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Surgical and non-surgical approaches in the management of lower limb post-thrombotic syndrome

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ABSTRACT

Introduction: Post-thrombotic syndrome (PTS) is a common lifelong condition affecting up to 50% of those suffering from deep vein thrombosis (DVT). PTS compromises function and quality of life with subsequent venous ulceration in up to 29% of those affected.

Areas covered: A literature review of surgical and non-surgical approaches in the prevention and treatment of PTS was undertaken. Notable areas include the use of percutaneous endovenous interventions and the use of graduated compression stockings (GCS) after acute proximal DVT.

Expert opinion: In patients with acute iliofemoral DVT, we think it is important to have a frank conversation with the patient about catheter-directed thrombolysis, aiming to reduce the severity of PTS experienced. We advocate ultrasound-accelerated thrombolysis with adjunctive procedures, such as deep venous stenting for proximal iliofemoral DVT. For patients with isolated femoral DVT, we believe that anticoagulation and GCS should be recommended. In patients with established PTS, we recommend GCS for symptomatic relief. We recommend that patients engage in regular exercise

where possible with the prospect of gaining symptomatic relief. For those with severe PTS that has a significant effect on quality of life, we discuss the patient's case at a multi-disciplinary team meeting to plan for endovenous intervention.

Keywords: Catheter-directed thrombolysis, Deep venous thrombosis, Deep venous stent, Endovenous ultrasound, Endovenous thrombectomy, Lower limb oedema, Iliac vein stent, Post-thrombotic syndrome, Ulceration

Article highlights

- There is uncertainty around the use of catheter-directed thrombolysis techniques after acute iliofemoral DVT in the prevention of PTS. However, the current evidence seems to suggest that thrombolysis and adjunctive endovenous procedures can reduce the severity of PTS.
- Anticoagulation is of critical importance in the management of patients with proximal DVT and seems to play a role in the prevention of PTS.
- Recent evidence has cast doubt on the value of graduated compression therapy in the prevention of PTS and its routine use is no longer recommended.
- Treatment options in PTS are relatively limited and the key appears to be in its prevention.
- However, deep venous stenting appears to be a potential therapy with further RCT evidence sought.

1. Introduction

Post-thrombotic syndrome (PTS) is a common lifelong condition complicating up to 50% of those suffering from deep vein thrombosis (DVT)(1). Professor John Homans first detailed the aetiology of PTS in 1916, describing the incompetence of the deep venous system following thrombosis resulting in the signs and symptoms of chronic venous disease(2). PTS manifests as a spectrum of chronic venous disease, most commonly pain and swelling, characterised by tenderness, redness, visible collateral veins, venous claudication and ultimately can progress to venous ulceration(3).

DVT has an annual incidence of 148 per 100,000 person years in Europe(4), with a substantial proportion of those experiencing DVT going on to develop PTS. However, a precise incidence of PTS is difficult to ascertain due to the differing definitions and diagnostic criteria within the literature(5,6).

The Villalta PTS scale has previously been recommended as the most suitable scale for diagnosing and staging PTS(6). However, most notably, it lacks the inclusion of venous claudication within its

classification prompting further discussion on how PTS should be defined and diagnosed.

Pragmatically, PTS can be defined as the presence of signs and/or symptoms of chronic venous disease secondary to DVT(7).

Our understanding of the pathophysiology of PTS remains fundamentally unchanged since it was first described. It is thought to be due to sustained venous hypertension from a combination of venous outflow obstruction and valvular incompetence. However, recent research has demonstrated complex cell signalling pathways occur in response to in situ thrombus with recruitment of inflammatory cells and mediators, and activation of matrix metalloproteinases resulting in scarring and thickening of the vein wall(5). Furthermore, intuitively, the more proximal the occlusion the higher the likelihood of developing PTS(8) as there are fewer alternative drainage routes around proximal vessels.

Those with PTS suffer from lifelong symptoms that compromise function and quality of life, with a disability burden easily comparable to chronic obstructive pulmonary disease(9). Disease-specific quality of life measures reveal a lower quality of life in those with PTS in comparison to those with non-thrombotic chronic venous disease(10). Furthermore, population cohorts suggest that the rate of venous ulceration is high with up to 29% of those with PTS demonstrating active or healed venous ulceration(10).

Published clinical practice guidelines in the prevention and management of PTS are generally inconsistent and often fail to offer a range of interventional therapies. An important distinction to recognise is the guidelines aimed at preventing PTS and those outlining how best to treat established PTS. An example of this inconsistency is the previous National Institute for Health and Care Excellence (NICE) (United Kingdom) and current American College of Clinical Pharmacy (ACCP) recommendations for preventing PTS after acute DVT include wearing graduated compression stocking (GCS) providing an ankle pressure >23mmHg, from the week after diagnosis for up to 2 years(11,12). NICE have more recently changed their treatment recommendation to not wearing GCS post DVT(13) which is also mirrored by the American College of Chest Physicians guideline Antithrombotic therapy for VTE disease(14).

Given the inconsistencies across clinical practice guidelines, in addition to the conflicting strategies on how best to diagnose and classify PTS, we offer an expert review on the interpretation of evidence on the surgical and non-surgical approaches to PTS. This review will detail the surgical, medical and conservative considerations in both the prevention and treatment of PTS.

