PROGNOSTIC FACTORS ASSOCIATED WITH THE DEVELOPMENT OF POST-THROMBOTIC SYNDROME AFTER A DEEP VEIN THROMBOSIS OF THE LOWER LIMB.

by

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Abstract

Within 10 years of experiencing a deep vein thrombosis of the lower limb, up to 60% of people will be classed as suffering from post-thrombotic syndrome (PTS). The cause and risk factors for PTS are not well understood and there are no universally agreed diagnostic criteria. This thesis aimed to identify prognostic factors associated with developing PTS, the method(s) of diagnosing PTS and their relative reliability in identifying PTS.

A systematic review of systematic reviews and a systematic review of primary studies was conducted to identify prognostic factors. Methods used to diagnose PTS were noted from these reviews. Prognostic factors from best evidence and methods of diagnosing PTS noted were presented to clinical experts for prioritisation via an e-Delphi study. Consensus was defined as ≥75% agreement.

Fifty one potential prognostic factors and seventeen methods of diagnosing PTS were identified from the reviews and initial exploration of experts' views. Experts reached consensus on eight prognostic factors and one method of diagnosing PTS.

The prognostic factors identified can be considered for the development of a prognostic model, while the method of diagnosing PTS found to be most reliable from experts' opinion should be considered when developing a reference standard for PTS diagnosis.

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A journey with a PTS sufferer **(a poem by Halima**

Olakareem)

The throbbing… heaviness…skin duskiness…..

Ah…this pain that lasts all day…..

The swelling in the evening that disappears by morning

I hear Raoul might have suffered same, I hear his fate was in his prayers…

But I'm not that religious…..

Can science save me? …..

If it's too late for me, can science save my beloved? …..

My beloved who now suffers the same symptoms I suffered two years ago, when it all started with one tender swollen leg…..

Is she destined to suffer the same fate as me? .....

If so, how can I tell the cycle has begun? …..

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LIST OF ABBREVIATIONS

AMSTAR	Assessment of multiple systematic reviews instrument
CEAP	Clinical etiological anatomical and pathophysiological classification
CI	Confidence interval
DVT	Deep vein thrombosis
NHS	National Health Service
PRISMA	Preferred reporting items for systematic reviews tool
PTS	Post-thrombotic syndrome
RCT	Randomised controlled trial
UK	United Kingdom
USA	United States of America
VCSS	Venous clinical severity score
VEINES-QoL/Sym	Venous Insufficiency Epidemiological and Economic study quality of life and symptoms
VTE	Venous thromboembolism

Aims of this thesis

The aims of this thesis were:

Primary aims

1. To identify factors associated with the development of the post-thrombotic syndrome after patients have suffered an episode of deep vein thrombosis of the lower limb from existing evidence
    - This was achieved with a systematic review of systematic reviews and a systematic review of primary studies where there were gaps in the evidence identified from the systematic review of systematic reviews.

2. To identify factors associated with the development of the post-thrombotic syndrome after patients have suffered an episode of deep vein thrombosis of the lower limb as determined by expert judgements.
    - This was achieved with an e-Delphi study

3. To prioritise identified factors
    - This was achieved with the e-Delphi study mentioned above

Secondary aims

1. To identify methods used to diagnose post-thrombotic syndrome in clinical practice and from the evidence on prognostic factors identified above

- Identification of methods of PTS diagnosis was achieved using the systematic reviews and e-Delphi study conducted on prognostic factors above

2. To compare methods used to diagnose post-thrombotic syndrome in terms of proportion of PTS diagnosed.
    - Comparison of PTS diagnostic methods was achieved by conducting a new systematic review

3. To prioritise identified methods for diagnosing post-thrombotic syndrome from aims 1 and 2 above.
    - This was achieved using the e-Delphi study mentioned earlier

Chapter 1: Background

1.1 Introduction

This chapter includes; i) a description of the relationship between venous thromboembolism, deep vein thrombosis and the post-thrombotic syndrome, ii) the definition of post-thrombotic syndrome, iii) a brief history of post-thrombotic syndrome, iv) an explanation of its pathophysiology as it is currently understood, v) an outline of methods used to diagnose PTS vi) data on incidence and prevalence of post-thrombotic syndrome and vi) outlines the current position of UK guidelines on the management and prevention of post-thrombotic syndrome, vii) describes the health economic burden of PTS, viii) a definition of prognostic factors and elaboration on the rationale for this thesis.

1.2 Venous thromboembolism, deep vein thrombosis and post-thrombotic syndrome

1.2.1 Venous thromboembolism and deep vein thrombosis

The term "Venous thromboembolism" (VTE) describes the formation of a blood clot in the venous system and or dislodgement of a formed blood clot, which may be carried via the blood from its point of origin to any other part of the venous system. The formation of blood clot occurs more commonly in the lower extremities than in the upper extremities.[1,2] Reasons for this predilection are not quite clear although it is likely linked to one of Rudolph Virchow's triad[3] of factors underpinning the pathophysiology of VTE. The triad includes hypercoagulability, injury to the endothelium, and venous stasis. Venous stasis is likely to occur more commonly in the lower extremities than in upper extremities due to gravity and may explain the higher incidence of VTE in the lower extremities than in the upper extremities. In some cases, blood clots formed in the extremities could dislodge and travel to the pulmonary arteries.[2] VTE is often described in terms of two main disease presentations which are dependent on where the blood clot is located; these elements are deep vein thrombosis (DVT) when the blood clot is located in the veins where they were formed and pulmonary embolism when the blood clot has travelled to the pulmonary arteries.

1.2.2 Deep vein thrombosis and post-thrombotic syndrome

DVT occurs more commonly than pulmonary embolism, with the incidence of DVT being up to twice that of pulmonary embolism.[2] The consequences of DVT include recurrent DVT, pulmonary embolism, the recognised psychological effects of pulmonary embolism similar to post traumatic disorder (PTSD)[4] and the post-thrombotic syndrome (PTS). PTS has been found to be more common than recurrent DVT.[5]

1.3 What is post-thrombotic syndrome?

1.3.1 Definition of PTS

PTS is described as a syndrome of chronic venous insufficiency following DVT consisting of the following spectrum of symptoms; persistent pain and swelling of the leg that is worse after long periods of walking or standing and gets better after resting or raising the leg (postural oedema); leg heaviness; itching; tingling; cramping and in some cases leg ulcers.[6] It involves obstructed and/or refluxed venous blood flow of the venous circulation draining the upper or lower extremities.[7] It has been described as the single most frequent complication of DVT.[8]

PTS may manifest with diverse signs and symptoms (see Table 1).[9] Various clinical scales have categorised PTS in to mild, moderate and severe depending on disease severity based on clinical features[10-12] (see Appendix 1, Section 1.1).

Table 1: Clinical features of Post-thrombotic syndrome

Symptoms	Signs
Heaviness or fatigue	Oedema (swelling of the limb)
Pain	Peri-malleolar telangiectasiae (spider veins around the ankle)
Swelling	Venous ectasia, varicose veins (distension of veins)
Itching	Hyperpigmentation
Cramps	Redness
Paraesthesia	Dependent cyanosis (bluish discolouration of affected extremity)
Bursting pain	Lipodermatosclerosis (chronic inflammation and fibrosis of the subcutaneous tissue)
Symptom pattern: worse with activity, standing, walking; better with rest, recumbence	Healed or open ulcer

Source: Kahn (2006)[9]

1.3.2 Difference between PTS and Chronic venous insufficiency

As explained above, PTS is used to describe the signs and symptoms of chronic venous insufficiency that occurs after an episode of DVT. Therefore, the main difference between PTS and chronic venous insufficiency is the presence of a previous history of DVT before the onset of signs and symptoms (present in PTS and absent in chronic

venous insufficiency). This difference has some implications for clinical diagnosis especially as it has been shown that asymptomatic DVT may sometimes be associated with subsequent development of PTS,[13] so that many patients suffering from PTS will be managed as a case of chronic venous insufficiency because the preceding DVT was not obvious. While currently chronic venous insufficiency and PTS are managed in the same manner, this misdiagnosis may still have implications as data on incidence and health burden of PTS will be underestimated. In addition, the role of asymptomatic DVT in the pathophysiology of what is thought to be primary chronic venous insufficiency needs further exploration as currently it is difficult to rule out that some cases of primary chronic venous insufficiencies are not as a result of a previous asymptomatic DVT.

1.3.3 History of PTS

The earliest possible indicator of PTS from history was from a case documented by Dexter and Mannuci in a twenty year old man named Roaul during the 13th century.[14,15] Roaul was an apparently healthy man who developed DVT like symptoms in the right lower limb, including swelling of his right ankle which subsequently extended to involve his thigh. Progressively the limb developed other symptoms which included discharging ulcers and fistulas. Although Dexter and Mannuci described this new development as a possible case of sepsis, it is also feasible that Raoul had developed PTS as indicated by progressive swelling and development of ulcers which are features of PTS after a period of lower limb swelling (likely a DVT).

Another account by Anning[3] suggests that PTS was also noted in the 16th century. It was documented that Francois Mauriceau, a leading obstetrician and surgeon at the time had

reported a unilateral leg swelling that occurred suddenly in his aunt after a long period of confinement. This swelling lasted thirty eight years. The report suggested that a unilateral leg swelling after a long period of confinement was probably a DVT while a subsequent lengthy period of swelling made it likely that the woman may have suffered from PTS after the initial DVT. Anning also reports other cases of swelling of the limbs after what may have been cases of DVT amongst postpartum women in the17th century.[3]

1.3.4 Terms used to describe PTS

From reports by Anning, it was suggested that PTS along with other causes of oedema in the 17th century may have been collectively referred to as leucophlegmatia.[3] More specific terms have since been used to describe the signs and symptoms of PTS after DVT. They include post-phlebitic syndrome and the venous stasis syndrome.[16]

1.3.5 Differential diagnosis of PTS

Symptoms and signs of PTS are not clear cut, neither are they peculiar to PTS. Therefore, a careful history taking is important. History suggestive of PTS should include a prior episode of DVT and should demonstrate the chronicity of symptoms. Investigations to rule out other differential diagnosis of DVT should be undertaken where relevant. Differential diagnosis of PTS include acute DVT (first three to six months following its onset), and causes of oedema such as congestive heart failure, lymphatic obstruction, and chronic venous insufficiency.[8,17]

Care must also be taken to differentiate PTS from other less reported complications of DVT such as, phlegmasia alba dolens (painful white oedema), phlegmasia cerulea

dolens (painful blue oedema), and venous gangrene. Phlegmasia alba dolens and phlegmasia cerulean dolens are both acute conditions following DVT that may lead to venous gangrene[18] in contrast to PTS which is a chronic condition.

As stated earlier, a history of DVT is the main differentiating factor that separates PTS from chronic venous insufficiency and should be properly explored from a patient's history. However, the absence of a history of DVT does not always rule out PTS because of asymptomatic DVT. In addition, presence of venous signs and or symptoms before a DVT makes it difficult to distinguish between PTS and chronic venous insufficiency.

Other disease entities that require ruling out before a diagnosis of PTS can be made include causes of chronic pain to the lower limbs such as trauma and reflex sympathetic dystrophy as well as any other condition that may cause chronic pain.[19]

1.4 Pathophysiology of PTS

There is generally a poor understanding of the pathophysiology of PTS. Despite this however, it is a widely accepted fact that it occurs mainly as a result of damage to the blood vessel (vein) after an episode of DVT.[7,20,21] This damage gives rise to both macrovascular and microvascular changes that contributes to the post-thrombotic phenomena.[7]

1.4.1 Mechanism of PTS

Whilst the pathophysiology of PTS is poorly understood there are two main mechanisms that have been identified and they include venous occlusion (obstruction to

venous flow) and venous reflux (backflow of blood).[20,22-24] Both mechanisms play important roles in the development of chronic venous hypertension (high blood pressure in veins) which gives rise to most of the signs and symptoms of PTS.[7,20,22] Another factor that has been identified by other studies is calf muscle pump dysfunction.[25-27]

The process by which both venous occlusion and venous reflux arises after an episode of DVT are described below.

1.4.1.1 Valvular reflux

During the inflammatory process associated with DVT, there is production of inflammatory molecules that assist in clot resolution.[28] In PTS, it is thought that in addition to causing resolution of the clot, production of inflammatory molecules may become overwhelming so that they attack nearby venous valves thereby causing destruction of the valves.[28] This will compromise the integrity of the valves leading to valvular incompetency; valvular incompetency can in turn lead to venous reflux, stasis and then venous hypertension.[28]

From the processes that lead to venous reflux summarised above, it is expected that reflux would occur in vein segments affected by DVT only. However, the development and progression of reflux does not always occur only in the vein segments affected by DVT. Venous reflux has been described in vein segments that are distant to the veins originally affected by DVT.[22] The process by which this occurs is incompletely understood, although a possible explanation is the extension of fibrosis beyond a thrombosed segment to these adjacent segments.[29] The inability to identify the exact mechanism by which venous reflux can occur beyond the original site of DVT contributes to the complexities of the pathophysiology of PTS.

1.4.1.2 Venous occlusion

After DVT, there may be residual blood clot in the venous system which may impede venous return.[30] This residual blood clot and or narrowing that may accompany DVT leads to venous occlusion. Research suggests that the extent of venous occlusion may determine the rate of recanalisation (restoration of blood flow in the vein)[31] which may in turn determine the occurrence of venous reflux.[32]

It can be deduced from the above information that the venous occlusion which occurs during an episode of DVT sets in motion the mechanism that eventually progresses to PTS. As mentioned earlier, chronic venous hypertension which occur from venous reflux and occlusion may account for the signs and symptoms of PTS such as limb redness, limb pain, varicose veins, peri-malleolar telangiectasiae, limb heaviness and dependent cyanosis.[30] The extravasations of red cells, release of fibrinogen and inflammatory markers that occurs in limbs with venous hypertension, can lead to ulcers later.[17,30]

The pathophysiology of PTS remains controversial and is still the subject of much debate.

1.5 Relationship between the pathophysiology and the course of PTS

The degree of venous reflux is variable over time in patients for unclear reasons.[33] This finding is consistent with those of Kahn et al[34] where it was demonstrated that the signs and symptoms of PTS exhibited by patients at various follow up visits was varied, so

that a patient with mild PTS at one visit may have no signs of PTS at follow up visits, or a patient with severe PTS may have mild PTS at follow up visits. These finding by Kahn et al led them to suggest that perhaps a more reliable diagnosis of PTS would be made if the diagnosis of PTS was made only after the threshold for making a diagnosis of PTS had been crossed on two consecutive occasions.

1.6 PTS diagnosis

PTS diagnosis is difficult as there is no reference standard for diagnosis and because of the variable time course of the disease process.[9] Several rating scales and radiological tools used in investigating chronic venous insufficiency have also been used to investigate patients with PTS because of the similarities between the two conditions. Attempts have also been made to devise a standard assessment scale for diagnosing PTS. This was done either by developing new scales specific for diagnosing PTS or adapting existing scales used in classifying chronic venous insufficiency for the purpose of diagnosing PTS.

Rating scales that have been used for PTS diagnosis include the Villalta scale,[10] Ginsberg measure,[35] Brandjes score,[11] Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification,[36] venous clinical severity score (VCSS) and the Widmer classification.[12]

Radiological tools have also been used for investigating and diagnosing chronic venous insufficiency and may be employed in the diagnosis of PTS.[37-39] These radiological tools can be invasive or non-invasive. Invasive radiological tools that have been used to diagnose PTS include venography[38] (ascending and descending venography) and

measurement of ambulatory venous pressure.[40,41] Non-invasive radiological tools that have been used to diagnose PTS include Duplex ultrasound (combination of ultrasound and Doppler scanning),[38,42] foot volumetry[42-44] and plethysmography[38,42] (air plethysmography or photo plethysmography also known as light reflection rheography).

