimal scarring to vein; the thrombus fails to resolve but adequate collaterals form, relieving symptoms; the thrombus partially resolves with recanalization, but leaves a residual outflow obstruction that does not affect valve function; a significant proximal post-thrombotic occlusion/stenosis causes distal valvular dysfunction due to vessel dilatation and haemodynamic changes; or venous reflux occurs because of valvular damage, secondary to inflammatory mediated fibrosis (occurring as the thrombus resolves). Combinations of these outcomes are likely to occur in individual venous segments of a DVT-affected limb and may reflect the heterogeneity in the severity of PTS between patients.

Deep venous reconstruction can involve open surgery, percutaneous balloon angioplasty and stenting, or a combination of both. Stenotic or occlusive lesions may be treated as well as valve incompetence and with advancements in technology (e.g. the development of dedicated venous stents) this is a rapidly growing field within vascular surgery. Invasive treatments for chronic deep venous disease are, however, reserved for those with severe clinical symptoms and signs that have been objectively measured. The decision to offer invasive treatment should be made by a multi-disciplinary team and based upon the patient's pre-morbid condition, the anatomical extent of disease, the likelihood of symptomatic improvement and the potential of the patient to enter into a commitment of post-operative anticoagulation and ultrasound surveillance. The post-thrombotic patients who are treated in this manner have limited function and a severe Villalta score prior to intervention and patients need to be advised of the potential to re-intervene and the risks of bleeding and in stent thrombosis. It is rare that their symptoms worsen following intervention, but the decision to proceed to surgery ultimately rests with the patient with their long-term improvement and ulcer healing being the goal.

Venous stenting

Venous stenting is usually a percutaneous intervention that involves traversing the occluded vein lumen with a wire using radiological guidance. Patients are placed in pneumatic compression boots and anticoagulated with unfractionated heparin prior to the procedure. Intravascular ultrasound (IVUS) is routinely

used by some operators to assess venous anatomy prior to intervention and to identify landing zones free of thrombotic disease that can not readily be seen on venography (Fig. 2). A high-pressure balloon is then inflated to create an adequate lumen within the vein, which is supported by placement of an uncovered bare metal stent. Post-dilation balloon venoplasty is routinely performed. Stent integrity is confirmed using IVUS and venography carried out to demonstrate adequate clearance of contrast agent. We believe that failure to be meticulous at checking stent placement, including an assessment of an adequate inflow at the time of insertion, is associated with poor outcomes. Treatment doses of low-molecular weight heparin are given to the patient post-operatively, and the patient is scanned with duplex ultrasonography the next day.

Until recently, a rigid braided stent made of cobalt, chromium and nickel was used, but the first-generation dedicated Nitinol venous stents are now available (Fig. 3). These have been designed to have rigidity to prevent external compression, but are also flexible to account for the curvature of the pelvis and groin. Medium- and long-term results from studies using these new devices are awaited, and it remains to be seen what the optimal design of a venous stent should be. Technical success from 17 studies evaluating stenting in the veins of over 2000 limbs, ranges between 87 and 100%.[31,61–76] Primary patency (an open stent without any additional procedures) is between 50 and 94%; primary assisted patency (an open stent but additional procedures are required to prevent occlusion) between 76 and 90%, and secondary patency (an open stent that required an