2. Surgical approaches to PTS

2.1 Preventing PTS (see Table 1)

Surgical approaches to preventing PTS include endovenous and open surgical interventions.

Endovenous procedures are now far more prevalent in comparison to, the almost historical, open surgical thrombectomy(15). Endovenous interventions include thrombectomy, thromb-aspiration, catheter-directed thrombolysis (CDT), ultrasound-assisted / accelerated catheter-directed thrombolysis (UACDT), pharmaco-mechanical thrombolysis (PMT) balloon venoplasty and venous stenting.

Contemporary techniques in the surgical approach to preventing PTS chiefly involve catheter-directed thrombus reduction techniques and thrombolysis, with adjunctive endovenous interventions such as balloon venoplasty or venous stenting to establish and maintain venous patency.

CDT is a procedure undertaken alongside fluoroscopic guidance in which an ipsilateral caudad venous puncture, such as the popliteal vein is undertaken and the deep venous system cannulated(16). Ipsilateral puncture is preferred as the valves in the venous system can make contralateral access difficult. Baseline venography is performed. A wire is then passed crossing the occlusion. A multi side hole infusing catheter, such as a Cragg-McNamara, is then passed into the thrombus and thrombolysis commenced. A follow-up angiogram is performed after 12–24 hours (as per individual centre guidelines). UACDT provides additional high-frequency low-intensity ultrasound which is believed to shorten the overall time to clot resolution and hence a reduction in thrombolysis administration and possibly haemorrhagic complications(17).

Adjunctive procedures are performed in addition to CDT to improve venous patency such as balloon angioplasty with venous stenting. More recently, this is followed by subsequent placement of a designated deep venous stent.

There have been three key randomised-controlled trials investigating interventions to prevent patients developing PTS after suffering from acute DVT. The post-thrombotic syndrome after Catheter-directed thrombolysis for deep Vein Thrombosis (CaVenT) study, published in 2012, randomised 176 patients with proximal iliofemoral DVT to either standard therapy with GCS and anticoagulation or to standard treatment plus percutaneous CDT(18). The co-primary outcome was venous patency rates at 6 months and incidence of PTS as assessed by the Villalta score at 2 years. The cut-off value for confirmation of PTS was a Villalta score ≥ 5 or presence of venous ulceration aligning with the International Society of Thrombosis and Haemostasis (ISTH) consensus scoring method(6). An important consideration was that as few as 42% of the intervention arm, and 34% of the control arm suffered from iliofemoral DVT – hence the majority of patients suffered from purely femoral DVT. Adjunctive endovascular treatment was undertaken in as few as 43.3% of the intervention arm, with just 25.6% undergoing deep venous stenting.

There was a significantly lower rate of developing PTS in the CDT arm in comparison to the standard therapy alone arm at 24 months (41.1% vs. 55.6%, $p=0.047$). This corresponds to an absolute risk reduction of 14.4% and a number-needed to treat of 7 participants. There were 20 bleeding complications in the intervention arm equating to 22.2% of participants undergoing CDT, with three of these classified as major bleeding events. The corresponding number needed to harm for major bleeding is approximately 30 participants. These major bleeding events included an abdominal wall haematoma, one compartment syndrome of the lower leg, and one access site haematoma. There were no bleeding events in the standard therapy alone arm. There was also a significantly higher rate of iliofemoral patency at 6 months in the CDT arm (65.9% vs. 47.4%, $p=0.012$).

Interestingly, this reduction in PTS in the intervention arm was maintained at 5-years (43% vs. 71% $p<0.0001$) with a subsequent lowering of the number needed to treat to just 4 participants. Importantly, this reduction in PTS was chiefly seen in the moderate category (Villalta score 10-14) in which the participants will have troublesome symptomology, with as few as 5.4% of the CDT arm affected in comparison to 20.6% of the standard therapy alone arm. However, the quality of life data was less promising with no difference demonstrated when comparing the CDT arm to the standard therapy alone arm using the generic EQ-5D or disease-specific VEINES-QOL/Sym (50.5 vs. 49.6, $p=0.37$) scoring measures(19). Further reflecting this, at 5-years there was no difference in the freedom from wearing compression stockings across the two groups (56% vs 58%). Complicating this further, a higher proportion of participants in the CDT arm were compliant with anticoagulation at follow-up in comparison to the control arm, although this was not statistically significant (61.1% vs. 52.6%).

The Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial, published 2017, also set out to investigate the use of thrombus removal and thrombolysis in addition to standard care for above-the-knee proximal deep vein thrombosis in the prevention of PTS(20). PMT was defined as “catheter-mediated, or device-mediated, intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting”(20). ATTRACT was a much larger RCT, the largest to date, and randomised a total of 692 patients. A staggering 28,507 patients met the inclusion criteria with subsequent exclusion of 26,715 participants – 31% of these participants were excluded for age and 24% for active cancer. Notably, the primary outcome was again dichotomous for presence or absence of PTS defined by Villalta score ≥ 5 or presence of ulceration between 6-24 months. Again, as few as 58% of the PMT arm and 55% of the standard therapy arm had DVT of the common femoral and or iliac vein. Nearly half of the participants ($n=300$) suffered from isolated femoropopliteal DVT. Adjunctive

endovascular interventions were undertaken in 88% of the intervention arm, with 28% of participants undergoing deep venous stenting. This is appreciably higher than the CaVenT study, however, the deep venous stenting was still undertaken in less than a third of procedures. There was no significant difference in the rate of PTS in the PMT arm in comparison to standard therapy alone at 6–24 months (46.7% vs. 48.2%, risk ratio 0.96, $p=0.56$). There was also no significant difference in disease-specific or generic quality of life measures between the two arms at 24 months. Major bleeding events were reported in 6 patients in the PMT arm consisting of two retroperitoneal bleeding events, two gastrointestinal bleeding events, and two access site bleeding events, in comparison to just a single gastrointestinal bleeding event in the control group (1.7% vs. 0.3%, $p=0.049$).