Other tests that have been employed in the investigation of chronic venous insufficiency and potentially PTS include the Tredenlenburg's test and the Ankle Brachial Index. These clinical examinations may be carried out by the bedside of the patient. Trendenlenburg's test may be used to detect venous reflux in patients with varicose veins,[45] while the Ankle Brachial Index may be used to detect arterial involvement in venous ulcer so that an arterial cause of PTS symptoms can be ruled out.[46] Both of these tests can be useful adjuncts in making a diagnosis of PTS.

Radiological tools cannot reflect patient's signs and symptoms (an essential component of PTS definition), hence may not reflect an accurate picture of PTS. Because of this same reason, they may not be reliable in measuring changes in PTS status especially where there is an improvement in PTS. They can however detect level of abnormality in the venous system and therefore can aid intervention.

In summary, this section highlights that there are multiple ways that may potentially be used to assess PTS based on its similarity with chronic venous insufficiency. It also highlights that specific assessment tools for PTS have also been developed and used for PTS assessment. However, it is not clear just how many of these methods are being used to diagnose PTS in research and clinical practice or how reliable they are in diagnosing PTS. These areas need further exploration to fully understand how reliable current PTS diagnostic tools are and which of them are actually being used in practice.

1.7 Incidence and prevalence of PTS

This section describes the incidence and of PTS in the general population and more specific populations. There are limited data on the prevalence of PTS after DVT. Therefore only the incidence of PTS is discussed here. To be noted when interpreting the data presented below on incidence of PTS is that patients presenting with signs and symptoms of venous insufficiency after asymptomatic DVT will most often not have an evidence of DVT and will consequently be treated as a case of chronic venous insufficiency. This could potentially lead to underestimations of existing data on incidence and prevalence of PTS.

1.7.1 Incidence of PTS in the general population

There is wide variation in reports on the incidence of PTS. This is most likely due to the different diagnostic criteria for PTS as well as variations in length of follow up of studies that have evaluated incidence of PTS. The incidence of PTS after DVT has been reported as 18% one year after DVT,[5] 24.5% to 43% after two years,[5,47] 29.6% after five years,[5] and 56.6% after ten years.[48] Despite the variation in the reported incidence of PTS, these figures show that there is a progressive increase in incidence of PTS across the years. The cumulative incidence of PTS has been reported to continue to rise for up to 20 years after an episode of DVT.[49]

Earlier studies[50-52] demonstrated that the majority of people that will develop PTS do so within the first three years following an initial episode of DVT. However more recent studies contradicted these findings as demonstrated in the studies by Prandoni et al and Kahn et al.[5,53] Both studies demonstrated that majority of patients will develop PTS

within the first two years, with a slight to moderate increase thereafter. Severe PTS which has the most effect on quality of life has the following incidence post DVT; 2.7% after one year[5]; 3% after two years[47]; and 8.1% after five years.[5] After this, the cumulative incidence of severe PTS did not appear to increase.[5]

In summary, the information on incidence of PTS implies that five years after an episode of DVT in the general population, we can expect approximately up to 43 in 100 people to develop any kind of PTS and eight in 100 people to develop severe PTS.

1.7.2 Incidence of PTS in specific groups

The incidence of PTS described above is in the general population of patients with DVT regardless of whether they received thromboprophylaxis or not prior to developing DVT. Some patients have been identified to be at increased risk of DVT (examples are patients after surgery and patients on prolonged bed rest) and so these patients may receive thromboprophylaxis to discourage the development of DVT. The incidence of PTS after DVT post an orthopaedic surgery was reported by three studies. The three studies assessed 14,[54] 25[55] and 91[56] patients that developed DVT post operatively on ultrasound or venography after arthroplasty. The studies reported the incidence of PTS as 21.4% after one year follow up[54] 5.5% after two to seven years follow up,[56] and 16% after three years follow up.[55] As with the studies on the incidence of PTS in the general DVT population, there were differences in the diagnostic criteria for PTS and different follow up time periods. Thromboprophylactic regimens also varied from study to study. These differences in diagnostic criteria and thromboprophylactic regimen across studies may explain the variation in their reports incidence of PTS.

In summary, the above evidence demonstrates that up to 16 in 100 DVT patients that receive thromboprophylaxis for DVT after an arthroplasty will develop PTS by three years after DVT.

1.8 Current methods used for prevention of PTS

Preventing first and recurring episodes of VTE, particularly in high risk patients is an important strategy in the prevention of PTS.[6,30] Reductions in the incidence of VTE would result in a decrease in the incidence of PTS, following the reasoning that VTE is the precursor of PTS,

Various strategies for the prevention of VTE have been researched into and employed in the prevention of VTE, with attention being paid to reducing the risk of developing VTE in the first instance. Examples of strategies employed in VTE prevention include the NICE guidelines recommended for use in the UK.[57] The guideline consists of the following steps:

1. Assessing the risk of individuals of VTE on admission to hospital. This is assessed by considering if they have risk factors for developing VTE.
2. If a patient is found at risk of VTE, chemical thromboprophylaxis may be used after balancing the risk of bleeding and having VTE, which varies from patient to patient (depends on co-morbidities and co-existing factors like reduced mobility relative to usual state).

3. In addition to chemical thromboprophylaxis, other measures such as compression stockings, preventing dehydration and encouraging mobilisation may be employed.

It is also worthy of note that DVT may occur in patients without any apparent risk factor (unprovoked DVT), and that these patients are at higher risk of DVT recurrence than patients in whom a provoking factor was identified.[58] Therefore, promoting other methods of PTS prevention besides preventing DVT in the first instance is a necessity.

As discussed previously, both venous occlusion and venous reflux have been implicated in the pathophysiology that leads to development of PTS.[22] Therefore, to prevent PTS directly, it may be beneficial to prevent valvular dysfunction, preserve valvular function as well as eliminate occlusion after DVT. As a result, most PTS preventive measures aim to do one or more of these.[22]

The main PTS preventive measures are listed below

1. Pharmacotherapy
    a. Thromboprophylaxis – involves the use of pharmaceutical agents (examples include low molecular weight heparin, Fondaparinux) to prevent the formation of clots in patients at high risk of developing clots.
    b. Anticoagulation for treating DVT – Oral anticoagulation includes the coumarin derivatives which act by antagonising vitamin K (warfarin, phenprocoumon and acenocoumarol), the more recently introduced direct factor Xa inhibitors (example, abixaban, edoxaban and rivaroxaban), and the direct thrombin inhibitors (dabigatran).

c. Thrombolysis - Thrombolysis involves the administration of a thrombolytic agent (examples include urokinase, streptokinase, tissue plasminogen activator, recombinant tissue plasminogen activator) for the purpose of dissolving an already formed clot.
    i. Systemic thrombolysis – thrombolytic agent is delivered via a venous site far from the affected limb
    ii. Loco-regional thrombolysis – thrombolytic agent is delivered via a venous access site in the affected limb
    iii. Catheter directed thrombolysis – thrombolytic agent is delivered directly in to the clot via a catheter

2. Mechanical measures
    a. Compression therapy – It uses external pressure to increase the pumping function of the limb and improve venous blood return. It includes the use of compression stockings (below knee or above knee) which can be elastic or non-elastic compression methods including bandages, Unna boots, intermittent pneumatic compression, and Venowave.
3. Pharmacomechanical measures

    As the name suggests, it consists of using a combination of mechanical measures and pharmacological agents for clot resorption. They include:
    a. Trellis device
    b. Angiojet system
4. Surgical measure
    a. Surgical thrombectomy – surgical removal of the clot from within the vein

PTS preventive measures such as thrombolysis generally and surgical thrombectomy have been associated with major bleeding and this risk of bleeding has been described as significantly more than when other methods of preventing PTS like pharmacomechanical measures are used.[59-61] PTS preventive measures such as thrombolysis and surgical thrombectomy require specialised expertise and may be more expensive compared to other preventive measures such as compression stockings.[62-65]

1.8.1 Prevention of PTS in the UK

Preventing and adequately treating DVT may reduce the incidence of PTS since DVT is the precursor to PTS. So it can be said that PTS prevention is done indirectly and is intertwined with the prevention and treatment modalities given to patients after DVT. This is particularly so, because currently there are no factors to identify patients that will develop PTS. Methods that can be employed in the prevention of DVT have been described above. In the UK, the treatments for DVT as advocated by NICE guidelines[66] included the use of compression stockings for at least two years from DVT diagnosis, with an aim of preventing future development of PTS. However based on findings from a recent study which found no benefit in the use of compression stockings with PTS prevention, this has been removed from the guideline. The current treatment strategy for DVT includes:[66]

- The use of low molecular weight heparin and a vitamin K antagonist for at least the first five days after diagnosis or until when the international normalised ratio is two or above whichever is longer

- Subsequent use of a vitamin K antagonist for three months or beyond (benefits and risks of continuing vitamin K antagonists should be assessed at three months)
- Offer low molecular weight heparin to patients with active cancer and confirmed proximal DVT or pulmonary embolism, and continue the low molecular weight heparin for six months (At six months, assess whether to stop or continue low molecular weight heparin based on balancing the risks and benefits of continuing anticoagulation)
- Consider catheter directed thrombolysis for patients with symptomatic ilio-femoral DVT in patients where all the following criteria are present:
    - symptoms of less than 14 days duration
    - good functional status
    - a life expectancy of one year or more
    - a low risk of bleeding
- Use of compression stockings for proximal DVT to relieve symptoms of DVT and not for prevention of PTS.

Therefore in the UK, the general preventive strategy for PTS can be said to consist of anticoagulation, with catheter directed thrombolysis only recommended in special circumstances as described above. There might be room to further tailor DVT treatment strategies to effectively prevent PTS in patients at higher risk of PTS if research is able to identify prognostic factors associated with developing PTS after DVT.

The literature presented so far on prevention of PTS suggest that PTS is preventable and that some of these preventive measures are expensive, may be associated with risks such as bleeding and may require expertise.

1.9 Current PTS treatment strategies

Little or no success have been seen with the management of PTS and the treatment modalities used for the condition are described as largely ineffective.[67] They are usually aimed at alleviating signs and symptoms of PTS and not curing the underlying pathology.[68] Methods that have been employed in the treatment of PTS are described below:

1. Mechanical measures
    a. Compression therapy - Compression therapy in particular compression stockings is regarded as the corner stone of managing PTS.[8,67] Other methods include the intermittent pneumatic compression and the Venowave device.[68,69] Intermittent pneumatic compression and/or Venowave device are usually reserved for severe PTS.[68]
2. Pharmacotherapy – Short term use of venoactive agents like Aescin (horse chestnut extract), Rutosides, Hidrosmina and Pycnogenol may be effective in managing PTS.[6,68,70] Pentoxifylline has also been found useful in the treatment of PTS ulcers.[16]
3. Surgical measures

    Surgery is presently advocated for patients with severe PTS including post-thrombotic ulcers that is refractory to conservative treatment.[68]

    a. Surgery for venous reflux – Surgical procedures aim to re-establish valvular function. This includes; sclerotherapy or laser ablation of valves for superficial venous reflux, valvuloplasty for deep venous reflux – valvuloplasty can be internal, external or transcomissural (the latter is

employed in cases where competency of the valves are sufficiently preserved).[41] Valvular transposition or autologous vein transplantation may be carried out where there has been complete valve destruction.[41]

b. Surgery for venous obstruction – Surgical options for venous obstruction elimination include; endovenectomy and endovascular stenting.[41,68] In cases where stenting fails or is not possible, bypass surgery to bypass the obstruction may be employed in the management of PTS.[41]

1.9.1 Management of PTS in the UK

There is currently no national guideline on the best management strategy to be employed by health professionals for the management of PTS in the UK. There is however a national guideline on the management of chronic leg ulcers.[71]

The evidence on management of PTS demonstrates that though there are multiple ways being employed in the management of PTS, the mainstay of treatment is still conservative – compression stockings.

1.10 Burden of PTS

1.10.1 Impact of PTS on quality of life

Some symptoms of PTS like pain, paraesthesia, itching, tingling and leg ulcers amongst others can be disabling, so that PTS has debilitating effects on quality of life. In support of this, it has been demonstrated that venous ulcers on their own may lead to socio-emotional problems such as social isolation, fear, anger, depression, and negative self-image.[72] These feelings can be complicated and made worse by loss of time from work

and job loss. The negative socio-emotional feelings that venous ulcer patients experience has been found to correlate with the time spent caring for the venous ulcer.[72] The longer the ulcer takes to heal as is anticipated with PTS (being a chronic condition), the longer the individual is likely to be subjected to these negative feelings and the subsequent dire effects they may have on the psychological health of the individual.

Presently quality of life in VTE sufferers may be measured with disease specific tools such as the Venous Insufficiency Epidemiological and Economic Study quality of life and symptoms (VEINES-QoL/Sym) questionnaire[73] and the venous thrombosis quality of life questionnaire. The VEINES-QoL/Sym questionnaire have been validated and found to be reliable and to meet required standards for assessing quality of life in patients with PTS.[74] Generic tools such as the SF-36 generic quality of life instrument[75,76] have also been used to assess quality of life after DVT.

A reduction in quality of life has been consistently associated with PTS using the disease specific tools (VIENES-QoL, VEINES symptoms and venous thrombosis quality of life questionnaire).[77-81] The generic tool (SF-36 questionnaire – comprising of a mental component scale and a physical component scale) has also demonstrated a poor quality of life in PTS sufferers. A series of studies with 181,[78] 161,[79] 25[80] and 18[82] PTS patients consistently demonstrated that SF-36 tool was associated with a poorer quality of life in patients that have PTS than in those that do not have PTS.[78-80,82] Not all four studies found the negative impact of PTS on quality of life to be statistically significant when the SF36 tool was used. However, all studies found the negative impact to be statistically significant when disease specific quality of life tools were used.

The severity of PTS was found to be directly proportional to poor quality of life after DVT.[77,78] The quality of life in PTS sufferers was also found to be worse than the quality of life in patients of similar age group with chronic lung diseases, hearing impairment, diabetes or arthritis. While patients with severe PTS will have quality of life that is comparable to patients with angina, neoplasia or heart failure.[77]

In general, a patient with PTS will tend to suffer a reduction in daily activities and in severe cases an increase in time taken off work due to leg ulcers may be observed.[72] This means a reduction in the contribution of the individual to the society, loss of work days, and an addition to the overall cost of managing DVT when care of leg ulcers is taken in to account. Indicating a net negative in income, this is particularly important to the economy in a country like the UK where the health costs of patients are met by the government in form of the National Health Service (NHS).

The consequences of PTS on quality of life in patients after DVT can be multidimensional, as it has an emotional, social and financial consequence on the patient. In addition the information implies that PTS is a health burden that is of economic importance. More details on the economic importance of PTS are discussed in section 1.10.2.

1.10.2 Cost of PTS

1.10.2.1 Cost of PTS to the UK

The cost of PTS to the National Health Service (NHS) in the United Kingdom is not well documented. However, a report to Parliament in 2004 utilized a hospital algorithm

and a community algorithm to calculate the direct and indirect cost of VTE to the NHS using an incidence based approach and a bottom up approach.

As the name implies, the incidence based approach only accounted for reported cases of VTE and most likely resulted in an underestimate of VTE costs, as asymptomatic cases as well as unreported cases were not accounted for in this approach. On the other hand the bottom up approach was most likely an over estimation of the costs of VTE as this approach took into account reported events as well as at risk populations. From these, it was estimated that the total cost of PTS using the bottom up approach was approximately £128 million. When the incidence based approach was used, total cost burden of PTS was £68 million.[83]

Issues with the diagnosis of PTS (as discussed in section 1.6) may have affected the portrayal of the true cost of PTS, as PTS is still an under researched area and the knowledge of PTS may be lacking amongst physicians to be diagnosed appropriately or comprehensively reported. This could potentially lead to under diagnosis and consequently an underestimation of the true cost of PTS.