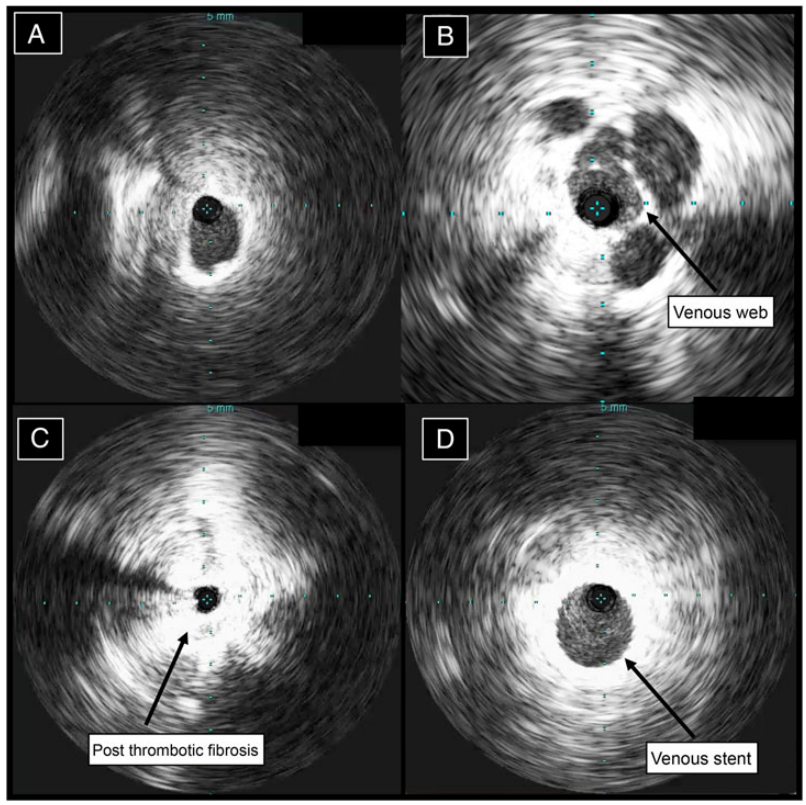

Fig. 2 Intravascular ultrasound (IVUS). (**A**) Appearance of normal vein, (**B**) appearance of 'webs' in a post-thrombotic vein, (**C**) occluded post thrombotic venous segment (now traversed with a wire) before stenting, (**D**) appearance of a venous stent in a previously occluded segment.

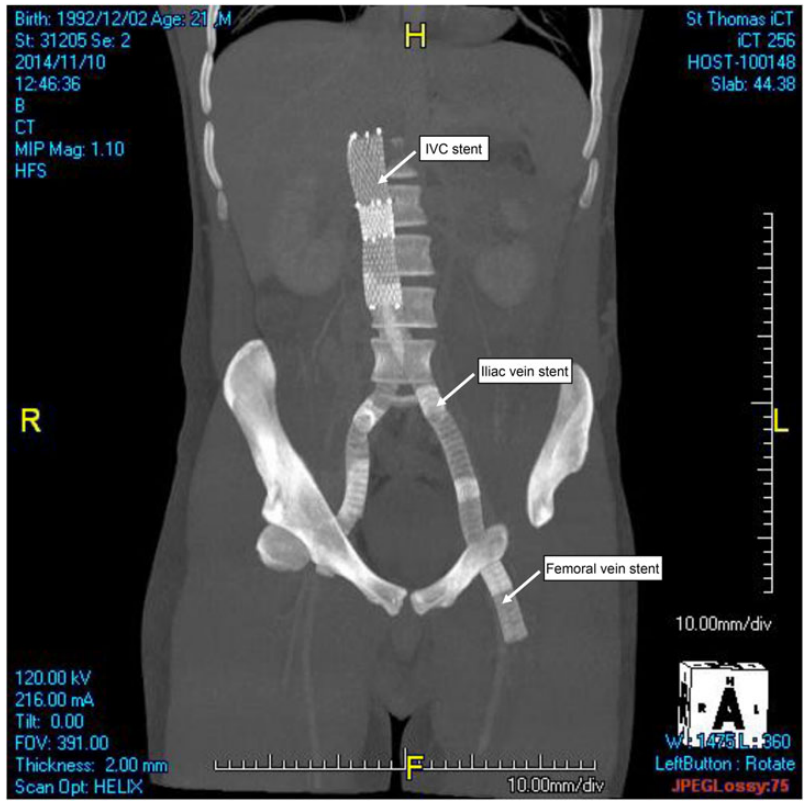

Fig. 3 Deep venous reconstruction. Computed tomography with contrast showing total reconstruction of the deep venous system using venous stents following a previous extensive iliocaval DVT.

additional procedure following occlusion) between 72 and 82% in follow-up ranging from 2 to 120 months.[31,61–76] These studies often, however, include patients with symptomatic non-occlusive, non-thrombotic (May-Thurner's) lesions and compare results alongside patients with occluded post-thrombotic limbs. The latter are significantly harder to treat. The severity and complexity of the lesion being treated should be considered when analysing results between studies. Cumulative patency rates when reported (of both thrombotic and non-thrombotic lesions) should be treated with caution.

There is a need to understand why stents occlude. Reasons are likely to include patient-based factors (such as the presence of a coagulopathy), as well as technical considerations (such as the need for an adequate inflow and outflow); but important other factors have probably yet to be identified. It is imperative that patients are compliant with anticoagulation following intervention to reduce the risk of re-thrombosis, although the optimal length of post-operative anticoagulation is unknown. We use warfarin for 1 year unless a longer duration is indicated due to other patient factors. The use of the DOACs and antiplatelet medications in these patients remains unknown and warrants investigation in a controlled trial.