A secondary outcome, the rate of moderate-severe PTS (defined as Villalta score ≥ 10), was found to be significantly lower in the PMT arm in comparison to standard therapy alone (18% vs. 24%, risk ratio 0.73, $p=0.04$). Use of compression stockings at 24 months was similar across both groups, hence there was no freedom from stockings gained by PMT. Overall, it was concluded that additional PMT did not reduce the rate of PTS but did result in a higher risk of major bleeding. Subsequent analysis on 391 patients with acute iliofemoral DVT comparing PMT in addition to standard therapy versus standard therapy alone demonstrated no difference in the rate of PTS at 24 months (49% vs. 51%, RR 0.95, $p=0.59$)⁽²¹⁾. Again, it was reported that PMT conferred a reduction in moderate-severe PTS from 14% to 6.6% with a risk ratio of 0.46 ($p=0.013$). Furthermore, in this subset of patients, it was reported that PMT conferred an improvement in disease-specific quality of life, quantified by the VEINES measure (21.45 vs. 16.24, $p=0.043$), which was not seen in the overall analysis including femoropopliteal DVTs. No difference was identified using the generic quality of life measurement SF-36.

Most recently, published 2020, the ultrasound-accelerated CAtheter-directed thrombolysis Versus Anticoagulation for the prevention of post-thrombotic syndrome (CAVA) trial set out to test if patients with true acute iliofemoral would benefit from thrombolysis as suggested by the CaVenT and ATTRACT trials. Initially, 184 patient with acute iliofemoral DVT were randomised to either UACDT in addition to standard therapy or standard therapy alone⁽²²⁾. This RCT was similar in size to the CaVenT study, containing far fewer participants than the ATTRACT trial.

Similar to, but distinct from the preceding RCTs, the primary outcome was the rate of PTS defined by a Villalta score ≥ 5 on two consecutive occasions at least 3 months apart or the presence of venous ulceration at least 6 months after DVT. Notably, when compared with the ISTH consensus scoring method, this resulted in a more conservative PTS diagnosis. All of the included participants suffered from thrombosis of the common femoral vein or more cephalad vein segments, i.e. proximal

iliofemoral DVT. Deep venous stents were placed in 35% of the intervention arm, with a total of 55% of the intervention arm undergoing adjunctive percutaneous transluminal angioplasty, thromb-aspiration, or stenting.

There was no significant difference in the rate of PTS at 12 months in the additional UACDT arm in comparison to the standard treatment arm (28.6% vs. 34.7%, OR 0.75, $p=0.42$). The severity of PTS experienced did not differ between the two arms. Quality of life as ascertained by the generic SF36 and EQ5D measures, and the disease-specific VEINES measure revealed no significant difference in change from baseline or overall quality of life at 12 months. There was a higher rate of major bleeding events, none of which were intracerebral or spinal in nature (5% vs. 0%). Notably, there was a high-rate of in-stent thrombosis, accounting for 70% (12 / 17) of thrombotic events in the intervention arm despite treatment with anticoagulation. The rate of thrombotic events in the intervention arm was considerably higher than that in the control arm (18% vs 6%).

However, subsequent analysis on those who achieved successful recanalization has suggested that there was a significant reduction in severe PTS(23). Within the UACDT, 41 (53.2%) were considered to be a success, i.e. achieving recanalization of the vein. There was a significant improvement in disease specific (VCSS: 3.50 vs. 4.82, $p=0.02$) and generic quality of life measures (EQ5D 40.2 vs. 23.4, $p=0.007$).

An important criticism of CAVA could be the possibility of it being under-powered. CAVA was powered for an effect size of 17% with a risk of PTS in the UACDT arm of 8%, requiring a sample size of 170 participants. This risk of PTS is folds lower than ever reported in any previous RCT and they failed to attain the sample size, ending with 152 participants – the power achieved here could be called into question.

Overall, RCTs investigating the use of additional thrombus removal and thrombolysis in the prevention of PTS have been plagued by low recruitment numbers. This has resulted in multi-centre trials not exclusively recruiting from specialist venous centres and subsequent relatively poor procedural results with low rates of recanalization.