1.10.2.2 Cost of PTS in other countries

Like the UK, the cost of PTS is not well documented in other countries. In the United States of America (USA), cost of managing PTS was estimated to be approximately $261 million annually using the incidence based approach.[84] This figure underestimates the cost of PTS to the USA for the following reasons: the community in which the study was based was a white majority community (96%), so that non-white population were not well represented (this was noted by the authors). Studies have shown that there is a higher incidence of PTS in some non-white groups for example African-Americans.[85]

Also the estimates were based on costs and PTS incidence based on the 1990 financial year (studies of the trends of incidence of DVT have shown that the incidence of DVT which precedes PTS continues to rise).[86,87] Therefore, it is safe to assume that the incidence of PTS today will be much higher than it was in 1990 based on this. This implies that the cost of PTS today using the incidence based approach will be much higher than it was in 1990. The same reasons may account for the huge difference in cost between the UK and USA estimates of PTS cost.

More recent studies from Brazil and USA have made estimates on an individual level and they show that mild to moderate PTS will cost an individual $400 to $839 in first year and $341 in subsequent years while patients with severe PTS will spend $1200 to $3817 in first year and $1677 in subsequent years.[88,89]

The evidence on cost of PTS demonstrates that PTS is an expensive condition to manage. It will therefore be of economic benefit to prevent it.

1.11 Thesis rationale and approach

1.11.1 Identification of prognostic factors associated with the development of PTS after a DVT of the lower limb

1.11.1.1 Rationale

The background to this thesis highlights that PTS is one sequelae of DVT that is better prevented than managed because of the impact it has on quality of life and economic resources in general. It is important to prevent the chronic and debilitating consequences of PTS so that eventual survivors of VTE will have a better quality of life than they currently have. This is particularly important as it was highlighted that treatment strategies for PTS are largely based on symptomatic relief and not cure.

It was also highlighted in the background that PTS maybe preventable after a DVT of the lower limb. However, PTS preventive measures may be associated with increased risks such as bleeding. They may also require expertise and high tech instruments to administer leading to increased costs. It was therefore anticipated that by identifying patients at risk of PTS after a DVT of the lower limb, PTS preventive measures may be administered to patients in most need of them (i.e. patients at risk of PTS). This would potentially save resources by limiting unnecessary expenses that will likely be involved in administering PTS preventive measures to patients that do not need it (i.e. patients

not at risk of PTS). It will also save patients that are not at increased risk of developing PTS from being exposed to unnecessary procedures and their attendant potential risks.

To identify patients at increased risk of developing PTS after a DVT of the lower limb, it is necessary to first identify prognostic factors associated with the development of PTS after a DVT of the lower limb as this thesis aims to address. A prognostic factor is defined as a "clinical or biologic characteristic that is objectively measurable and that provides information on the likely outcome of the disease in an untreated individual".[90] In this instance the disease concerned is DVT and the outcome we need information about is PTS.

The identification of prognostic factors associated with developing PTS after a DVT of the lower limb would potentially equip clinicians with the information needed to educate patients that have suffered DVT on their risk of developing PTS afterwards. This education can help high risk patients make informed decisions on whether to accept PTS preventive measures such as catheter directed thrombolysis with their attendant risks or not (where they are offered).

Identification of these prognostic factors can also potentially provide necessary information required for the development of a prognostic model which can in turn be easily implemented in clinical practice to risk stratify patients.

1.11.1.2 Methods

The method used to address the identification of these prognostic factors initially was a systematic review of systematic reviews. This was considered appropriate because it had the following advantages; there were already systematic reviews on DVT therapy

which may have identified factors associated with developing PTS after DVT of the lower limb; it could combine all available evidence in to one (for ease of access for clinician and researchers); prevent reproduction of work that may already have been done; help assess the scope and limitations of existing systematic reviews on prognostic factors associated with PTS and identify how they can be improved if needed. Therefore, Chapter 2 of this thesis is the systematic review of systematic reviews conducted to address this question. Subsequently, a systematic review of primary studies (see Chapter 3) was conducted to address the gaps identified in the systematic review of systematic reviews. Lastly, the judgements of experts were sought on prognostic factors via an e-Delphi study with an aim to identify any additional prognostic factor and to prioritise prognostic factors (see Chapter 6).

1.11.2 Identification of the most reliable method for PTS diagnosis

1.11.2.1 Rationale

It was highlighted in the background to this thesis that; i) there was lack of a reference standard for PTS diagnosis; ii) there were variable methods being employed in the diagnosis of PTS; and iii) there was limited evidence on the reliability of methods used to diagnose PTS. These issues with PTS diagnosis potentially limits the ability to compare studies, leading to inconclusive evidence and hence limits the growth of research in PTS. So that it was decided that further work was required to achieving a reference standard for PTS diagnosis or at the minimum detecting the most reliable method for diagnosing PTS.

It was anticipated that identifying the most reliable method for diagnosing PTS would reduce heterogeneity in PTS research by encouraging the use of the most PTS diagnostic method found to be most reliable. This would potentially encourage research by reducing some of the limitations currently encountered when making conclusions from PTS research.

1.11.2.2 Method

The variation in methods of PTS diagnosis was explored further by identifying the different PTS diagnostic methods utilised in the systematic reviews conducted to identify potential prognostic factors (see Chapter 4). Where there was the evidence to do so, PTS diagnostic methods were compared to each other in terms of proportion of PTS diagnosed – this was done via a systematic review of primary studies (see Chapter 5). It was anticipated that there might be different methods being used for PTS diagnosis in clinical practice. So experts in PTS were asked about what methods of PTS they were using in their daily clinical practice via an e-Delphi study (see Chapter 6) – this was done to further assess variation in PTS diagnosis. Their judgements on the reliability of all identified methods for PTS diagnosis were then sought in an attempt to prioritise PTS diagnostic methods according to their reliability from expert judgement.

Chapter 2: Identification of potential prognostic factors associated with the development of PTS after a DVT of the lower limb (systematic review of systematic reviews)

2.1 Introduction

The previous chapter highlights that it would be useful to identify factors associated with the development of PTS after DVT (prognostic factors) so that clinicians could reinforce PTS preventive measures in patients at risk of developing PTS after DVT (patients with unfavourable prognostic factors). This will help conserve resources and limit the exposure of patients that do not require PTS preventive measures to the side effects associated with them.

This chapter aimed to address this need by conducting a systematic review of available systematic reviews that have looked at one or more factor that may be associated with the development of PTS after DVT. Existing evidence was assessed to identify factors that may be associated with the development of PTS and the strength of any identified association.

A systematic review of systematic review was considered efficient and appropriate because it was identified from a scoping search that there were existing systematic reviews that had assessed DVT treatment in relation to subsequent development of PTS. Thus it would potentially prevent reproduction of work, help assess scope of existing reviews and identify how they can be improved.

2.2 Research question

Based on evidence from existing systematic reviews, what prognostic factors are associated with the development of PTS in a population with a previous DVT of the lower limb?

2.3 Objectives

- To systematically identify and map of coverage of systematic reviews with regards to factors associated with the development of PTS
- Where there is overlap between reviews, to identify the most comprehensive and robust reviews for further scrutiny
- To consider the robustness of the evidence on any identified association and the strength of the association
- To identify if there is a need to update the evidence on identified factors associated with developing PTS after DVT of the lower limb
- To assess if there is the need for further systematic review(s) of primary studies to identify additional factors associated with PTS after DVT of the lower limb

2.4 Methods

2.4.1 Systematic review of systematic reviews

A protocol was developed prior to commencement of this review and was used as a guide. The review consisted of standard searches to identify published systematic reviews; specific criteria were used to select relevant systematic reviews to be included in this systematic review. Assessment of the quality of included systematic reviews was done using an appropriate tool and findings of the included systematic reviews were extracted and synthesised.

2.4.2 Search strategy

A search of the following databases up to September 2012 was conducted using relevant index terms and free terms combined with an appropriate BOOLEAN operator; Cochrane Library (which includes the Cochrane databases of systematic reviews (CDSR), Database of Abstracts and Reviews of Effectiveness (DARE) and the Health Technology Assessment (HTA) database, MEDLINE (Ovid) and EMBASE (Ovid). Multiple databases were used so that database bias was minimised and chances of identification of relevant systematic reviews was maximised. The search terms were modified as necessary for each electronic database searched. A methodological filter for systematic reviews was applied to the EMBASE and MEDLINE database to limit results to systematic reviews.

The search strategy was developed with the help of an information specialist (Sue Bayliss). Search terms selected were deliberately broad so that the search strategy

would yield all systematic reviews that may have looked at factors associated with the development of PTS.

The search strategy included combinations of search terms that described the relevant population (DVT) and the relevant end outcome (PTS). As explained in Chapter 1, PTS is known by several names such as chronic venous insufficiency, venous stasis syndrome and post-phlebitic syndrome. Therefore, to identify relevant studies, the search strategy was developed to include these descriptors of PTS. Terms for DVT were combined using the Boolean operator 'OR', the same was done for terms for PTS. Both of these sets were combined with the Boolean operator 'OR' as in the following:

('Venous thrombosis' OR 'Venous thromboembolism' OR 'Deep vein thrombosis' OR 'Deep vein thromboses' OR 'DVT' OR 'VTE') OR ('Post thrombotic syndrome' OR 'postthrombotic syndrome' OR 'PTS' OR 'Post phlebitic syndrome' OR 'Venous stasis syndrome' OR 'Chronic venous insufficiency' OR 'chronic vein insufficiency' OR 'Venous ulcer').

References of identified reviews were also checked to identify any potentially relevant review not already identified by the search strategies used. The search results from implementing the search strategy were then entered into reference management software (Endnote X4 version). An inbuilt algorithm in Endnote X4 was used to automatically remove duplicate records. Remaining duplicate records were searched for and removed manually.

Appendix 2, Sections 2.1 and 2.2 shows the search strategy used for each database.

2.4.3 Study screening and selection

Records resulting from implementing the search strategy to the aforementioned databases were inputted into reference management software (Endnote X4.0.2, Thomson Reuters). Duplicate entries were initially removed automatically by using an inbuilt algorithm, left over duplicates were then manually removed. To ensure rigor during the selection process, the primary reviewer Halima Olakareem (HO) and a colleague Adeniyi Yomi-Adeleke (AY) independently screened titles and abstracts of records. Records that were potentially relevant to the systematic review were identified (if their population and outcomes matched those of this review of reviews). Full texts of the identified records were then obtained. HO and AY independently applied the inclusion and exclusion criteria to the full texts to determine their eligibility. Those that did not meet the inclusion criteria were excluded and articles that satisfied the inclusion criteria were included in this systematic review. All disagreements on eligibility of articles were resolved by discussion between HO and AY. Where enough information to determine the eligibility of an article was not reported, an email was sent out to the corresponding author requesting further information. If no response to the query was received within a week, a reminder email was sent. Following this, if there was still no response from the author, the article was listed as having insufficient information to make a selection decision.

A Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram[91] was used to summarise the study selection process. Information about excluded articles and the reasons for exclusion were recorded.

Inclusion criteria

Patients – Eighteen years or greater that have had at least one episode of confirmed DVT of the lower limb. Reviews that reported on mixed population were included if data for the population relevant to this review were reported separately.

Setting – Reviews in all settings were considered

Outcomes – The occurrence of PTS. This could be either a primary or a secondary outcome of the systematic review.

Study design – Systematic reviews with or without meta-analysis. A systematic review is defined by the Cochrane handbook[92] as a study that attempts to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Therefore, the systematic reviews had to have searched at least one electronic database and had inclusion and exclusion criteria for primary studies to be included in their reviews.

Follow up duration – Systematic reviews should have included at least one study that has followed up patients for three months or longer after the initial episode of DVT and the data on this study should be extractable. This is because PTS can be easily confused with ongoing symptoms of an acute DVT within the first three months after a DVT episode therefore PTS is better diagnosed at least three months after an episode of DVT.

There was no restriction on the language of publication of systematic reviews.

2.4.4 Data extraction

Data extraction from the eligible studies was carried out independently by HO and AY using a data extraction form constructed a priori to retrieve the following information from the articles where applicable:

Systematic review methods

Information about the systematic review methods including, aim or objective, number and types of databases searched, areas of grey literature searched, years searched (range); study designs of primary studies included (type and number), studies excluded (n) and reasons for their exclusion

Details of studies reported by the systematic reviews

These included, method of DVT measurement, total population assessed for PTS (n), PTS measures used, time points of PTS measurements, total follow up period, potential prognostic factors assessed, length of exposure to potential prognostic factor (for example duration of treatment), average time from DVT to exposure to potential prognostic factor where relevant (for example time after DVT that a patient received an intervention).

Results of systematic reviews

Findings of systematic reviews including, measures of effect (Relative Risk, Odds Ratio, Hazard Ratios, Proportions), sizes of effect measures and assessment of potential bias in primary studies as well as whether there was an assessment for publication bias in the review.

2.4.5 Quality assessment

The quality of included articles was assessed with the assessment of multiple systematic reviews (AMSTAR) tool.[93] The tool is an 11 item questionnaire specific for exploring the quality of systematic reviews (see Appendix 2, Section 2.4). The assessment was carried out by two reviewers independently (HO and AY). Disagreements were resolved through discussion and a third reviewer was available to adjudicate where consensus could not be reached, but was not required.

In order to get an overview of the quality of included systematic reviews, a graphical representation of the summary of the quality assessment in percentages of systematic reviews that did or did not fulfil each quality criteria was done.

2.4.6 Mapping of the evidence

Potential prognostic factors that were assessed for an association with the development of PTS in the systematic reviews were subsequently grouped into treatment factors (factors associated with DVT treatment) and non-treatment factors (factors that are not associated with DVT treatment). Examples of treatment factors would include pharmacologic treatment, compression therapy, pharmacomechanical therapy and surgical therapy. Examples of non-treatment factors would include, age and gender.

2.4.7 Analysis

Characteristics of identified systematic reviews and their findings were reported narratively.

Systematic reviews were reported under each identified potential prognostic factor they had assessed. For every identified potential prognostic factor, themes across relevant reviews in terms of effect measures, effect sizes and direction of effect were identified and reported. The characteristics that may explain differences or similarities in direction and or size of effects between reviews that assessed the same factor were identified. This was done by examining systematic reviews for differences in study designs of included primary studies, study populations, outcome measures and time points of outcome measures. Approaches used to combine results by individual reviews were also assessed for their suitability.

Conclusions made by this review on findings on each potential prognostic factor were made based on strengths of the evidence on systematic reviews that had reported on the factors. It took in to account the quality and level of evidence of each review.

2.4.8 Assessment of need to update the evidence on potential prognostic factors identified from the systematic review of systematic reviews

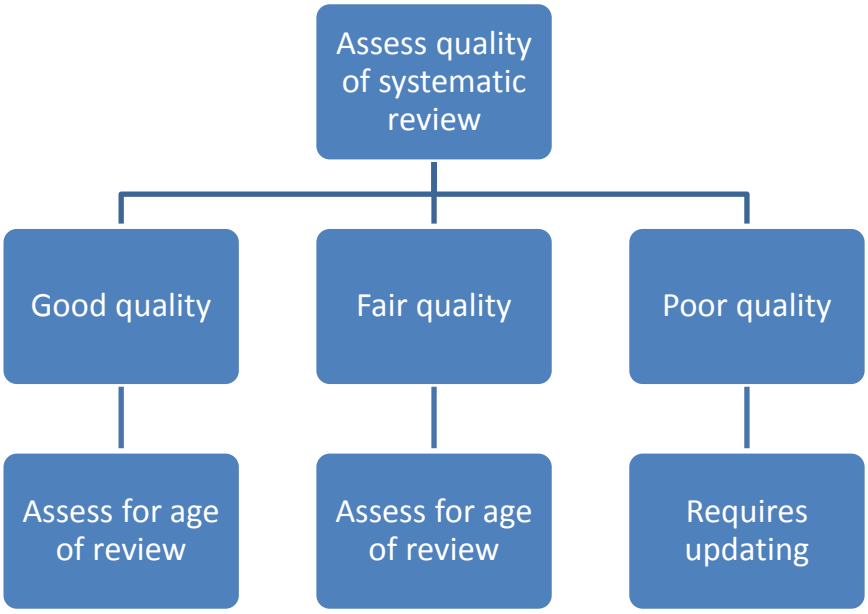
Systematic reviews were assessed to identify if there was a need to conduct a systematic review of primary studies to update the current evidence. Where a need to update the evidence was identified, new relevant studies on potential prognostic factors starting from the end date of the search strategies covered by corresponding systematic reviews would be conducted (see Chapter 3). A method to assess which potential prognostic factor required an update of the evidence was therefore developed in this review.