Ultimately, the most relevant end point in the assessment of venous stenting is clinical outcome. Hard measures, such as ulcer healing, vary from 47 to 100%, while overall improvement of pain is seen in around half of patients, and a reduction in swelling varying between 32 and 61%.[60] Studies in the future should be designed to include robust

quality of life scores to examine whether there is significant improvement following intervention. Patient expectation should, however, be tempered as it is unlikely that a chronic post-thrombotic limb will ever be completely normal, even with a patent stent. The main aims of treatment should be to improve symptoms and limb function.

Open surgery

Open surgical options to treat deep venous disease include femoro-femoral bypass (Palma bypass when saphenous vein is used), femoro-iliac-infrahepatic inferior vena cava bypass, common femoral vein patch plasty (with or without an arterio-venous fistula), valvuloplasty and transposition or transplantation of a valve containing venous segment. There is a paucity of data regarding outcomes in these patients and the skill set for performing these procedures is concentrated into a few specialist centres. Open surgical repairs for chronic venous obstructions are generally currently offered if endovascular treatments are not possible (e.g. if the iliac vein is occluded as a result of an iatrogenic injury that involved ligation or clipping of the veins, or in patients with true venous hypoplasia).[77] Similar to venous stenting, consideration should be made regarding the need for adequate inflow and outflow. Patients should also be prepared for an arterio-venous fistula, which may be necessary to keep the bypass open by maintaining high flow. Data from a single centre shows 5-year primary and secondary patency range from 44 to 86% depending on the location of the bypass.[78] Early occlusions were seen in 17% of patients, though clinical scores improved with graft patency.

Surgery on deep venous valves

There have been a number of techniques that have been described to repair, replace or create a venous valve in the lower limb. Studies are generally small, and patients are often treated during management of both the superficial and deep system. Similar to venous bypass procedures, the skill set for these operations is exclusive to specific centres. Although results in the short term appear favourable, ulcer healing rates vary between 54 and 100% up to 5 years.[60] In the long-term, surgery in patients with primary valve insufficiency appears to be more successful than those with PTS.[79] Patients should be treated with compression therapy and anticoagulation after surgery. Percutaneous techniques that use mechanical and bioprosthetic venous valves, implanted using a transcatheter technique with a vascular stent for valve attachment, have been developed, but none have so far shown success in the clinic.[80] A more promising technique will, perhaps, be through the percutaneous construction of a new valve using the native vein wall, and a clinical trial is awaited.[81] Understanding the genetic and molecular regulation of vein valve development may also lead to novel treatment options for the generation of biological valves or the maintenance of existing valves damaged by pathology.[82]

Conclusions

The recent introduction of DOACs has changed the medical management of DVT patients, who were previously reliant on VKAs. With laboratory monitoring no longer required, patients and physician attention have been focused on using these new anticoagulants, and UK guidelines are rapidly changing to incorporate these drugs as part of best medical practice. To some extent, this has detracted attention away from the other paradigm shift in the area, which has been the development of dedicated minimally invasive technology to treat deep venous disease in both the acute and chronic setting. In selected patients, these percutaneous treatments have the potential to minimize the risk of developing PTS and can effectively treat those who have established complications. The haemorrhagic risks associated with thrombolytic medication, although still present, appear lower if lysis is targeted directly into the thrombus. Novel imaging methods, for example MR T_1 mapping, are also being developed to better identify patients in whom lysis has the greatest potential. While use of adjunctive procedures to CDT may confer patient benefit, evidence from well-constructed clinical trials is lacking. These are only likely to emerge if experience in the

surgical treatment of DVT is focussed into a few specialist centres. These centres will need specific infrastructure and cross-disciplinary support from physicians and healthcare workers to establish a safe and robust service. Improvements in the design of venous stents, through structural changes and/or drug coating, are likely to translate into better patency rates (mirroring those seen in arteries); however, the most important test for any new technology will be to show a sustained long-term improvement in clinical outcomes.

Conflict of interest statement

S.B., Consultancy contracts with Veniti, Cook Medical, Medtronic, Optimed and Volcano; P.S., Honorarium from Bayer Healthcare, Cook Medical and Veniti.