Surgical thrombectomy has fallen out of practice with the advancement in catheter-directed therapies, with numbers at rock-bottom in the UK since the early 2000s with as few as 26-45 procedures performed annually(15); it is likely that even these few open thrombectomy procedures are not exclusively related to primary DVT and include cases for restoring flow within venous bypass grafts. Although no longer routinely practiced, some centres in Europe still undertake surgical thrombectomy, hence it will be briefly mentioned here. The usual technique is to perform a surgical cut down to the common femoral vein as a minimum, with addition of access to the crural veins such as the posterior tibial vein if required(24). If there is involvement of the inferior vena cava, a

proximal filter is usually placed to avoid pulmonary embolisation during thrombectomy. Intra-operative venography is used to visualise the obstruction and aid passage of the Fogarty catheter. The catheter is passed to a cephalad point prior to balloon inflation and thrombectomy undertaken. Intra-operative injection thrombolysis and stenting procedures can also be undertaken as an adjunct to open surgical thrombectomy. A surgical arteriovenous fistula can be created at the femoral vessels to improve venous patency.

Current guidelines from the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum offer a level II, grade C recommendation for open thrombectomy in those whom have an acute iliofemoral DVT and contraindication to thrombolysis(25). However, evidence to support open surgical thrombectomy is poor, with the limited evidence suggesting better outcomes with catheter-directed therapies(25,26).

The effect of placement of inferior vena cava filters on incidence of PTS after acute proximal DVT has been explored in a single RCT(27). Notably, incidence of PTS was a secondary outcome and PTS diagnosis was vague, being defined as worsening of at least 1 of the following “objective” features: oedema, varicose veins, trophic disorders, or ulcers. A total of 400 participants with proximal deep-vein thrombosis were randomised to inferior vena cava filter in addition to standard anticoagulant treatment or to standard anticoagulant treatment alone for at least 3 months. There was no difference in the incidence of PTS.

Despite this conflicting evidence, there are an increasing number of deep venous stents being placed with 1416 percutaneous venous angioplasty/stenting procedures in 2018-2019 reported in the National Health Service Hospital Statistics(28). This increase is occurring without level I evidence. Reflecting the conflicting results, current UK NICE guidelines, state that CDT for people with symptomatic iliofemoral DVT can be considered in those who have symptoms lasting less than 14 days, good functional status, a life expectancy of 1 year or more and a low risk of bleeding(13). The guidance around UACDT and percutaneous mechanical thrombectomy necessitate that special arrangements for clinical governance, consent and audit or research are currently required(29). These recommendations are mirrored in the early American Heart Association guidelines from 2014(11). The American Heart Association guidelines state that surgical thrombectomy can be considered in experienced centres for those who are not a candidate for CDT.

2.2 Treating PTS

Endovenous treatments for PTS include balloon venoplasty and venous stenting. Open surgical approaches to restoring venous return include venous bypass, endophlebectomy and patch venoplasty, with creation of arteriovenous fistula being a strategy for maintaining venous patency.

Prevention of venous reflux can be undertaken through segmental vein valve transfer/transposition, valvuloplasty (internal or external) and neo-valve reconstruction (e.g. Maleti). Endovenous and surgical techniques can be combined in hybrid endovenous interventions.

Currently, there is limited published RCT evidence exploring endovascular deep venous reconstruction, including venoplasty and venous stenting, in the treatment of patients with established PTS, with a single RCT exploring the use of deep venous stenting in the treatment of established iliac venous obstruction(30). Rossi et al. randomised 58 patients with chronic venous disease who had >50% iliac vein obstruction to receive iliac vein stenting in addition to best medical therapy, or best medical therapy alone. Included participants had C3–C6 chronic venous disease as per the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification system and were symptomatic (visual analogue scale (VAS) pain score >3, venous clinical severity score (VCSS) >10) after a year of treatment. The primary outcome was a change from baseline in VAS pain score, VCSS, and SF-36 quality of life measures.

At 6 months, there was a significant reduction in VCSS in the iliac stenting arm in comparison to the best medical therapy alone arm (18.5 to 11 vs. 15 to 14, $p<0.001$). Furthermore, there was a significant improvement in the VAS pain score and SF-36 quality of life measure at 6 months. Importantly, this single centre trial with a small number of participants mainly recruited non-thrombotic iliac vein lesions (73.4%), with as few as 16 (27.6%) of participants having PTS.

Hence, one cannot utilise this evidence as proof of efficacy in established PTS. Furthermore, 6 months is a short duration of follow-up for participant's undergoing deep venous stenting, as the long-term patency of venous stents is uncertain, with known high reintervention rates. Longer follow-up duration may demonstrate a loss of benefit(31). This is of particular importance because dedicated venous stents were not deployed in this RCT. Furthermore, some would argue that a patient with C3 disease alone, with a non-occlusive iliac vein lesion, would be unlikely to benefit from iliac vein stenting. Given that 46% of the stenting group comprised of participants with C3 venous disease, it could be argued that this trial recruited a population that is not representative of those with PTS seen in specialist practice, limiting its generalisability.

A retrospective single centre cohort of patients with iliofemoral venous occlusion and PTS, defined by a Villalta score ≥ 5 at least 12 months after acute DVT is the most contemporary evidence for interventional treatment of established PTS(31). Dedicated Vici Venous stents were deployed in all 88 patients. The median baseline Villalta score was 14, with 48% of patients having severe PTS (Villalta ≥ 15). There was a significant reduction in median Villalta score to 8, with a significant reduction at 6, 12 and 24 months ($p<0.001$). However, the primary patency rates of these dedicated

stents was as low as 51% at 2 years, with up to 43% of patients requiring reintervention. There is a high-risk of bias encountered when interpreting these results, particularly the relatively subjective Villalta scoring by unblinded assessors.