So far, there are no objective methods to assess whether the evidence from a review requires an update, so that most methods used in the literature to assess the need to update a systematic review are subjective.[94,95] Factors that are thought to be important include, the quality of the existing systematic review, age of the systematic review, the strength of the evidence and the availability of new relevant studies.[94,95] These elements were considered in making the decision to update the evidence on a potential prognostic factor or not. The method used is described and presented below. See Appendix 2, Section 2.6 for details on why these elements were considered.

Quality of the systematic review –For the purpose of this review, a systematic review was considered to be of good quality if it satisfied eight to 11 criteria on the AMSTAR tool, fair quality if it satisfied four to seven criteria and poor quality if it satisfied less than four criteria.

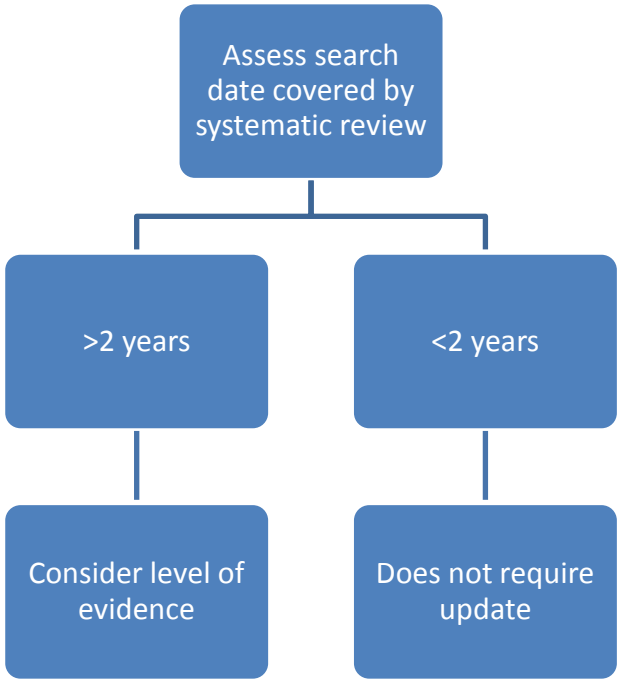
Where a systematic review was found to be of poor quality on the AMSTAR tool, the potential prognostic factor it explored was put down as "requires updating of the evidence" if no other systematic review of a fair or good quality has assessed it. Where one or more systematic review that have assessed a factor is found to be of fair to good quality, the search dates covered by these systematic reviews was then assessed.

Figure 1: Assess quality of systematic review



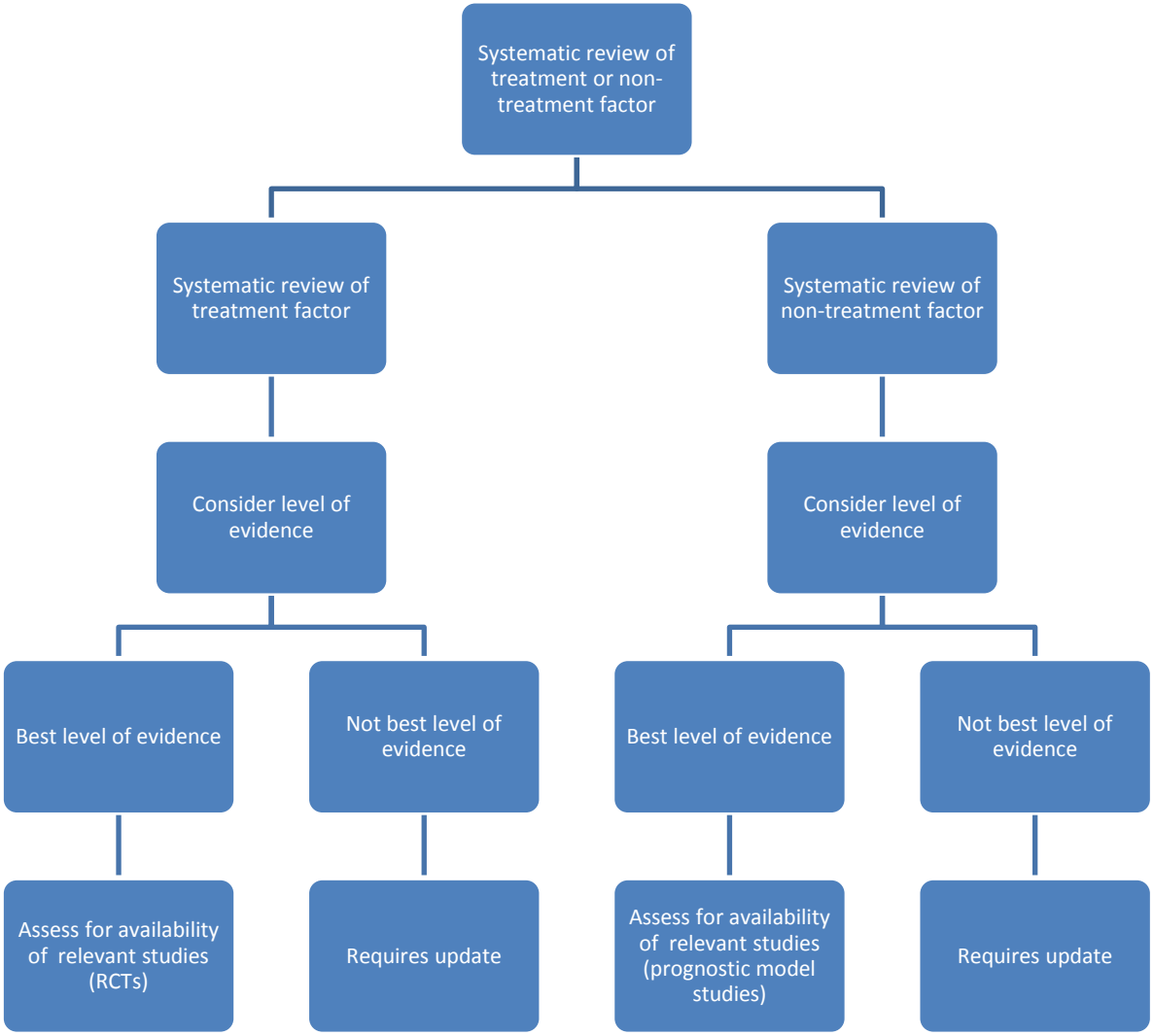
Age of the evidence – The next stage in the process was to assess the age of the systematic reviews. A two year cycle updating policy was used. So that a review of less than two years did not require an update while a review of two years or more may require an update depending on the availability of new relevant studies.[94] This systematic review of systematic reviews concluded in 2012, therefore if the search strategy of at least one fair to good quality systematic review that assessed a factor was between 2010 and 2012, a need for an update of the evidence on the factor was ruled out. Otherwise, the level of evidence was considered.

Figure 2: Assess age of evidence



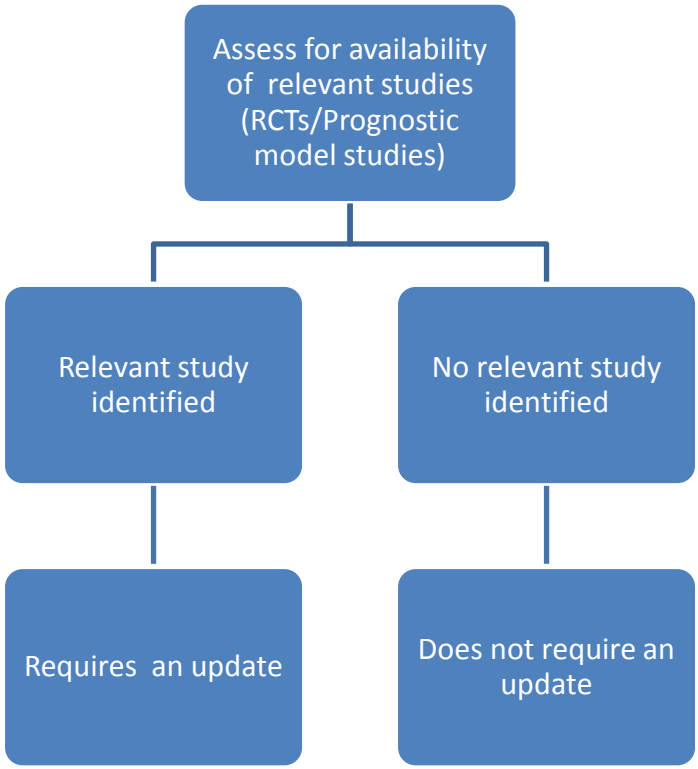
The level of evidence – Consideration of level of evidence was carried out based on the Oxford centre for evidence-based medicine reference for level of evidence.[96] Systematic reviews of prognostic model studies are the best level of evidence for studies on prognosis (see Appendix 2, Section 2.6.1 for the Oxford centre for evidence-based medicine reference for level of evidence). Where this was not available, a systematic review of prospective cohort studies was considered the best level of evidence for non-treatment factors and systematic review of RCTs was considered the best level of evidence for treatment factors (i.e. the standard effectiveness of the treatment after DVT with respect to subsequent development of PTS was used to measure prognosis). Systematic reviews that were not the best level of evidence according to the reference scale were categorised as requires updating.

Figure 3: Consideration of level of evidence



Determination of availability of new relevant studies – A "relevant study" in this case means a study that would best complement existing evidence for example, RCTs to complement evidence on treatment factors (systematic review of RCTs) or prospective cohort studies to complement the evidence on non-treatment factors (systematic review of prospective cohort studies). For potential prognostic factors with the best level of evidence, the availability of new relevant studies was assessed by conducting a scoping search on PUBMED and EMBASE from the end date of the search coverage of the systematic review to 2012 (the Boolean operator "AND" was used to combine the terms describing the potential prognostic factor and PTS). Where new relevant studies were identified, the evidence on the factor was put down as requires updating, otherwise, the evidence on the factor was categorised as does not require an update.

Figure 4: Assess for availability of relevant studies

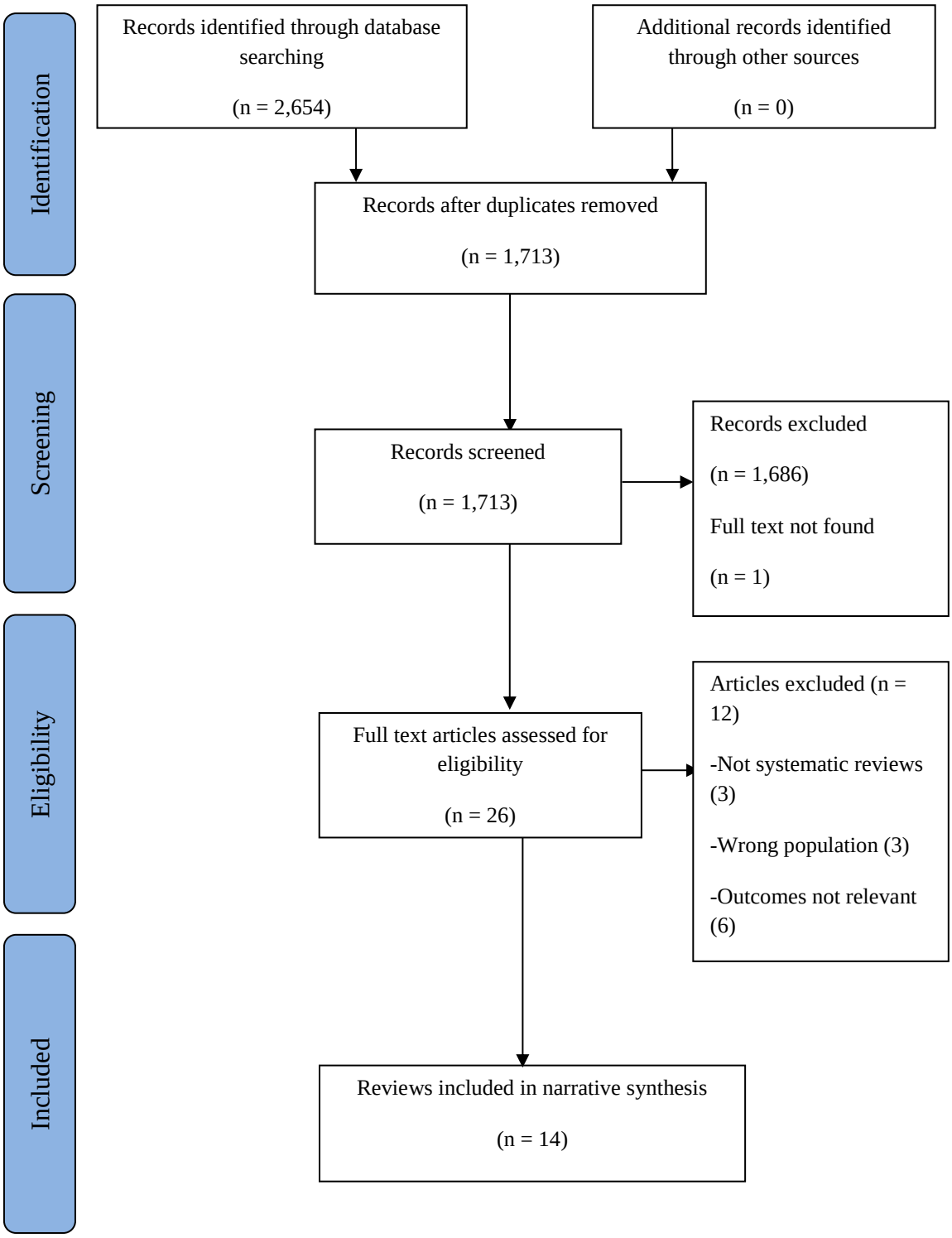


2.5 Results

One thousand seven hundred and thirteen unique records were identified by the search. Screening based on titles and abstracts identified 27 records that were potentially relevant to the review. The full texts of 26 articles were obtained and assessed for eligibility based on the review selection criteria. The full text of one record[97] was not found despite repeated attempts to contact the corresponding author. Fourteen systematic reviews were included in this review. Reasons for exclusion of articles include; not a systematic review (n=3),[98-100] irrelevant outcome (n=6)[101-104,105] and wrong target population (n=3).[106-108] Excluded articles and reason for exclusion are listed in Appendix 2, Section 2.3.

Figure 5 is the PRISMA flow diagram illustrating a summary of the search and review selection;

Figure 5: PRISMA flow diagram of systematic review screening and selection



2.5.1 Characteristics of included systematic reviews

Fourteen systematic reviews met the inclusion criteria for this systematic review. The aims of included systematic reviews were mainly to evaluate the efficacy of DVT treatments. The publication years of identified reviews ranged from 1998 up to the year 2012.

No systematic review of prognostic model studies was identified. The systematic reviews included RCTs and or observational studies.

Reviews included patients with acute or past DVT of the limb who had been followed up for a period ranging between two months and 12 years. All reviews reported that DVT was objectively confirmed. Twelve out of 14 reviews reported that this was done by one or more of the following methods; venography, Doppler ultrasonography vascular nuclear magnetic imaging, nuclide scanning, or impedance plethysmography, while six systematic reviews did not report the diagnostic tests used for DVT in the primary studies they included in their systematic review.[59,109-113] Due to the lack of a reference standard PTS diagnostic method, it was not unexpected that systematic reviews reported a wide range of PTS diagnostic methods across primary studies. Chapter 4 has been dedicated to the detailed description of PTS diagnostic methods reported by systematic reviews identified in this systematic review.