References

1. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756–64.
2. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis* 2009;28:465–76.
3. Saha P, Humphries J, Modarai B, et al. Leukocytes and the natural history of deep vein thrombosis: current concepts and future directions. *Arterioscler Thromb Vasc Biol* 2011;31:506–12.
4. Fuchs TA, Brill A, Duerschmied D, et al. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci USA* 2010;107:15880–5.
5. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol* 2013;13:34–45.
6. Modarai B, Burnand KG, Humphries J, et al. The role of neovascularisation in the resolution of venous thrombus. *Thromb Haemost* 2005;93:801–9.
7. Rose PE. Audit of anticoagulant therapy. *J Clin Pathol* 1996;49:5–9.
8. Lang KJ, Saha P, Roberts LN, et al. Changing paradigms in the management of deep vein thrombosis. *Br J Haematol* 2015;170:162–74.
9. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
10. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.
11. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
12. Sharma M, Cornelius VR, Patel JP, et al. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation* 2015;132:194–204.
13. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013;121:3554–62.
14. Mo Y, Yam FK. Recent advances in the development of specific antidotes for target-specific oral anticoagulants. *Pharmacotherapy* 2015;35:198–207.
15. Yeh CH, Gross PL, Weitz JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood* 2014;124:1020–8.
16. Meissner MH, Manzo RA, Bergelin RO, et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg* 1993;18:596–605; discussion 6–8.
17. Popuri RK, Vedantham S. The role of thrombolysis in the clinical management of deep vein thrombosis. *Arterioscler Thromb Vasc Biol* 2011;31:479–84.
18. Okrent D, Messersmith R, Buckman J. Transcatheter fibrinolytic therapy and angioplasty for left iliofemoral venous thrombosis. *J Vasc Interv Radiol* 1991;2:195–7; discussion 8–200.
19. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochr Database Syst Rev* 2014;1:CD002783.
20. Baekgaard N, Klitfod L, Broholm R. Safety and efficacy of catheter-directed thrombolysis. *Phlebology/Venous Forum R Soc Med* 2012;27(Suppl. 1):149–54.
21. Baekgaard N, Broholm R, Just S, et al. Long-term results using catheter-directed thrombolysis in 103 lower limbs with acute iliofemoral venous thrombosis. *Eur J Vasc Endovasc Surg* 2010;39:112–7.
22. Sillesen H, Just S, Jorgensen M, et al. Catheter directed thrombolysis for treatment of ilio-femoral deep venous thrombosis is durable, preserves venous valve function and may prevent chronic venous insufficiency. *Eur J Vasc Endovasc Surg* 2005;30:556–62.
23. Comerota AJ, Aldridge SC, Cohen G, et al. A strategy of aggressive regional therapy for acute iliofemoral venous thrombosis with contemporary venous thrombectomy or catheter-directed thrombolysis. *J Vasc Surg* 1994;20:244–54.

24. Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:257S–98S.
25. Karthikesalingam A, Young EL, Hinchliffe RJ, et al. A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2011;41:554–65.
26. Francis CW, Blinc A, Lee S, et al. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. *Ultrasound Med Biol* 1995;21:419–24.
27. Engelberger RP, Spirk D, Willenberg T, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis. *Circ Cardiovasc Interv* 2015;8:e002027.
28. Baekgaard N, Broholm R, Just S. Indications for stenting during thrombolysis. *Phlebology/Venous Forum R Soc Med* 2013;28(Suppl. 1):112–6.
29. Baekgaard N, Just S, Foegh P. Which criteria demand additive stenting during catheter-directed thrombolysis? *Phlebology/Venous Forum R Soc Med* 2014;29:112–8.
30. O'Sullivan GJ, Sheehan J, Lohan D, et al. Iliofemoral venous stenting extending into the femoral region: initial clinical experience with the purpose-designed Zilver Vena stent. *J Cardiovasc Surg* 2013;54:255–61.
31. de Wolf MA, de Graaf R, Kurstjens RL, et al. Short-term clinical experience with a dedicated venous nitinol stent: initial results with the sinus-venous stent. *Eur J Vasc Endovasc Surg* 2015;50:518–26.
32. Sharifi M, Bay C, Mehdipour M, et al. Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial: midterm results. *J Endovasc Ther* 2012;19:273–80.
33. Enden T, Sandset PM, Klow NE. Evidence-based practice for patients with severe venous thrombosis. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, ny Raekke* 2012;132:1215–6.
34. Vedantham S, Goldhaber SZ, Kahn SR, et al. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with proximal deep vein thrombosis. *Am Heart J* 2013;165:523–30 e3.
35. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet* 2012;379:31–8.
36. Arnoldussen CW, Wittens CH. An imaging approach to deep vein thrombosis and the lower extremity thrombosis classification. *Phlebology/Venous Forum R Soc Med* 2012;27(Suppl. 1):143–8.
37. Strijkers RH, Arnoldussen CW, Wittens CH. Validation of the LET classification. *Phlebology/Venous Forum R Soc Med* 2015;30:14–9.
38. Jayaraj A, Meissner MH. A comparison of Villalta-Prandoni scale and venous clinical severity score in the assessment of post thrombotic syndrome. *Ann Vasc Surg* 2014;28:313–7.
39. Saunders JH, Arya PH, Abisi S, et al. Catheter-directed thrombolysis for iliofemoral deep vein thrombosis. *Br J Surg* 2013;100:1025–9.
40. Andia ME, Saha P, Jenkins J, et al. Fibrin-targeted magnetic resonance imaging allows in vivo quantification of thrombus fibrin content and identifies thrombi amenable for thrombolysis. *Arterioscler Thromb Vasc Biol* 2014;34:1193–8.
41. Saha P, Andia ME, Modarai B, et al. Magnetic resonance T1 relaxation time of venous thrombus is determined by iron processing and predicts susceptibility to lysis. *Circulation* 2013;128:729–36.
42. Phinikaridou A, Andia ME, Saha P, et al. In vivo magnetization transfer and diffusion-weighted magnetic resonance imaging detects thrombus composition in a mouse model of deep vein thrombosis. *Circ Cardiovasc Imaging* 2013;6:433–40.
43. Kahn SR. How I treat postthrombotic syndrome. *Blood* 2009;114:4624–31.
44. Ziegler S, Schillinger M, Maca TH, et al. Post-thrombotic syndrome after primary event of deep venous thrombosis 10 to 20 years ago. *Thromb Res* 2001;101:23–33.
45. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: a public health concern. *Am J Prev Med* 2010;38:S495–501.
46. Phillips T, Stanton B, Provan A, et al. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. *J Am Acad Dermatol* 1994;31:49–53.
47. O'Donnell TF Jr, Browse NL, Burnand KG, et al. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res* 1977;22:483–8.
48. Couzan S, Leizorovicz A, Laporte S, et al. A randomized double-blind trial of upward progressive versus degressive compressive stockings in patients with moderate to severe chronic venous insufficiency. *J Vasc Surg* 2012;56:1344–50 e1.
49. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet* 2014;383:880–8.
50. O'Meara S, Cullum N, Nelson EA, et al. Compression for venous leg ulcers. *Cochr Database Syst Rev* 2012;11:CD000265.

51. Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. *BMJ* 2007;335:83.
52. O'Meara S, Martyn-St James M. Foam dressings for venous leg ulcers. *Cochr Database Syst Rev* 2013;5: CD009907.
53. O'Meara S, Martyn-St James M. Alginate dressings for venous leg ulcers. *Cochr Database Syst Rev* 2013;4: CD010182.
54. O'Meara S, Al-Kurdi D, Ologun Y, et al. Antibiotics and antiseptics for venous leg ulcers. *Cochr Database Syst Rev* 2010;CD003557.
55. Stacey MC, Jopp-Mckay AG, Rashid P, et al. The influence of dressings on venous ulcer healing—a randomised trial. *Eur J Vasc Endovasc Surg* 1997;13:174–9.
56. Martinez MJ, Bonfill X, Moreno RM, et al. Phlebotonics for venous insufficiency. *Cochr Database Syst Rev* 2005; CD003229.
57. Danielsson G, Jungbeck C, Peterson K, et al. A randomised controlled trial of micronised purified flavonoid fraction vs placebo in patients with chronic venous disease. *Eur J Vasc Endovasc Surg* 2002;23: 73–6.
58. Rabe E, Jaeger KA, Bulitta M, et al. Calcium dobesilate in patients suffering from chronic venous insufficiency: a double-blind, placebo-controlled, clinical trial. *Phlebology/ Venous Forum R Soc Med* 2011;26:162–8.
59. Rabe E, Stucker M, Esperester A, et al. Efficacy and tolerability of a red-vine-leaf extract in patients suffering from chronic venous insufficiency—results of a double-blind placebo-controlled study. *Eur J Vasc Endovasc Surg* 2011;41:540–7.
60. Wittens C, Davies AH, Baekgaard N, et al. Editor's Choice - management of chronic venous disease: clinical practice guidelines of the european society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2015;49: 678–737.
61. Alhadad A, Kolbel T, Herbst A, et al. Iliocaval vein stenting: long term survey of postthrombotic symptoms and working capacity. *J Thromb Thrombolysis* 2011;31: 211–6.
62. de Graaf R, Arnoldussen C, Wittens CH. Stenting for chronic venous obstructions a new era. *Phlebology/ Venous Forum R Soc Med* 2013;28(Suppl. 1):117–22.
63. Hartung O, Loundou AD, Barthelemy P, et al. Endovascular management of chronic disabling ilio-caval obstructive lesions: long-term results. *Eur J Vasc Endovasc Surg* 2009;38:118–24.
64. Kurklinsky AK, Bjarnason H, Friese JL, et al. Outcomes of venoplasty with stent placement for chronic thrombosis of the iliac and femoral veins: single-center experience. *J Vasc Interv Radiol* 2012;23:1009–15.
65. Lou WS, Gu JP, He X, et al. Endovascular treatment for iliac vein compression syndrome: a comparison between the presence and absence of secondary thrombosis. *Korean J Radiol* 2009;10:135–43.
66. Meng QY, Li XQ, Qian AM, et al. Endovascular treatment of iliac vein compression syndrome. *Chin Med J* 2011;124:3281–4.
67. Nayak L, Hildebolt CF, Vedantham S. Postthrombotic syndrome: feasibility of a strategy of imaging-guided endovascular intervention. *J Vasc Interv Radiol* 2012; 23:1165–73.
68. Nazarian GK, Austin WR, Wegryn SA, et al. Venous recanalization by metallic stents after failure of balloon angioplasty or surgery: four-year experience. *Cardiovasc Intervent Radiol* 1996;19:227–33.
69. Neglen P, Hollis KC, Olivier J, et al. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. *J Vasc Surg* 2007;46:979–90.
70. O'Sullivan GJ, Semba CP, Bittner CA, et al. Endovascular management of iliac vein compression (May-Thurner) syndrome. *J Vasc Interv Radiol* 2000;11:823–36.
71. Oguzkurt L, Ozkan U, Ulusan S, et al. Compression of the left common iliac vein in asymptomatic subjects and patients with left iliofemoral deep vein thrombosis. *J Vasc Interv Radiol* 2008;19:366–70; quiz 71.
72. Oguzkurt L, Tercan F, Ozkan U, et al. Iliac vein compression syndrome: outcome of endovascular treatment with long-term follow-up. *Eur J Radiol* 2008;68:487–92.
73. Raju S, Hollis K, Neglen P. Obstructive lesions of the inferior vena cava: clinical features and endovenous treatment. *J Vasc Surg* 2006;44:820–7.
74. Rosales A, Sandbaek G, Jorgensen JJ. Stenting for chronic post-thrombotic vena cava and iliofemoral venous occlusions: mid-term patency and clinical outcome. *Eur J Vasc Endovasc Surg* 2010;40:234–40.
75. Titus JM, Moise MA, Bena J, et al. Iliofemoral stenting for venous occlusive disease. *J Vasc Surg* 2011;53: 706–12.
76. Ye K, Lu X, Li W, et al. Long-term outcomes of stent placement for symptomatic nonthrombotic iliac vein compression lesions in chronic venous disease. *J Vasc Interv Radiol* 2012;23:497–502.
77. Gloviczki P, Kalra M, Duncan AA, et al. Open and hybrid deep vein reconstructions: to do or not to do? *Phlebology/Venous Forum R Soc Med* 2012;27(Suppl. 1): 103–6.
78. Garg N, Gloviczki P, Karimi KM, et al. Factors affecting outcome of open and hybrid reconstructions for

nonmalignant obstruction of iliofemoral veins and inferior vena cava. *J Vasc Surg* 2011;53:383–93.
79. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. *J Vasc Surg* 1994;19:391–403.
80. Pavcnik D, Uchida B, Kaufman J, et al. Percutaneous management of chronic deep venous reflux: review of experimental work and early clinical experience with bioprosthetic valve. *Vasc Med* 2008;13:75–84.
81. Rosales A. Valve reconstructions. *Phlebology/Venous Forum R Soc Med* 2015;30:50–8.
82. Bazigou E, Lyons OT, Smith A, et al. Genes regulating lymphangiogenesis control venous valve formation and maintenance in mice. *J Clin Invest* 2011;121:2984–92.