Furthermore, the Accelerated Thrombolysis for Post-Thrombotic Syndrome Using the Acoustic Pulse Thrombolysis Ekosonic Endovascular System, known as the ACCESS PTS Study, was a single arm non-randomised study prospective trial of UACDT and venoplasty in established PTS(32). The primary efficacy outcome was defined as a reduction of ≥ 4 points in the Villalta score at 30 days. 78 patients with a mean Villalta score of 15.5, i.e. severe PTS, with a total of 82 affected limbs, were treated. Deep venous stents were placed in 42 (87.5%) of patients. 51 of the limbs achieved a ≥ 4 point reduction in the Villalta score at 30 days. Importantly, at 1 year, this reduction was maintained and $>90\%$ of segments had patency on ultrasound. The disease-specific VEINES-QoL also significantly increased at 1 year (61.9 vs. 82.6, $p < 0.0001$). Criticisms of this study include that not all patients underwent venous stenting or achieved complete recanalization, with the analysis being uncontrolled and unblinded.

Recently, Williams et al. pooled evidence on the use of venous stenting in those with chronic occlusions /stenosis of the lower limb deep veins or inferior vena cava in the form of a meta-analysis including 3812 stented lower limbs(33). Notably, dedicated venous stents were used in as few as 740 participants. Symptomatic improvement and ulcer healing was seen in 79% and 71% of participants respectively, however there is a lack of certainty in the evidence due to a paucity of RCTs. Overall, the post-procedural complication rate was very low ($<1\%$). The primary patency rate, using dedicated venous stents, was 78.8% at 12 months suggesting a significant proportion of participants required re-intervention. However, this patency rate was much improved if the pathology was due to a compressive rather than post-thrombotic pathology, with patency rates of 96% and 73% respectively. Sub-group analysis from a different meta-analysis including 1122 participants with non-thrombotic CVD and 1118 participants with PTS demonstrated promising ulcer healing rates as high as 81.1% in non-thrombotic pathologies after deep venous stenting(34). Additionally, primary patency rates in non-thrombotic and PTS cases were similar, reported as 96% and 79% respectively. These findings are echoed elsewhere in a previous systematic review and meta-analysis on the use of deep venous stenting in established chronic venous disease secondary to either PTS or non-thrombotic iliac vein obstruction. This identified 16 relevant articles reporting on successful deep venous stenting for post-thrombotic or non-thrombotic disease in 2,586 limbs in 2,373 patients(35). There was a single RCT, discussed above, in addition to 14 before-and-after studies and a single case series. Overall, it was concluded that the quality of existing evidence to support the use of deep venous stenting to treat obstructive chronic venous disease is poor.

Open surgical approaches to treating established PTS have a poor evidence base(36), with no RCTs or high-quality evidence published in this field and low numbers of procedures performed making the future prospect of this challenging. An area where open surgical intervention is being employed less infrequently is during hybrid procedures where endophlebectomy and fistula are created to facilitate patency of deep venous stents in the context of limited inflow from more caudad venous disease in the ipsilateral lower limb.

Hybrid procedures utilising a combination of venous stenting, endophlebectomy and arteriovenous fistula creation can be used to overcome intraluminal synechiae which can push against the orifices of inflow vessels potentially decreasing stent inflow. Endophlebectomy involves removal of endoluminal synechiae and masses, also known as disobliteration. Wolf et al. reported a consecutive cohort of 70 patients with PTS and extensive post-thrombotic vein damage treated with by hybrid venous reconstruction(37). Villalta score at 1-year decreased by a median of 7 points. However, primary patency rate was as low as 51% at 12 months. Complications were frequent with as many as 29% developing a wound infection and 39% developing a lymphatic leak.

Interventions for the treatment of established PTS is an area of evolving research(38), however current emphasis is being placed in its prevention. Contemporary research is further exploring the use of catheter-directed therapies in established PTS in addition to non-thrombotic iliac vein lesions.

3. Non-surgical approaches to PTS

3.1 Preventing PTS – anticoagulation

Anticoagulation plays a key role in the management of acute DVT in order to prevent thrombus propagation and possible fatal complications such as pulmonary embolism. However, it is also thought to play an instrumental role in the prevention of PTS.

The risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis (REVERSE) study explored the impact of anticoagulation on the development of PTS(39). 349 participants with unprovoked proximal DVT, defined as proximal to and including the popliteal vein, were prospectively followed and assessed for PTS at 5–7 months. PTS was defined by a Villalta score of >4. 28% of participants with unprovoked DVT developed PTS despite anticoagulation and graduated compression stockings. The incidence of PTS was higher in patients with subtherapeutic anticoagulation in comparison to those therapeutically anticoagulated (achieving less than 20% of the time out of range) (33.5% vs. 21.6%, $p=0.01$). This finding has been echoed in another non-interventional observational prospective series by van Dongen et al. who