The reviews provided information on the association between subsequent development of PTS after DVT of the lower limb and the following factors; anticoagulation,[39] systemic thrombolysis,[59,109,114,115] loco-regional thrombolysis,[109] any thrombolysis (systemic and loco-regional thrombolysis),[59] catheter directed thrombolysis,[38,109,110]

compression therapy,[110,111,116-118] inferior vena cava filters,[112] thrombectomy,[38,113] and physical activity.[111,119]

Table 2: Summary characteristics of identified systematic reviews

Authors	Relevant objective as specified in the systematic review	Years covered by search strategy	Inclusion criteria (study design and participants)	Main factors assessed	Design of studies that met the inclusion criteria of the systematic review Number of patients assessed for PTS in systematic review	Additional treatment (if any)
Alesh 2007[109]	To evaluate the effectiveness of CDT compared to systemic and loco-regional thrombolysis in DVT patients	1966 –2006	*Design*: Prospective studies *Participants of included studies*: Patients with active DVT (Confirmed by venography or Doppler ultrasonography)	CDT (t-PA, UK) Loco-regional thrombolysis (t-PA, UK) Systemic thrombolysis (SK, UK)	3 RCT 3 Observational 469 patients	Some patients receiving CDT were co-treated with angioplasty, thrombectomy, stent, systemic heparin
Casey 2012[38]	To compare the efficacy of three treatments for acute ilio-femoral DVT: systemic anticoagulation, surgical thrombectomy, and CDT	Unspecified start date –2012	*Design:* Clinical trials cohort studies *Participants of included studies:* Patients with acute ilio-femoral DVT	CDT (rt-PA, UK) Surgical thrombectomy	10 RCT 769 patients	Some patients receiving thrombectomy had additional treatment with compression stockings for 2-6mth (1 RCT), balloon venoplasty (1 RCT), AV fistula (3 RCTs) Some patients receiving CDT had additional angioplasty and stenting
Fox and Kahn 2008[112]	To assess the frequency of signs and symptoms of PTS in relation to IVC filter placement	1966 –2007	*Designs:* All study designs *Participants:* Patients with DVT	IVC filter	1 RCT 7 Observational 1,103 patients	Co-treatment with CS, long anticoagulation in some patients

Authors	Relevant objective as specified in the systematic review	Years covered by search strategy	Inclusion criteria (study design and participants)	Main factors assessed	Design of studies that met the inclusion criteria of the systematic review Number of patients assessed for PTS in systematic review	Additional treatment (if any)
Giannoukas et al 2006[111]	To assess whether compression with or without early ambulation after proximal DVT reduces the risk of PTS	1966 – 2005	*Design*: RCT *Participants*: Patients with DVT	Compression stockings, Physical activity	4 RCT 493 patients	None reported
Hull et al 2011[39]	To examine whether LMWH rather than oral anti coagulation reduced development of PTS after DVT	Unspecified start date –2009	*Design*: Prospective studies *Participants*: Patients with DVT Follow up for ≥ 3months	Anticoagulation (Heparin, Warfarin)	3 RCT 682 patients	None reported
Kahn et al 2008[119]	To assess the risks of physical activity in patients with acute or previous DVT of the leg	Unspecified start date –2007	*Design*: RCT, prospective cohort studies *Participants:* Patients with acute or previous DVT of the leg	Physical activity	1 RCT 37 patients	None reported
Kakkos et al 2006[116]	To investigate the effect of GCS after DVT	1954 –2006	*Design*: RCT *Participants*: Objectively confirmed DVT on Venography or Ultrasonography	Compression stockings	3 RCT 421 patients	None reported

Authors	Relevant objective as specified in the systematic review	Years covered by search strategy	Inclusion criteria (study design and participants)	Main factors assessed	Design of studies that met the inclusion criteria of the systematic review Number of patients assessed for PTS in systematic review	Additional treatment (if any)
Kolbach et al 2003[117]	To determine the relative effectiveness of, and the rate of complications using non-pharmaceutical interventions in people with DVT in the prevention of PTS	1966 –2005	*Design*: RCT or CCT *Participants*: Patients with objectively confirmed PTS Ultrasound, Venography, impedance Plethysmography	Compression stockings	3 RCT 421 patients	None reported
Luo et al 2006[113]	To evaluate the effectiveness and safety of surgical thrombectomy for acute deep venous thrombosis of lower extremities	1966 – 2006	*Design*: RCT *Participants*: Patients with confirmed DVT	Surgical thrombectomy	3 RCT 127 patients	None reported
Musani et al 2010[118]	To determine the effectiveness of venous compression stockings or compression bandages on the reduction of PTS in patients with DVT	Unspecified start date –2009	*Design*: RCTs *Participants*: Patients with objectively confirmed PTS	Compression stockings	5 RCTs 624 patients	None reported
Ng et al 1998[114]	To compare efficacy and safety of SK (followed by heparin) and heparin alone in DVT	1966 –1996	*Design*: RCTs *Participants*: Patients DVT documented on Venography. Follow up ≥6months	Thrombolysis (SK) Heparin	4 RCTs 110 patients	None reported
Segal et al 2007[110]	To review evidence on the efficacy of interventions for treatment of DVT and PE	1950 –2006	*Design*: RCT, systematic review, observational studies *Participants:* Patients with confirmed DVT	CDT Compression stockings	5 Observational 3 RCTs 421 for Compression stockings. Number not clear for CDT	None reported

Authors	Relevant objective as specified in the systematic review	Years covered by search strategy	Inclusion criteria (study design and participants)	Main factors assessed	Design of studies that met the inclusion criteria of the systematic review Number of patients assessed for PTS in systematic review	Additional treatment (if any)
Watson et al 2004[59]	To assess the effects of thrombolysis versus anticoagulation	1969 – 2004	*Design*: RCTs *Participants*: Patients with acute DVT confirmed via venography, duplex ultrasound	Loco-regional thrombolysis (SK, t-PA, UK) Systemic thrombolysis (SK, t-PA, rt-PA)	2 RCTs 101 patients	CS and bed rest were co treatments
Wells and Forster 2001[115]	To synthesize the published literature regarding the use of three thrombolytic agents SK, UK and rt-PA for DVT treatment	1966 –2000	*Design*: RCTs *Participants:* Patients with DVT	Systemic thrombolysis (SK, t-PA, rt-PA)	6 RCTs 222 patients	OACs, UFH were co-treatments

Key:

CB – Compression bandages

CS – Compression stockings

GCS – Graduated compression stockings

RCT – Randomised controlled trial

SK – Streptokinase

PE – Pulmonary embolism

UK - Urokinase

CDT – Catheter directed thrombolytic therapy

DVT – Deep vein thrombosis

OACs – Oral anticoagulants

rt-PA – Recombinant tissue plasminogen activator

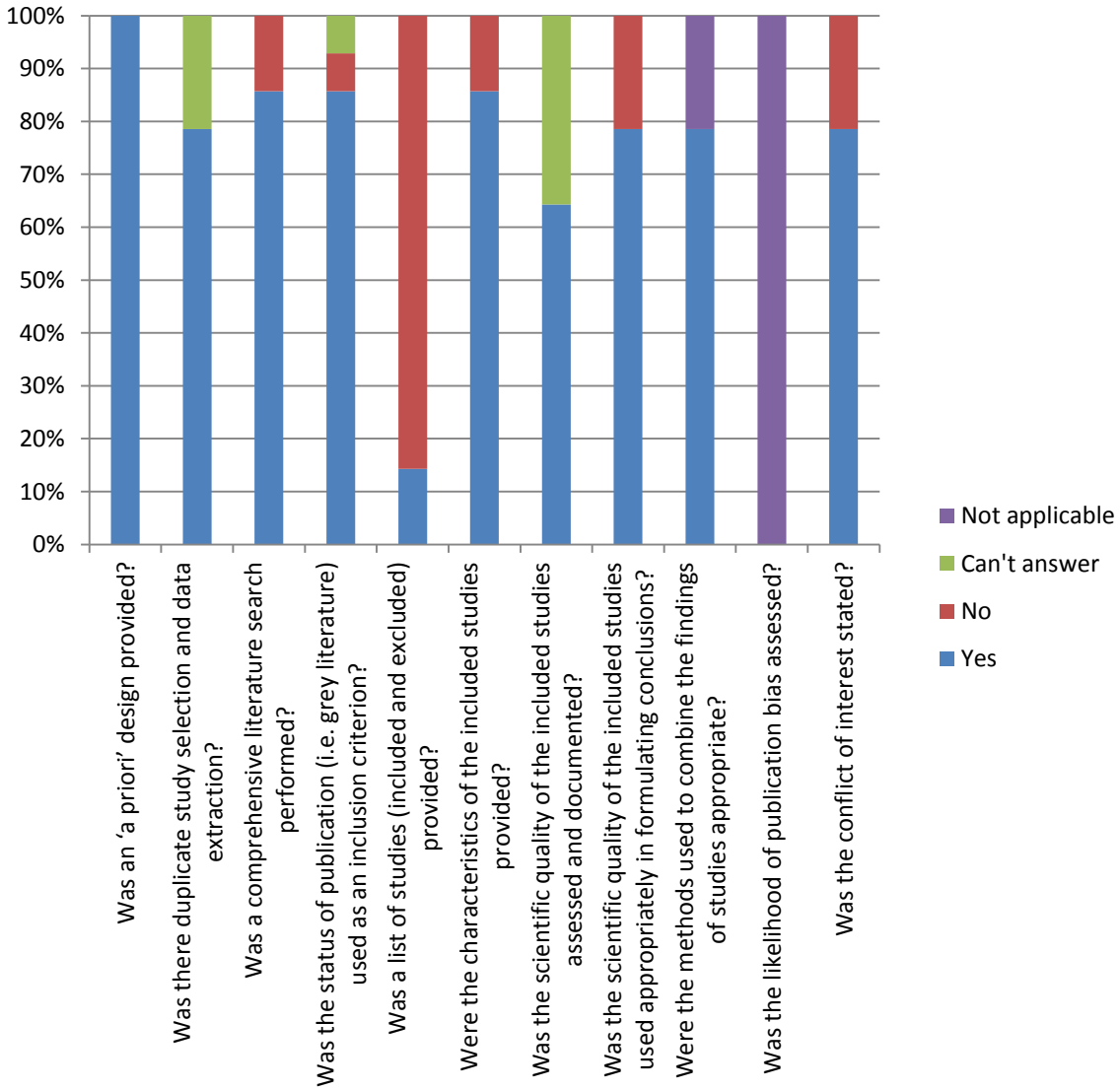
t-PA – Tissue plasminogen activator

UFH – Unfractionated Heparin

2.5.2 Quality assessment

The quality assessment of identified systematic reviews using the AMSTAR tool is summarised in Appendix 2, Section 2.5. See Figure 6 below for proportion of systematic reviews that fulfilled each criterion on the AMSTAR tool.

Figure 6: The percentage of quality criteria fulfilled by systematic reviews



It was noted that the systematic review that fulfilled the least criteria on the AMSTAR tool was the oldest.[114] Newer systematic reviews fulfilling more criteria might be explained by the availability of and encouragement of the use of guidelines for the conduction of research such as the Cochrane hand book of systematic reviews[92] and PRISMA checklist.[91] Two out of 14 systematic reviews were rated as being of poor quality.[111,114]

All systematic reviews presented aims of their reviews as well as a search strategy and the inclusion criteria to be met by primary studies. Only two out of 14 systematic reviews did not conduct a comprehensive search as defined by the AMSTAR tool – with only one electronic database searched in both reviews[114,118] However areas of grey literature were searched for relevant studies in these reviews.

In 13 systematic reviews it was mentioned whether only published studies were searched or whether other areas of grey literature were searched. In the remaining systematic review,[113] it was not clear if unpublished data and or published data were sought or whether publication status was an inclusion criterion.

A list of excluded studies was presented in only two systematic reviews (both Cochrane reviews).[59,117] A list of included studies and study characteristics was provided in all but one systematic review.[110]

In most reviews it was stated that there were two reviewers that independently conducted the screening and selection stage as well as data extraction. This was however not clear in three systematic reviews.[109,114,115]

In most reviews the quality of primary studies was assessed. Tools used for this purpose varied from systematic review to systematic review. These tools included the Cochrane

collaboration tool for assessment of risk[120] used in one systematic review;[117] grading of recommendations assessment development and evaluation (GRADE) tool[121] in one systematic review;[38] guidelines and recommendations from Strength of Recommendation Taxonomy (SORT)[122] in one systematic review;[110] guidelines for the evaluation of articles on therapy and on prognosis[123] in one systematic review;[119] two quality assessment tools (the Jadad score and the Schultz score[124,125]) were used in one systematic review.[59] It was not clear from five systematic reviews whether quality assessment of included primary studies was done or not.[109,111,112,114,116] In another four systematic reviews,[113,118,39,115] it was not stated that a quality assessment tool was used though it was mentioned that quality assessment was done. In these reviews, quality assessment of primary studies was supported by the reporting of activities such as allocation concealment, blinding of outcome evaluation, loss to follow up and assessment for biases such as selection bias and performance bias. The possible effects of the quality of primary studies on overall results were mentioned in all included reviews.

In all 14 systematic reviews analysis was conducted appropriately, that is, data was only combined where it was appropriate to do so (conducting a narrative summary or a quantitative summary of effects where suitable). Measures of heterogeneity were provided when a meta-analysis was carried out[38,39,59,111,113-118] except in one review.[115] In one review[59] it was reported that a sensitivity analysis (based on quality of studies – higher quality studies versus all studies) was carried out to explore heterogeneity in the meta-analysis done. None of the reviews reported that a sub-group analysis was carried.

An assessment for publication bias was not done in the only systematic review that included 10 primary studies which they summarised in a meta-analysis. The other 13

reviews included less than ten primary studies. It is usually recommended to carry out an assessment for the possible presence of publication bias if a meta-analysis includes ten or more primary studies.[126,127]

In 11 systematic reviews, sources of support and or potential sources of conflict were stated while in three systematic reviews this was not stated.[111,113,116]

In summary, the least fulfilled criteria by systematic reviews were the assessment of publication bias and the provision of a list of included and excluded studies (see Appendix 2 Section 2.5)

2.5.3 Prognostic factors

Only treatment potential prognostic factors (i.e. the treatment employed after DVT) were identified from included reviews. No review eligible to be included in this systematic review of systematic reviews had assessed non-treatment potential prognostic factors for developing PTS after DVT of the lower limb. One review[97] that had reported on possible non treatment factors was identified but it could not be ascertained if it was eligible for inclusion. This review evaluated the role of location of DVT and extent of DVT on the incidence of PTS. It was presented in a conference however full information on this review could not be found despite repeated attempts to contact the corresponding author.

Results on potential prognostic factors identified from included reviews are detailed below.

2.5.3.1 Pharmacological factors

Four of the identified potential prognostic factors were pharmacological factors. They are, anticoagulation with low molecular weight heparin, systemic thrombolysis, loco-regional thrombolysis and catheter directed thrombolysis.

2.5.3.1.1 Anticoagulation

The association between anticoagulation and incidence of PTS after a DVT of the lower limb was assessed in one systematic review (see Table 3).[39]

The systematic review compared low molecular weight heparin for three to six months with standard anticoagulation therapy (an initial period of low molecular weight heparin or unfractionated heparin (approximately three days), followed by vitamin K antagonists (for three to six months).

This systematic review was published in 2011 and was of good quality as it fulfilled most of the AMSTAR criteria.

The search strategy of the systematic review covered up to 2009.

Three RCTS with follow up duration between one and five years were included in the systematic review.

In the systematic review, a narrative analysis demonstrated that anticoagulation with low molecular weight heparin was associated with a lower incidence of PTS than standard therapy. Effect size and statistical significance of this finding was only reported in one of the included primary studies, odds ratio 0.77, 95% CI (0.67 to 0.90) p-0.001. In a second study, only the statistical significance of the finding was reported

(p-0.43). In the third study, it was reported that 60.7% in the low molecular weight heparin group developed PTS compared to 70.5% in the standard anticoagulation group. Results from the three individual primary studies show the same trend though the difference where reported was not always statistically significant.

There was no report on additional DVT treatments that could potentially confound the findings of primary studies on the association between anticoagulation with low molecular weight heparin and the incidence of PTS. For example use of compression therapy.

Overall there was a lower risk of PTS signs and symptoms with the use of low molecular weight heparin compared to standard anticoagulation in all three RCTS. The result of this systematic review suggests that anticoagulation using low molecular weight heparin is a favourable prognostic factor and may reduce the development of PTS after an episode of DVT compared to standard anticoagulation.

Table 3: Summary of systematic reviews on anticoagulation and development of PTS

	Hull et al 2011[39]
Designs of included studies that assessed PTS/PTS signs and symptoms	3 RCT
Total population(n) assessed for risk of PTS/PTS signs and symptoms	682
Follow up duration of included primary studies (range)	3 months – 5 years
Potential prognostic factor assessed	Anticoagulation (LMWH versus standard anticoagulation therapy)
Outcomes measured	Incidence of PTS
PTS diagnostic method	Villalta scale, self-reported symptoms (questionnaire), clinical assessments
Evaluation of outcome (blinding)	There was blinding of evaluation of outcomes in all studies
Method of analysis	Narrative analysis
Findings	Overall there was a lower risk of PTS signs and symptoms with the use of LMWH compared to oral anticoagulation in all 3 RCTS. Effect size and statistical significance of this finding was only reported in one of the included primary studies OR 0.77 (95% CI 0.67-0.90) p-0.001. In a second study only the statistical significance of the finding was reported (p-0.43). In a third study 60.7% of patients in the LMWH group developed PTS compared to 70.5% in the anticoagulation group

Key: CEAP – Clinical etiologic anatomic and pathophysiologic CI – Confidence interval

LMWH – Low molecular weight heparin OR – Odds ratio PTS – Post-thrombotic syndrome

RCT – Randomised controlled trial

As the only systematic review that was identified under anticoagulation[39] was of good methodological quality, the searches were up to 2009, it included RCTs and, through a scoping search (2009 to 2012) no new RCTs were identified, therefore there was no need to update the evidence on anticoagulation.

2.5.3.1.2 Systemic thrombolysis

The association between systematic thrombolysis and incidence of PTS after a DVT of the lower was assessed in four systematic reviews (see Table 4).[114,115,59,109]

In all four systematic reviews, systemic thrombolysis using various agents was compared to standard anticoagulation in relation to subsequent development of PTS. In two reviews[114,115] the agent used for thrombolysis was streptokinase only. In the other reviews[59,109] streptokinase or urokinase was used for thrombolysis in one[109] while streptokinase, urokinase or tissue plasminogen activator was used in another review.[59] In one of these reviews,[59] systemic thrombolysis and loco-regional thrombolysis were assessed for an association with PTS but were not reported separately.

The systematic reviews were published in 1998,[114] 2001,[115] 2004[59] and 2006.[109]

Three out of four systematic reviews[59,109,115] fulfilled most of the AMSTAR quality tool criteria and were rated as being of good quality while the remaining one was of poor quality. The years covered by the search strategies of the systematic reviews collectively spanned from 1966 to 2006.

Three of the systematic reviews reported follow up periods greater than three months while the fourth systematic review[115] reported a follow up of less than this duration (two months) in one of the included primary studies. This did not appear to have had an

impact on the findings from that systematic review, because the findings were similar to those of the other systematic reviews.[59,109,114]

Three of the systematic reviews results were combined in a meta-analysis.[114,59,115] Of these systematic reviews, measures of heterogeneity was presented in two[114,59] while in the third systematic review, no measure of heterogeneity was presented.[115]

Findings from all four systematic reviews regardless of their quality showed a lower incidence of PTS in patients on systemic thrombolysis when compared to the control group on anticoagulation. In three of the systematic reviews,[59,114,115] results were summarised in a meta-analysis which showed statistically significant findings; thrombolysis with streptokinase with odds ratio 0.46, 95% (CI 0.21 to 0.99), X^2 8.03;[114] thrombolysis with streptokinase with relative risk 0.66, 99% (CI 0.47 to 0.97), I^2 0.0%;[59] and thrombolysis with streptokinase, urokinase or tissue plasminogen activator with odds ratio 0.3, 95% (CI 0.2 to 0.7) (no measure of heterogeneity reported).[115] In one review data on loco-regional and systemic thrombolysis were combined and separate details for each were not available.[59] This review is reported here only.

Reviews did not report on additional DVT treatments that could potentially confound the findings of primary studies on the association between systemic thrombolysis and the incidence of PTS.

This evidence suggests that systemic thrombolysis regardless of agent used for thrombolysis is a favourable prognostic factor for DVT and may reduce the development of PTS after an episode of DVT. The clot burden of included patients was not described in all the systematic reviews. However, it is important to note that

systemic thrombolysis is used more in patients with a large clot burden.[128] Therefore these results may not be generalisable to the general DVT population.

Table 4: Summary of systematic reviews on systemic thrombolysis and development of PTS

	Alesh et al 2007[109]	**Ng et al 1998[114]**	**Watson et al 2004[59]**	**Wells and Forster 2001[115]**
Designs of included studies that assessed PTS/PTS signs and symptoms	2 RCT	4 RCT	2 RCT	6 RCTs
Population(n) assessed for risk of PTS/PTS signs and symptoms	230	110	101	222
Follow up period of included primary studies (range)	1-6 years	0.5-5.2 years	1-6 years	0.17-12 years
Potential prognostic factor assessed	Systemic thrombolysis with streptokinase or urokinase	Systemic thrombolysis with streptokinase	Any thrombolysis (systemic and loco-regional) with streptokinase or urokinase or t-PA	Systemic thrombolysis with streptokinase
Outcomes measured	Incidence of PTS	Incidence of PTS	Incidence of PTS	Incidence of PTS
PTS diagnostic methods	Not reported	Clinical assessment and Venography	Clinical assessment	Clinical scales used (not named)
Evaluation of outcome (blinding)	Not reported	Not reported	There was blinding in all included studies	Not reported

	Alesh et al 2007[109]	**Ng et al 1998[114]**	**Watson et al 2004[59]**	**Wells and Forster 2001[115]**
Method of analysis	Narrative analysis	Meta-analysis	Meta-analysis	Meta-analysis
Findings	24% of patients treated with systemic thrombolysis using streptokinase developed PTS compared to 50% of patients in the anticoagulation group. 67% of patients treated with systemic thrombolysis using urokinase developed PTS compared to 89% of patients in the anticoagulation group.	24% of patients treated with systemic thrombolysis using streptokinase developed PTS compared to 67% of patients in the anticoagulation group OR 0.46 (95% CI 0.21-0.99) X^2=8.03, df=3, p<0.05	Incidence of PTS was lower in patients on any systemic thrombolysis (47.5%) than in patients in the anticoagulation group (65%) RR 0.66 (99% CI 0.47-0.97) I^2=0%	42.5% of patients treated with systemic thrombolysis using streptokinase developed PTS compared to 69.6% of patients in the anticoagulation group. OR 0.3 (95% CI 0.2-0.7) (I^2 or X^2 not reported)

Key: CI – Confidence interval df – Degree of freedom I^2 – Measure of heterogeneity OR – Odds ratio PTS – Post-thrombotic syndrome RCT – Randomised controlled trial RR – Relative risk

Three out of four systematic reviews that assessed systemic thrombolysis were of fair to good methodological quality.[59,109,115] The search strategy across these reviews was up to 2004 and the reviews included RCTs. However, through a scoping search (from 2004 to 2012) no new RCTs were identified, therefore there was no need to update the evidence on the systemic thrombolysis.

2.5.3.1.3 Loco-regional thrombolysis

The association between loco-regional thrombolysis and incidence of PTS after a DVT of the lower was assessed and reported separately in only one systematic review[109] (see Table 5). A second systematic review by Watson et al[59] that assessed loco-regional thrombolysis in relation with PTS was identified, however the review did not separate findings of systemic thrombolysis from loco-regional thrombolysis in relation to PTS. This systematic review has been described in more detail under systemic thrombolysis above.

The systematic review that reported findings on the association between loco-regional thrombolysis and PTS compared standard anticoagulation therapy with loco-regional thrombolysis (using urokinase or tissue plasminogen activator) in relation to the incidence of PTS.

It was published in 2007. The review was of fair quality on the AMSTAR tool criteria.

The review's search strategy covered the time period between 1966 and 2006.

Follow up period of included primary studies ranged from one to six years.

The systematic review did not report whether there was any additional treatment that could potentially confound results of the association between loco-regional thrombolysis and PTS.

In this systematic review, findings from two RCTs were reported in a narrative analysis. There appeared to be a lower incidence of PTS in patients treated with loco-regional thrombolysis compared to patients treated with anticoagulation alone. This evidence suggests that loco-regional thrombolysis may be a favourable prognostic factor for DVT and may reduce the development of PTS after an episode of DVT.

Table 5: Summary of systematic review on loco-regional thrombolysis and development of PTS

	Alesh et al 2007[109]
Designs of included studies that assessed PTS/PTS signs and symptoms	2 RCT
Population(n) assessed for risk of PTS/PTS signs and symptoms	280
Follow up duration of included primary studies (range)	1-6 years
Potential prognostic factor assessed	Loco-regional thrombolysis with full dose urokinase or t-PA
Outcomes measured	Incidence of PTS
PTS diagnostic method	Not reported
Evaluation of outcome (blinding)	Not reported
Method of analysis	Narrative analysis
Findings	67% of patients treated with urokinase developed PTS compared to 85% of patients in the anticoagulation group OR 0.34 (95% CI 0.15 – 0.80) 76% of patients treated with t-PA developed PTS compared to 87% of patients in the anticoagulation group [OR 0.66 (95% CI 0.32 – 1.36)][c]

Key: CI – Confidence interval [c] – Calculated (not reported) OR – Odds Ratio

PTS – Post-thrombotic syndrome RCT – Randomised controlled trial t-PA – Tissue plasminogen activator

The quality of the only systematic review identified here[109] was fair. The search strategy of this review covered up to 2006. However, the level of evidence on this factor was not the best (see Appendix 2, Section 2.6.1 for levels of evidence). Therefore there was a need to update the evidence on loco-regional thrombolysis.

2.5.3.1.4 Catheter directed thrombolysis

The association between catheter directed thrombolysis and the incidence of PTS after a DVT of the lower was assessed in three systematic reviews (see Table 6).[38,109,110]

Two of the systematic reviews[109,110] evaluated the incidence of PTS after use of catheter directed thrombolysis to treat DVT. The third and more recent systematic review compared catheter directed thrombolysis with standard therapy (anticoagulation). Urokinase, recombinant tissue plasminogen activator or tissue plasminogen activators were the agents used for catheter directed thrombolysis by primary studies in all three systematic reviews.

They were published in 2007[109,110] and 2012.[38] The three reviews fulfilled most of the AMSTAR quality tool criteria. Two were of good quality while one was of fair quality.[109]

The search period covered by the systematic reviews was up to 2006 for two reviews[109,110] and up to 2012 for the third review.[38]

Follow up of primary studies included in the three systematic reviews was up to seven and half years.

Conclusions based on narrative analysis including observational studies were made from two older systematic reviews,[109,110] while in the third and more recent systematic

review[38] conclusions were based on a meta-analysis of two RCTs All three systematic reviews demonstrated that catheter directed thrombolysis was associated with a lower risk of PTS. This association was reported to be statistically significant by the systematic review that conducted a meta-analysis, relative risk 0.18, 95% CI (0.05 to 0.62) with I^2 of 64%.[38] The other two systematic reviews which involved only observational studies did not report effect sizes or strengths of association.

There were reports of additional treatment with angioplasty, stent and thrombectomy in some primary studies included in two systematic reviews.[38,109] No additional treatment for DVT that could confound findings on the association between catheter directed thrombolysis and the PTS was reported by the third systematic review.

This evidence suggests that catheter directed thrombolysis may be a favourable prognostic factor for DVT and may reduce the development of PTS after an episode of DVT. However, catheter directed thrombolysis is used in clinical practice for extensive clot burden,[66] yet the clot burden of patients included in the reviews was not well described. Therefore, these findings may not be generalisable to the overall DVT population.

Table 6: Summary of systematic reviews on catheter directed thrombolysis and development of PTS

	Alesh et al 2007[109]	**Casey et al 2012[38]**	**Segal et al 2007[110]**
Designs of included studies that assessed PTS/PTS signs and symptoms	3 Observational	2 RCT	5 Observational
Population(n) assessed for risk of PTS/PTS signs and symptoms	62	158	Patients with DVT Total number of population not clear
Follow up duration of included primary studies (range)	1-3 years	0.75-7.5 years	Followed up duration not clear but not less than 3 months
Potential prognostic factor assessed	CDT with full dose t-PA or urokinase (additional treatment with stent angioplasty, or thrombectomy)	CDT (any agent)	CDT (any agent)
Outcomes measured	Incidence of PTS	Incidence of PTS	Incidence of PTS
PTS diagnostic methods	Not reported	Venography, duplex ultrasound	Not reported
Evaluation of outcome (blinding)	Not applicable	Not reported	Not Applicable
Method of analysis	Narrative analysis	Meta-analysis	Narrative analysis

	Alesh et al 2007[109]	**Casey et al 2012[38]**	**Segal et al 2007[110]**
Findings	10% of patients treated with CDT-urokinase developed PTS 30.8% of patients treated with CDT-t-PA developed PTS (CDT was not compared to another DVT treatment)	Across studies, risk of PTS was lower in patients treated with CDT (11.5%) than in patients treated with anticoagulation (72%). RR 0.18 (95%CI 0.05-0.62). I^2=64%	Reports that result of primary studies suggest that patients treated with CDT had a lower incidence of PTS when compared to patients without CDT. No statistics reported.

Key: CDT – Catheter directed thrombolysis CI – Confidence interval RCT – Randomised controlled trial

RR – Relative risk PTS – Post-thrombotic syndrome t-PA – Tissue plasminogen activator

All three systematic reviews that assessed catheter directed thrombolysis were of fair to good methodological quality.[38,109,110] The search strategy across these reviews covered up to 2012. Therefore, there was no need to update the evidence on catheter directed thrombolysis.

2.5.3.2 Mechanical factors

Two mechanical factors were identified. These were compression stockings and inferior vena cava filters. Findings on both factors are elaborated on below.

2.5.3.2.1 Compression stockings

The association between compression stockings and the incidence of PTS after a DVT of the lower was assessed in five systematic reviews (see Table 7).[110,111,116-118]

They all had the same aim which was to evaluate the incidence of PTS after use of compression therapy for the management of DVT compared to no compression therapy. Different forms of compression therapy exists as explained previously in the background, however all five reviews explored the association between PTS and compression stockings only, no identified review looked at other types of compression. The compression pressure of stockings reported by reviews ranged from 20mmHg to 40mmHg. One systematic review did not report on compression pressure.[110] Time interval between diagnosis of DVT and use of compression stockings also varied from immediately after diagnosis to one year afterwards.

The systematic reviews were published in 2003,[117] 2006,[111,116] 2007,[110] and 2010.[118] The search periods covered by the systematic reviews was from 1950 to 2009.

One out of the four systematic reviews was of poor quality[111] while the remaining four were of good quality and fulfilled most of the AMSTAR tool quality criteria. One of the systematic reviews conducted a narrative synthesis,[110] the remaining four systematic reviews conducted a meta-analysis. All four meta-analysis assessed and reported on the statistical heterogeneity of included primary studies.

Standard anticoagulation used in the treatment of DVT was used in all primary studies of the systematic review. There was no reporting of any other additional therapy with the use of compression stockings by any of the systematic reviews. Only one[116] of the systematic reviews reported on compliance of patients with the compression stockings.