followed a series of 244 participants with acute DVT and reported an odds ratio of 2.71 (95% CI: 1.44–5.10) for developing PTS in those with an INR <2 for 50% of their anticoagulation duration(40). The use of low-molecular weight heparin (LMWH), which has a reliable pharmacokinetic profile and requires reduced monitoring in comparison to warfarin, has been investigated as community therapy post-acute DVT(41,42). The LITE trial, a multicentre RCT of 480 patients with acute proximal DVT, randomised participants to either the LMWH tinzaparin for 12 weeks or warfarin (with LMWH bridging)(42). At 3-months, the 8 assessments for signs and symptoms of PTS demonstrated a beneficial effect of LMWH, with an overall odds ratio of 0.77 (95% CI 0.67-0.90, $p=0.001$) of having PTS symptoms in the LMWH group. It must be noted that PTS assessment was in the form of a questionnaire and not experienced clinical examination. Importantly, leg ulceration occurred less frequently in the LMWH group in comparison to the warfarin group (0.5% vs. 4.1%, $p=0.02$). Interestingly, this effect was seen despite a lower compliance with graduated compression stockings and a significantly earlier cessation in anticoagulation in the LMWH group, with individuals in the warfarin group more readily prescribed further anticoagulation past the duration of the study ($p<0.01$).

Furthermore, in a prospective randomised assessor-blinded trial, 165 participants with first-episode DVT were anticoagulated with either the LMWH enoxaparin or warfarin for at least 3 months(41). PTS was defined and graded by the Villalta score. Thrombus regression was graded on venography and scored by the Marder score. The prevention of PTS, i.e. failure to meet PTS criteria, was higher in the LMWH group but this failed to meet significance (39.3% vs. 29.5%). Furthermore, a lower proportion of participants in the LMWH group went on to develop severe PTS (19.6% vs. 29.5%). Interestingly, there was a significantly lower incidence of DVT recurrence in the LMWH group in comparison to the warfarin group (19.3% vs. 36.6%, $p=0.02$). The Marder score was significantly improved in both groups.

The trend towards reduced incidence and severity of PTS with LMWH could be due to a more stable anticoagulation profile. Summation of the evidence suggests that adequate anticoagulation, with a reduction in the time out of therapeutic range, is important in the prevention of PTS. Debate regarding the exact agent for anticoagulation is ongoing.

3.2 Preventing PTS – graduated compression stockings (see Table 1)

Graduated compression stockings are an elastic stocking that apply the greatest amount of pressure at the ankle which reduces gradually up the limb. This provides graduated pressure encouraging blood and lymph to flow from distal to proximal. It is important to note that graduated compression stockings for this use differ from those used for the prevention of thrombo-embolism. Stockings

used for the prevention of thrombo-embolism are designed to apply graduated pressure in the context of an immobile rather than in an ambulant individual. Compression stockings can be classified by size and grade, i.e. the pressure the stocking applies to the limb. Within the UK, grade II compression stockings (18-24mmHg, or medium compression) are commonly prescribed for chronic venous disease and for the prevention of PTS(43).

Prandoni et al. undertook an RCT with blinded-assessment, published 2004, consisting of 180 participants with proximal DVT allocated to anticoagulation with the addition of below-knee compression elastic stockings for 2 years in comparison to anticoagulation alone(3). These compression stockings provided 30 to 40 mm Hg at the ankle, equating to a UK class II (18-24mmHg, or medium compression) stocking. Importantly, 45.5% of participants had isolated popliteal DVT. PTS was defined as a Villalta score >4. The risk of developing PTS was significantly lower in the compression stockings group (24.5% vs. 49.1%) with a hazard ratio of 0.47 ($p=0.004$), with a corresponding number-needed to treat of 4.3 patients. Rates of recurrent thrombotic events did not differ between groups, casting doubt on previous hypothesis that the effect of compression was to reduce these recurrent DVTs. These trial results reinforced earlier findings from Brandjes et al. published 1997(44). These results were reflected in clinical practice guidelines internationally. However, recent evidence has prompted a change in direction. In the UK, NICE states in the 2020 clinical practice guidelines "Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or VTE recurrence after a DVT."(13). This change stems from the publication of the SOX trial in 2014(1). The compression stockings to prevent post-thrombotic syndrome trial, named SOX, was a placebo-controlled double-blind RCT which assigned 803 participants to receive graduated compression stockings (30–40 mmHg) or placebo stockings which were identical in appearance (<5 mmHg)(1). PTS was defined by the Ginsberg criteria of ipsilateral pain and swelling of at least 1 month's duration for the primary outcome. This was powered for a 10% difference in risk of PTS with an expected event rate of 30% in the control arm. The Villalta score was used as a secondary outcome. A lower proportion of patients in the SOX trial had isolated popliteal vein DVT in comparison to the patient cohort in Prandoni et al. (30.3% vs. 45.5%), hence the SOX trial cohort was felt to be at higher risk of development of PTS.

The cumulative incidence of PTS at 750 days of follow-up, as defined by the Ginsberg criteria, did not differ between groups with 14.2% in the intervention arm vs. 12.7% in the placebo arm (HR 1.13, 0.73–1.76). Furthermore, the cumulative incidence of PTS, as defined by Villalta, was 52.6% in the intervention arm in comparison to 52.3% in placebo arm. These figures resemble the incidence of PTS as seen in other RCTs utilising the Villalta score. Importantly, there were no significant differences in disease-specific or generic quality of life measures. These results are in contrast to the Prandoni trial.

A notable difference was the adherence to graduated compressions stockings, with 86.6% of the intervention arm in Prandoni compliant in comparison to just 55.6% in the SOX trial. This lack of compliance in the SOX trial was further reflected by as many as 59% of patients did not know whether they were receiving active or placebo stockings suggesting a large proportion had not been wearing the stockings. These criticisms have cast doubt on the conclusion that graduated compression stockings fail to prevent PTS.

The American Heart Association, alike NICE, also amended their guidelines to reflect the results of the SOX trial, suggesting that “The effectiveness of ECS [elastic compression stockings] for PTS prevention is uncertain, but application of ECS is reasonable to reduce symptomatic swelling in patients with a diagnosis of proximal DVT”(11).

3.3 Treating PTS – compression stockings

Despite the widespread use and recommendation for use of grade II (18-24mmHg, or medium compression) elastic compression stockings, there is little evidence to support this practice(11,45). A recent Cochrane systematic review identified just two studies investigating the use of graduated compression stockings in the management of established PTS(45).

Lattimer et al. investigated the haemodynamic effects of differing classes of compression stockings on 34 participants with PTS, diagnosed with the Villalta scale(46). The venous filling index and venous volume improved significantly with all grades of graduated compression stocking in comparison to no stockings.

Ginsberg et al. undertook a double-blind RCT, assigned 35 participants with PTS to graduated compression stocking (30 to 40 mmHg) or a placebo stocking. PTS was defined by the Ginsberg criteria. The primary outcome was treatment failure, this had a complex definition but generally consisted of: continued failure to provide symptomatic benefit, worsening of symptoms, or ulceration. At ~2 years follow-up, there were 8 treated failures in the intervention arm in comparison to 10 treatment failures in the control arm (61.1% vs. 58.8%, $p>0.99$). This RCT can be criticised for being under-powered and having an unclear composite outcome, however, there is little evidence to support the use of graduated compression in the treatment of PTS. However, as compression represents a relatively low-risk and low-cost intervention, a trial to improve symptoms is often recommended. This is mirrored in both the NICE and American Heart Association guidelines(11,13).

3.4 Treating PTS – compression devices

Newer technologies have been developed in order to aid venous return and ease symptoms of PTS. Venous assist devices and pneumatic compression are therapies that lack a significant body of evidence. Intermittent pneumatic compression devices consist of a pneumatic pump and an inflatable sleeve worn on the limb. The segments of the inflatable sleeve are inflated to apply a desired pressure to the limb compartments and the deep venous system within. Ginsberg et al. undertook a small randomised crossover trial, published in 1996, that assigned 15 participants to either a therapeutic intervention pressure (50 mm Hg) or a placebo pressure (15 mm Hg) for 4 weeks, with subsequent crossover(47). It was reported that symptom scores were significantly better in the intervention arm in comparison to the control arm (16.5 vs. 14.4, $p=0.007$). This symptom score pre-dates validation of the Villalta scale.

More recently, portable compression assist devices have been developed and reached the market. Venowave™ is a battery-powered portable device that is strapped to the wearer's calf. It contains a motor which generates a wave-like displacement through a plastic interface into the calf and aims at improving venous return(48). In an 8-week double-blind randomised cross-over trial of 32 participants with severe PTS, the Venowave™ was compared with a placebo-device. The mean Villalta score was significantly lower in the intervention arm in comparison to the control arm (12.2 vs. 15.0, $p=0.004$). Furthermore, the mean disease-specific quality of life measure (VEINES-QoL) was significantly higher in the intervention arm in comparison to the control arm ($p=0.004$). The duration of therapy was brief and the number of participants small, hence there is little certainty that venous assist devices should feature in the management of PTS.

Overall, the body of evidence to support compression devices is small. Current guidelines deem compression devices to be a low-risk intervention and hence the American Heart Association recommend that they are trailed in moderate to severe PTS alongside compression stockings.

3.5 Treating PTS – exercise

Studies of supervised exercise testing in participants with PTS revealed that exercise did not exacerbate symptoms in the acute setting and appeared to reduce calf stiffness(49). Kahn et al. conducted an RCT allocating 43 participants with PTS to either a six-month supervised exercise programme or to a control arm consisting of regular monthly telephone appointments(50). Participants underwent a total of 15 exercise sessions across the 6 months. The Villalta score was used to diagnose and grade the severity of PTS. At 6 months, there was a greater improvement in the disease-specific quality of life measure (VEINES-QoL) for the exercise arm in comparison to the control arm (6.0 vs. 1.4, $p=0.027$). Furthermore, a greater improvement in mean Villalta score was seen in the exercise arm, although this did not reach statistical significance (-3.6 vs. -1.6 , $p=0.14$). There is limited RCT evidence to support the use of exercise in the management of PTS which is

reflected in the lack of mention in current clinical practice guidelines. However, exercise is a low-risk intervention that may be considered as an option for individuals with PTS.

Novel approaches to treating PTS

Most novel, is the use of neuromuscular electrical stimulation which is believed to increase arterial in-flow and venous return(51). The device comes in the form of an endplate that the user applies the base of their feet on which uses electrical stimulation to activate the muscles of the lower limb and calf pump. There is currently no high-quality evidence to support their use in PTS. However, in a recent RCT in patients with chronic venous disease the REVITIVE device was shown to improve disease-specific quality of life in comparison to a placebo device. Other technologies such as the wearable transcutaneous geko™ device provides neuromuscular stimulation along the common peroneal nerve activating the calf pump(52). This device can be strapped to the limb not requiring a separate endplate device. Again, this is currently no high-quality evidence to support their use in PTS but do represent potential areas of future research.