Four systematic reviews[111,116-118] conducted a meta-analysis and all found that compression stockings reduced the incidence of PTS compared to when no compression therapy was used. This association was found to be a significant one by all four meta-analysis; OR 0.35, 95% CI (0.24 to 0.52) I^2 53.1%;[111] RR 0.47, 95% CI (0.36 to 0.61) I^2 0%;[116] OR 0.31, 95% (0.20 to 0.48) I^2 0%;[117] RR 0.54, 95% CI (0.44 to 0.67) I^2 not reported.[118] Findings from the systematic review that conducted a narrative review also demonstrated that compression stockings reduced incidence of PTS.

Three of the systematic reviews had identical primary studies,[110,116,117] and therefore identical findings. The other two systematic reviews published in 2006[111] and 2010[118] had included in their review one more and three more RCTs respectively.

Overall, regardless of difference in quality, majority of the evidence from the systematic reviews demonstrated that compression stockings were associated with a lower incidence of PTS. This evidence suggests that compression stocking is a favourable prognostic factor for reducing incidence of PTS after an episode of DVT.

Table 7: Summary of systematic review on compression therapy and development of PTS

	Giannoukas et al 2006[111]	**Kakkos et al 2006**[116]	**Kolbach et al 2003**[117]	**Musani et al 2010**[118]	**Segal et al 2007**[110]
Designs of included studies that assessed PTS/PTS signs and symptoms	4 RCT	3 RCT	3 RCT	5 RCT	3 RCT
Population(n) assessed for risk of PTS/PTS signs and symptoms	493	421	421	662	421
Follow up duration of included primary studies(range)	0.25 – 5 years	3 – 4.2 years	Not clear	1.4 – 5 years	Almost 5 years

	Giannoukas et al 2006[111]	**Kakkos et al 2006**[116]	**Kolbach et al 2003**[117]	**Musani et al 2010**[118]	**Segal et al 2007**[110]
Potential prognostic factor assessed	Compression stockings (pressure varied between 20-40mmHg, type of compression stockings varied-below knee and thigh, time from diagnosis of DVT to use of compression varied-immediate, 9 days, and 2-3 weeks).	Compression stockings (pressure varied between 20-40mmHg, type of graduated compression stockings varied-below knee and thigh, time from diagnosis of DVT to use of compression varied-immediate, 5-10 days, 7 months, 12 months).	Compression stockings (pressure varied between 20-40mmHg, location varied-below knee and thigh, time from diagnosis of DVT to use of compression varied-immediate, 9 days ,and 2-3 weeks).	Compression stockings (pressure varied between 20-40mmHg; location varied-below knee(91%), thigh length (17%), thigh bandages (4%);time from diagnosis of DVT to use of compression varied-immediate, 9 days, 5-10 days, and 2-3 weeks, 6 months, 1 year).	Compression stockings (pressure not defined)
Compliance	Not reported	93% from 2 RCTs	Not reported	Not reported	Not reported
Relevant outcome measured	Incidence of PTS	Incidence of PTS	Incidence of PTS	Incidence of PTS	Incidence of PTS
PTS diagnostic methods	Not reported	Villalta scale Presence of chronic pain and leg swelling 6months after DVT	Standardised scale (Not specific)	Villalta scale CEAP classification Presence of chronic pain and leg swelling 6months after DVT	Not reported
Evaluation of outcome (blinding)	Not reported	Not reported	Overall adequate blinding was reported	Not reported	Overall inadequate blinding was done
Method of analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Narrative synthesis

	Giannoukas et al 2006[111]	**Kakkos et al 2006**[116]	**Kolbach et al 2003**[117]	**Musani et al 2010**[118]	**Segal et al 2007**[110]
Findings	24% of patients treated with compression stockings developed PTS compared to 46% of patients who did not receive compression therapy. OR 0.35 (95% CI 0.24-0.52) I^2=53.1%.	Patients treated with compression stockings had a lower incidence of PTS (25.2%) than patients who did not receive compression stockings (54%). RR 0.47 (95% CI 0.36-0.61). NNT was 4 (95% CI 2.7-5.0). I^2=0%	20% of patients treated with compression stockings developed PTS compared to 43.1% of patients who did not receive compression therapy. OR 0.31 (95%CI 0.20-0.48). I^2=0%	Patients treated with compression stockings had a lower incidence of PTS (26.3%) than in patients who did not receive compression therapy (46.3%). RR 0.54 (95% CI 0.44-0.67) p<0.001. Heterogeneity p=0.301 (I^2 not reported)	Patients treated with compression stockings had a lower incidence of PTS when compared to patients who did not receive compression stockings. Hazard ratio 0.49 (95% CI 0.29-0.84). One RCT did not demonstrate any benefit or harm with compression stockings after 1 year follow up (statistic not reported).

Key: CI – Confidence Interval I^2 – Measure of heterogeneity NNT – Numbers needed to treat OR – Odds ratio

PTS – Post-thrombotic syndrome RCT – Randomised controlled trial RR – Relative risk

CEAP – Clinical etiologic anatomic and pathophysiologic classification

There were four systematic reviews of good methodological quality that had assessed compression stockings.[110,116-118] The search strategy across these reviews was up to 2009 and the reviews included RCTs. However, through a scoping search (from 2009 to 2012) no new RCTs were identified, therefore there was no need to update the evidence on compression stockings.

2.5.3.2.2 Inferior vena cava filters

The association between inferior vena cava filters and incidence of PTS after a DVT of the lower was assessed in one systematic review (see Table 8).[112]

The systematic review compared the incidence of PTS in DVT patients who had inferior vena cava filters (for secondary prevention of pulmonary embolism after an initial episode of DVT) and incidence of PTS in patients who did not have inferior vena cava filters.

It was published in 2008. This systematic review was of good quality and fulfilled most of the AMSTAR criteria except not assessing publication bias and providing a list of excluded studies.

The search period covered was 1966 to 2007. Seven observational studies and one RCT were included in the systematic review, however, only the RCT met the inclusion criteria of this systematic review (population DVT of the lower limb as opposed to other included studies that did not have DVT patients differentiated from patients with pulmonary embolism as well as compared two groups of patients in relation to whether they developed PTS or not). The findings of this RCT were reported separately. Only the findings of the systematic review in relation to the relevant study are reported.

The RCT followed 400 patients for an eight year period. The result of the RCT study demonstrated a slightly higher incidence of PTS in patients treated with inferior vena cava filters for secondary prevention of pulmonary embolism than in patients who were not (59.4% versus 51.9%).

The RCT reported that all patients had additional treatment with anticoagulation therapy for at least three months and approximately 90 percent of patients in each of the study wore compression stockings throughout the follow up period.

Overall, this systematic review demonstrated that inferior vena cava filters may be associated with an increased incidence of PTS when it is used for secondary prevention of pulmonary embolism after a DVT of the lower limb. This evidence suggests that inferior vena cava filter may be an unfavourable prognostic factor. This finding is not surprising as patients who have inferior vena cava filters inserted are usually not suitable for anticoagulation therapy so that the clot remains without any active resorption causing ongoing symptoms and in some cases even propagate.[129]

Table 8: Summary of systematic review on inferior vena cava filter and development of PTS

	Fox and Kahn 2008[112]
Designs of included studies that assessed PTS/PTS signs and symptoms	1 RCT
Population(n) assessed for risk of PTS/PTS signs and symptoms	400
Follow up duration of included primary studies (range)	8 years
Potential prognostic factor assessed	IVC filter for secondary prevention of pulmonary embolism after DVT
Outcomes measured	Incidence of PTS
PTS diagnostic method	Clinical assessment
Evaluation of outcome (blinding)	Not reported
Method of analysis	Not applicable
Findings	59.5% developed PTS in the IVC filter group compared to 51.9% in the no IVC filter group after a follow up period of 8 years

Key**:** CI – Confidence interval IVC – Inferior vena cava PE – Pulmonary embolism

PTS – Post-thrombotic syndrome RCT – Randomised controlled trial

The only systematic review identified under this factor[112] was of fair methodological quality. The scope of the search strategy of this systematic review covered up to 2007, in addition the level of evidence was not the best (see Appendix 2, Section 2.6.1 for levels of evidence). Therefore there was a need to update the evidence on inferior vena cava filters.

2.5.3.3 Surgical factors

One surgical factor was identified from the systematic reviews – surgical thrombectomy. Findings on this factor's association with PTS are reported below.

2.5.3.3.1 Surgical thrombectomy

The association between surgical thrombectomy and the incidence of PTS after a DVT of the lower limb was assessed in two systematic reviews (see Table 9).[38,113]

Both systematic reviews compared surgical thrombectomy for the treatment of DVT to standard anticoagulation in relation to the incidence of PTS.

They were published in 2006[113] and 2012.[38] They were both of good quality. However, the most recent systematic review[38] was of better quality. It also included more primary studies (eight RCTs) than the older systematic review (three RCTs).

The search period covered by the reviews was from an unspecified date to 2006 for one review[113] and up to 2012 in the second review.[38] They both combined results in a meta-analysis.

The range of follow up period across primary studies was from six months to five years.

Overall, both systematic reviews demonstrated that surgical thrombectomy was associated with a lower incidence of PTS compared to patients on anticoagulation therapy alone, and this association was seen from as early as six months up to ten years of follow up. This association was found to be statistically significant when a meta-analysis was done, relative risk 0.67, 95% CI (0.52 to 0.87) I^2 0%[38] and odds ratio 0.18, 95% CI (0.06 to 0.60) I^2 53.5%.[113]

In both reviews, surgical thrombectomy was sometimes combined with an arteriovenous fistula, angiography or stent. One systematic review reported that some patients who had surgical thrombectomy also received heparin and coumarin (anticoagulation) as well as compression therapy for two to six months after surgical thrombectomy.[38] These additional treatments could potentially confound results of primary studies.

Overall, the evidence suggests that surgical thrombectomy is a potential favourable prognostic factor for PTS after an episode of DVT. The patients included in the systematic reviews had acute ilio-femoral DVT suggesting extensive clot burden, therefore, these findings may not be generalisable to the entire DVT population.

Table 9: Summary of systematic reviews on surgical thrombectomy and development of PTS

	Casey et al 2012[38]	**Luo et al 2006[113]**
Designs of included studies that assessed PTS/PTS signs and symptoms	8 RCT	3 RCT
Population(n) assessed for risk of PTS/PTS signs and symptoms	611	127
Follow up duration of included primary studies (range)	6 – 10 years	0.5 – 10 years
Potential prognostic factor assessed	Surgical thrombectomy alone or with arteriovenous fistula or angiography and stenting	Surgical thrombectomy alone or with arteriovenous fistula
Outcomes measured	Incidence of PTS	Incidence of PTS
PTS diagnostic method	Clinical examination, questionnaire, self-report, photoplethysmography venography, duplex ultrasound	Not reported
Evaluation of outcome(blinding)	Overall, inadequate blinding was reported	Overall, inadequate blinding was reported
Method of analysis	Meta-analysis	Meta-analysis
Findings	Patients treated with thrombectomy had a lower risk of developing PTS (41.2%) than patients on anticoagulation therapy (60.9%). RR 0.67 (95% CI 0.52-0.87). I^2=0%.	Patients treated with thrombectomy had a lower incidence of PTS compared to anticoagulation group at 5 years, 37.5% versus 65.9% OR 0.18 (95% CI 0.06-0.60). I^2=53.5%. p=0.005

Key: I^2 – Measure of heterogeneity OR – Odds ratio PTS – Post-thrombotic syndrome

RCT – Randomised controlled trial RR – Relative risk CI – Confidence interval

As both systematic reviews were of good methodological quality[38,113] and the search strategies across reviews covered up to 2012, therefore there was no need to update the evidence on surgical thrombectomy.

2.5.3.4 Physical activity

The association between physical activity and the incidence of PTS was assessed by 2 systematic reviews.[111,119]

One systematic review was of poor quality[111] while the second systematic review was of good quality and fulfilled most of the criteria on the AMSTAR tool.

They were published in 2006[111] and 2008[119]. The search period covered by both studies was up to 2007.

Both reviews reported only one study[130] (one RCT conducted in 2004), as a result both studies had the same findings.

The identified study was an RCT of 37 patients with objectively confirmed acute proximal DVT that were treated with anticoagulation (Dalteparin 200 IU/Kg (low molecular weight heparin) followed by Pheprocumon (oral anticoagulant)). Patients were randomised to receive either ambulation and compression therapy or compression therapy alone for nine days after which they were all encouraged to walk in addition to using compression stockings. They were assessed for development of PTS two years later.

Besides compression therapy and standard anticoagulation therapy, no other additional treatment was reported.

The study demonstrated that immediate ambulation after the diagnosis of DVT was associated with a lower incidence of PTS with relative risk of 0.66, 95% (CI 0.42 to 1.03). This association was not statistically significant (see Table 10).

This evidence suggests that immediate ambulation may be a favourable prognostic factor for reducing incidence of PTS after DVT of the lower limb. However it may also be associated with a small increased risk of PTS.

Table 10: Summary of systematic reviews on physical activity and development of PTS

	Giannoukas et al 2006[111] and Kahn et al 2008[119]
Designs of included studies that assessed PTS/PTS signs and symptoms Population(n) assessed for risk of PTS/PTS signs and symptoms Follow up duration of included primary studies (range)	1 RCT 37 0.25-5 years
Potential prognostic factor assessed	Physical activity (immediate ambulation after DVT)
Outcomes measured	Incidence of PTS
PTS diagnostic methods	Villalta scale
Evaluation of outcome (blinding)	Not reported
Method of analysis	Not applicable
Findings	54% of patients who ambulated immediately developed PTS compared to 82% of patients on bed rest alone. There was risk reduction of 34%. RR 0.66; 95% CI 0.42-1.03

Key: CI – Confidence interval PTS – Post-thrombotic syndrome

RCT – Randomised controlled trial RR – Relative risk

There was at least one systematic review of good methodological quality that assessed physical activity.[119] The search strategy of this review covered up to 2007 and it was not the best level of evidence. Therefore, there was a need to update the evidence on physical activity.

2.6 Discussion

Eligible reviews mostly included primary studies that assessed the effects of treatments of DVT on later development of PTS. The identified reviews reported on eight potential prognostic factors assessed for an association with the later development of PTS after DVT of the lower limb, see Table 11.

Table 11: Potential prognostic factors identified from systematic review of systematic reviews

Favourable prognostic factors	**Unfavourable prognostic factprs**
Anticoagulation with LMWH	Inferior vena cava filters[#]
Catheter directed thrombolysis	
Loco-regional thrombolysis	
Surgical thrombectomy	
Systemic thrombolysis	
Physical activity*	

Key: * – Non-statistically significant finding # – Statistical significance not reported

LMWH – Low molecular weight heparin

2.6.1 Favourable potential prognostic factors (associated with a reduced risk of PTS after DVT of the lower limb)

The evidence from a good quality systematic review suggests that compared with standard anticoagulation using vitamin K antagonist, anticoagulation with low molecular weight heparin was significantly associated with a lower risk of developing PTS.[39] This means that low molecular weight heparin may be preferable to vitamin K antagonists in the long term management of DVT. In addition, low molecular weight heparin has been shown to be safer (lower risk of bleeding) and does not require frequent visits to a thrombosis centre for monitoring unlike vitamin K antagonists.[131] The main drawbacks to use of low molecular weight heparin are cost (it is expensive) and acceptability. Rare drawbacks include a risk of heparin induced thrombocytopaenia, hyperkalaemia, elevated liver enzymes and osteoporosis.[131,132] However, low molecular weight heparin has been demonstrated to be associated with a lower risk of major bleeding compared to warfarin in studies on cancer associated thrombosis.[133,134] Therefore it might be that there is a long term overall cost effectiveness with use of low molecular weight heparin for DVT treatment compared to vitamin K antagonists.