4. Conclusion

Post thrombotic syndrome occurs frequently after acute iliofemoral DVT. There is uncertainty around the use of catheter-directed thrombolysis techniques after acute iliofemoral DVT in the prevention of PTS. However, the current evidence seems to suggest that thrombolysis and adjunctive endovenous procedures can reduce the severity of PTS. Anticoagulation is of critical importance in the management of patients with proximal DVT and seems to play a role in the prevention of PTS. Recent evidence has cast doubt on the value of graduated compression therapy in the prevention of PTS and its routine use is no longer recommended.

Treatment options in PTS are relatively limited and the key appears to be in its prevention. However, deep venous stenting appears to be a potential therapy with further RCT evidence sought.

Compression stockings are often trialled for symptomatic relief however there is little evidence to support this. On-going research in relation to the use of compression devices and the use of exercise in managing PTS may be helpful in guiding future management.

Expert Opinion

From our own experience in a Vascular Unit in a central London hospital with a specialist interest in venous pathologies, we offer the following opinion in the prevention and treatment of PTS.

5.1 Preventing PTS

When treating a patient with acute iliofemoral DVT (at and/or cephalad to the common femoral vein), we think it is important to have a frank conversation with the patient about the potential to undertake catheter-directed thrombolysis, regarding the potential benefits in the reduction of

severe PTS alongside the very important risks such as major bleeding, including intracerebral. These conversations need to highlight the uncertainties generated by the recent randomised controlled trials. We also explain that the patient is likely to experience some degree of PTS, regardless of whether thrombolysis is completed. Patients should be given appropriate time to consider thrombolysis, however be advised of the fact that the time window for thrombolysis is limited and hence should not be considered beyond the 14 to 21 day timepoint. We would advocate the use of adjunctive procedures (namely venoplasty and venous stenting, guided by intravascular ultrasound), with the aim of achieving and maintaining deep venous patency. For patients with DVT caudad to the common femoral vein, we believe that anticoagulation and GCS alone should be recommended alone as we feel that current evidence does not demonstrate sufficient benefit for thrombolysis in this patient group. We appreciate that the SOX trial concluded that the use of GCS provided no additional benefit in the prevention of PTS, however, we believe there to be some considerations regarding the methodology and adherence that cast doubt on this. The role of graduated compression stockings has been called into question by the SOX trial, however, future research ensuring higher compliance is required. Anticoagulation is achieved with a LMWH initially, bridging to therapeutic anticoagulation with warfarin. Patients in whom safe and reliable therapeutic anticoagulation with warfarin is not possible, anticoagulation with LMWH should be arranged.

5.2 Treating PTS

In patients with established PTS, we recommend graduated compression stockings for the mainstay of symptomatic relief as it represents a low-risk, low-cost intervention. We also recommend that patients engage in regular exercise where possible to increase overall health with the prospect of gaining symptomatic relief.

For those with severe PTS that is inhibiting occupation or has a significant impact upon quality of life, we discuss the patient's case at a multi-disciplinary setting to plan deep venous reconstruction. This is chiefly in the form of venoplasty and deep venous stenting with a dedicated venous stent, guided by intravascular ultrasound. This practice is followed by regular audit and is aligned with national and international guidelines.

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matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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** of considerable interest

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*Highlighted are the three key RCTs investigating the use of catheter-directed thrombolysis post acute DVT in the prevention of PTS. This includes the ATTRACT trial which is the largest RCT in the field.

**Highlighted here is the largest RCT investigating the use of GCS to prevent PTS.

Table 1: Key RCTs investigating the prevention of PTS after acute DVT

Surgical interventions						
First author	Year	Trial name	Intervention arm vs. control arm	Rate of PTS intervention arm	Rate of PTS control arm	PTS definition
Haig et al.	2012	CaVenT	CDT vs BMT	(37 / 90) 41.10%*	(55 / 99) 55.60%*	Villalta score
Vedantham et al.	2017	ATTRACT	PMT vs BMT	(157 / 336) 46.7%	(171 / 355) 48.2%	Villalta score
Notten et al.	2020	CAVA	UACDT vs BMT	(22 / 77) 28.6%	(26 / 75) 34.7%	Villalta score
Non-surgical interventions						
First author	Year	Trial name	Intervention arm vs. control arm	Rate of PTS intervention arm	Rate of PTS control arm	PTS definition
Prandoni et al.	2004	Prandoni	GCS vs no GCS	(23 / 90) 25.6%*	(44 / 90) 48.9%*	Villalta score
Kahn et al.	2014	SOX	GCS vs sham GCS	(44 / 409) 14.2%	(37 / 394) 12.7%†	Ginsberg criteria

PTS: post thrombotic syndrome

BMT: best medical therapy or standard therapy including anticoagulation and graduated compression stockings

CDT: catheter-directed thrombolysis

PMT: pharmaco-mechanical thrombolysis defined as “catheter-mediated, or device-mediated, intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting”

UACDT: ultrasound-accelerated catheter-directed thrombolysis

GCS: graduated compression stockings

*=p<0.05

†: as defined by original trial results