The evidence from four systematic reviews (one poor quality, one fair quality and two good quality systematic reviews)[59,109,114,115] suggest that additional use of systemic thrombolysis for management of DVT was associated with a reduced risk of developing PTS than with anticoagulation alone in a statistically significant relationship. Regardless

of the difference in quality of the systematic reviews, they all had similar findings that suggest systemic thrombolysis is a favourable prognostic factor for PTS.

Three systematic reviews of fair to good quality demonstrated that use of catheter directed thrombolysis in addition to standard anticoagulation therapy was associated with a reduced risk of PTS compared to anticoagulation alone when used in the management of DVT.[38,109,110] This association was found to be statistically significant in the review that presented this statistic. In the reviews, it was reported that there was additional treatment with catheter directed thrombolysis such as angioplasty, stent and or thrombectomy. So it was not possible to determine how much of the identified effect could be attributed to catheter directed thrombolysis alone.

Overall, across systematic reviews there appeared to be an increase in risk of both major and minor bleeding in patients on any kind of thrombolysis compared to patients on anticoagulation alone. For systemic and loco-regional thrombolysis, this association was found to be statistically non-significant while the significance was not reported for catheter directed thrombolysis. Despite the non-statistically significant association between increased bleeding risk and systemic and loco-regional thrombolysis, this finding of a probable increased risk of bleeding with thrombolysis should be considered with care. This is because every patient's treatment should be tailored according to individual needs. For example, it might be better to avoid systemic thrombolysis in patients at increased risk of bleeding based on this evidence.

The findings from five fair to good quality systematic reviews (one poor, two fair and two good quality reviews),[110,111,116-118]demonstrated a statistically significant reduced incidence of PTS when compression stockings was used with anticoagulation in the

treatment of DVT compared to when anticoagulation alone was used. This association did not appear to be affected by reported differences across systematic reviews such as differences in the extent of compression (for example, below knee or thigh length compression), interval from DVT to use of compression and duration of compression. One systematic review's findings[116] demonstrated a much more reduced incidence of PTS in patients with an ankle pressure of at least 30mmHg compared to other patients with compression stockings exerting lower ankle pressures. Therefore, the compression pressure of the compression stockings may be a contributing factor in the ability of compression stockings to reduce PTS. Findings from this systematic review of systematic reviews justify the use of compression stockings for treating DVT. Of all types of compression therapy, only reviews on compression stockings were identified by this systematic review of systematic reviews. Other forms of compression therapy and how they may affect the development of PTS need to be explored further.

The evidence from one fair[113] and one good quality systematic review[38] found surgical thrombectomy to be significantly associated with a reduced incidence of PTS when compared to anticoagulation alone.[38,113] This risk lowering effect of surgical thrombectomy may persist for up to ten years after the procedure when compared to anticoagulation. Both systematic reviews reported that in some primary studies, there was co-treatment with angiography, stent and or arteriovenous fistula. However, primary RCTs where only surgical thrombectomy was reported as method of treatment of DVT showed a statistically significant PTS lowering association much like other studies where there were co-treatments using arteriovenous fistulas, stents, and angiography.

The evidence from two good quality systematic reviews[111,119] showed that there was a non-significant reduction in risk of developing PTS in patients that received immediate ambulation after DVT as an intervention when compared to patients on bed rest immediately after DVT. There was only one relevant RCT identified by both reviews.[130] There was additional treatment with compression stockings indicating that strong conclusions on the prognostic ability of physical activity and incidence of PTS after DVT could not be made from this evidence. In addition, the reported confidence interval (see Table 10) demonstrates that there is a very small risk that physical activity was associated with an increased incidence of PTS. Future research may help with clarifying whether physical activity has any significant relationship with the development of PTS after DVT of the lower limb. However, evidence suggests that physical activity may play a strong role in the prevention and treatment of other venous thromboembolism related illnesses. An RCT found early adoption of ambulation in addition to compression stockings to be associated with better resolution of DVT signs and symptoms without an additional risk of pulmonary embolism when compared to patients that are physically inactive immediately after DVT.[135] Another study has identified physical inactivity to be associated with an increased risk of idiopathic pulmonary embolism.[136] While older evidence have already established that sedentary lifestyle and prolonged bed rest are associated with an increased risk of DVT.[137] The role of physical activity in the development of PTS needs to be clarified by more primary studies, as only one study suggests that it may be a favourable prognostic factor for developing PTS after DVT, this was a statistically non-significant finding.

2.6.2 Unfavourable potential prognostic factors (associated with an increased risk of PTS after DVT of the lower limb)

The evidence from one systematic review[112] that included one relevant RCT suggests that use of inferior vena cava filters for secondary prevention of pulmonary embolism in patients post DVT may be associated with an increased incidence of PTS. with be an unfavourable prognostic factor for PTS.[112] The risk of PTS was found to be higher in patients that received heparin while having an inferior vena cava filter in situ. Strong conclusions could not be made from this study because of the type of evidence made from the nine observational studies and the one RCT included in the analysis. The nine observational studies found the association to be a harmful one, while the RCT found there was no difference. Inferior vena cava filters are usually offered to patients that cannot tolerate anticoagulation therapy (primary prevention of pulmonary embolism) or in patients that have recurrent DVT or pulmonary embolism despite adequate anticoagulation treatment (secondary prevention of pulmonary embolism).[66] Therefore, inferior vena cava is not routinely used in practice except when absolutely necessary because of the following concerns; it is expensive, requires invasive procedure to fit, requires clinical expert, poor evidence on safety of inferior vena cava filters.[138] The evidence from this systematic review of systematic reviews further supports the relegation of inferior vena cava filters as a last option in the prevention of pulmonary emboli. The finding of this systematic review may have implications for clinical practice where the use of inferior vena cava filter for prevention of pulmonary embolism will need to be balanced against a possible increased risk of PTS associated

with their use. More primary studies are needed to confirm the association between inferior vena cava filters and PTS.

2.6.3 Strengths and limitations of included systematic reviews

No review specifically looking at prognostic factors for PTS were identified. Reviews on treatment of DVT were the only ones identified and these were used to identify potential prognostic factors.

Most of the systematic reviews included in this review conducted a comprehensive search of databases. This suggests that almost all available evidence at the time they were conducted were included in their reviews.

Limitations of included systematic reviews include; the poor reporting of PTS diagnostic criteria used by primary studies in some instances, and the lack of predictive accuracy of identified prognostic factors.

Most systematic reviews gave poor reporting of the interval between diagnosis of DVT and implementation of treatment potential prognostic factors as well as length of exposure and dosage of treatment potential prognostic factors. Where these were reported, there were variations. These poor reporting and variations may reduce the strength of conclusions that can be made from findings of reviews.

It was only in one systematic review[38] that co-morbidities of patients from primary studies such as the presence of cancers in the patients being assessed for PTS were reported. Though existing reviews, has not demonstrated whether cancers or any other

co-morbidities predisposes to developing PTS or not, it would be beneficial to have this information to increase robustness of conclusions, as this may enable comparisons to be made on the incidence of PTS in patients that have co-morbidities and those that do not.

Identified systematic reviews did not report whether the DVT in their population was unprovoked DVT or provoked DVT. Reports on the type of DVT would have increased the robustness of information about the identified prognostic factors for developing PTS. This information may have helped identify if a prognostic factor was dependent on whether the initial DVT was provoked or unprovoked.

Publication bias was not assessed in all identified systematic reviews probably because they all included less than ten primary studies with respect to each prognostic factor (the minimum number of primary studies required to assess for publication bias is ten). There was also variable reporting on whether grey literature was searched or not. It is now evident that publication bias may allow the exaggeration of treatments effect, this may be reduced by searching areas of grey literature when conducting a systematic review.[93] Assessment of publication bias would be particularly important here because most of the potential prognostic factors associated with PTS identified so far are DVT treatment related and effects may be exaggerated by only positive findings being published if there are negative treatment findings in the background. However, research in PTS is only recently gaining recognition as an important field. It is therefore probable that there will be few relevant primary studies excluded from these systematic reviews for the time periods covered if at all there are any.

Overall quality of systematic reviews on prognostic factors identified so far was good. However, the quality of primary studies included in these systematic reviews varied

from good to poor. This problem can be overcome by researchers applying better methodology to their studies.

2.6.4 Strengths and limitations of this systematic review of systematic reviews

The search strategy for this systematic review was applied to four different electronic databases in addition to checking references of included systematic reviews. This ensured that a large body of evidence was searched rendering the likelihood of missing a relevant systematic review very low.

Two independent systematic reviewers undertook the screening of articles, the quality assessment and the data extraction stage of this systematic review of systematic reviews. This minimised the risk of bias while selecting relevant systematic reviews and quality appraising them. A list of excluded references and the reasons for exclusion were also provided to reflect transparency used during the selection stage.

A transparent process was used to make explicit when key quality markers were met or not met. This was done by assessing the quality of included systematic reviews using a widely validated tool – the AMSTAR tool. This added robustness to conclusions that were made from findings of the review.

This review identified information on treatment potential prognostic factors only.

2.7 Conclusion

Evidence from this systematic review of systematic reviews highlights that treatment adopted for managing DVT may be important in modulating the risk of a patient developing PTS after DVT. The systematic review of systematic reviews identified eight treatment potential prognostic factors that may be associated with the development of PTS after DVT of the lower limb. They include anticoagulation with low molecular weight heparin, all types of thrombolysis (systemic, loco-regional, and catheter directed thrombolysis), compression therapy, inferior vena cava filters, surgical thrombectomy and physical activity. Suggested favourable prognostic factors identified were anticoagulation with low molecular weight heparin, thrombolysis (systemic, loco-regional, and catheter directed thrombolysis), compression therapy, surgical thrombectomy and physical activity. The presence of inferior vena cava filters in situ for prevention of pulmonary embolism after DVT was an unfavourable prognostic factor.

The evidence on loco-regional thrombolysis, inferior vena cava filters and physical activity were found to require an update. A systematic review to update the evidence on these factors as well as identify other potential prognostic factors where possible is therefore required. This will potentially improve the quality of information available on prognostic factors for developing PTS after DVT.

Chapter 3: Identification of potential prognostic factors associated with the development of PTS after a DVT of the lower limb (systematic review of primary studies)

3.1 Introduction

In the previous chapter, it was demonstrated that the treatment employed in the management of DVT may have an impact on whether a patient develops PTS after DVT of the lower limb.

This chapter is a systematic review of primary studies that was undertaken to address the gaps identified from the previous chapter. It aimed to update the evidence on potential prognostic factors identified as requiring an update from Chapter 2, as well as identify new factors associated with the development of PTS after DVT that were not already identified from the previous systematic review.

3.2 Aims

1. To update the evidence on prognostic factors identified to need updating from the previous chapter
2. To identify prognostic factors associated with the development of PTS after DVT of the lower limb not identified from the previous chapter

3.3 Objectives

- To systematically identify and assess the quality of studies that have reported on one or more factors that are associated with developing PTS after DVT of the lower limb
- To determine the strength of association between identified factors and the development of PTS after DVT of the lower limb

3.4 Methods

3.4.1 Systematic review

Systematic review methodology was employed in answering the research question. A protocol was developed prior to commencement of this review and was used as a guide. This was published on PROSPERO international prospective register of systematic reviews (PROSPERO 2014:CRD42014002530). The review consisted of standard searches to identify published primary studies; specific criteria were used to select relevant studies to be included in this systematic review. Assessment of the quality of

included studies was done using an appropriate tool and findings of the included studies were extracted and synthesised.

3.4.2 Search strategy

The search strategy aimed to identify primary studies including those that developed prognostic models.

A search of the following databases up to April 2015 was conducted; Cochrane Library including Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE classic (Ovid) and MEDLINE (Ovid). Conference manuscripts from 2011 onwards were searched via Zetoc database. This included abstracts from the following conferences; European Venous Forum, British society for Haematology, American society of Haematology, the European Haematology Association and International society on Thrombosis and Haemostasis. The WHO International Clinical Trials Registry Platform, the UK Clinical Research Network study portfolio and the metaRegister of Controlled Trials were searched for ongoing studies. Reference lists of included primary studies were searched to identify any further studies.

The search strategy was developed with the help of an information specialist (Sue Bayliss). Keywords selected were deliberately broad so that the search strategy would be sensitive in yielding primary studies that may have looked at factors associated with the development of PTS. The search strategy was modified as necessary for each database searched (See Appendix 3, Sections 3.1 to 3.4). The strategy applied to bibliographic databases had been piloted in PUBMED to ensure it was sensitive to identifying relevant studies.

The search strategy included combinations of search terms that described the relevant population (DVT) and the relevant end outcome (PTS). A combination of both text words and indexed terms were used. Terms for DVT were combined using the Boolean operator 'OR', same was done for terms for PTS. Both of these sets were combined with the Boolean operator 'AND' as in the following:

('Venous thrombosis' OR 'Venous thromboembolism' OR 'Deep vein thrombosis' OR 'Deep vein thromboses' OR 'DVT' OR 'VTE') AND ('Post thrombotic syndrome' OR 'Postthrombotic syndrome' OR 'PTS' OR 'Post phlebitic syndrome' OR 'Venous stasis syndrome' OR 'Chronic venous insufficiency' OR 'chronic vein insufficiency' OR 'Venous ulcer').

The search results from implementing the search strategy were then entered into reference management software (Endnote X4 version). An inbuilt algorithm in Endnote X4 was used to automatically remove duplicate records. Remaining duplicate records were searched for and removed manually.

Appendix 3, Sections 3.1 to 3.4 shows the search strategy used for each database.

3.4.3 Study screening and selection

Two reviewers HO and AY independently screened the titles and abstracts of records to identify those relevant to the review. Relevance was determined based on population, study designs and outcomes. Disagreements were resolved by discussion with a third reviewer DM if required.

Hard copies of relevant articles were subsequently obtained and the full inclusion and exclusion criteria (described below) applied to them by the same reviewers. Studies that

met all the inclusion criteria were included in the review. Studies that did not meet the inclusion criteria were excluded.

The Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram[91] was used to present a summary of the selection process.

Inclusion criteria

Patient group – Adults that have had at least one episode of objectively confirmed DVT of the lower limb.

Exclusion: Patients with pre-existing PTS

Setting – Studies in all settings were considered.

Outcomes – PTS was the outcome of interest. Studies were included if they had a pre-defined method of determining PTS.

Study design – The following study designs were considered for inclusion in this systematic review;

- Prospective cohort studies
- Retrospective cohort studies
- Clinical trials
- Case-control studies
- Case series

Type of potential prognostic factor assessed by primary study – Potential prognostic factors assessed by a previous systematic review of systematic reviews but found to require updating of the evidence were included. Studies that fell within the search scope

of the previous systematic review were not included in this review. Only studies outside the search scope of the previous systematic review (as described in the previous chapter) were assessed for inclusion. For example, for physical activity, the search scope of the corresponding systematic review covered up to 2007. Therefore all primary studies assessing the relationship between physical activity and PTS up to 2007 were excluded from this systematic review if this was all they explored. Where other potential prognostic factors were explored by the same study, they were also assessed against the inclusion and exclusion criteria. The factors identified as requiring an update and years of publications searched were;

- Physical activity (from 2008 onwards)
- Loco-regional thrombolysis (from 2007 onwards)
- Inferior vena cava filters (from 2008 onwards)

Other potential prognostic factors not already identified by the previous systematic review of systematic reviews were included.

Exclusion: The following factors were excluded due to sufficient evidence (see Chapter 2):

- Anticoagulation with low molecular weight heparin
- Catheter directed thrombolysis
- Compression therapy
- Surgical thrombectomy
- Systemic thrombolysis

Follow up duration – Studies had to include patients who suffered from DVT at least three months prior to assessment for PTS. This minimum time interval between DVT and PTS assessment is important because PTS can be confused with ongoing symptoms of an acute DVT.

There was no maximum duration to follow up.

Language – Studies in all languages were considered for inclusion

3.4.4 Data extraction

Data extraction was carried out by OH and checked by AY. The following details were extracted.

Study details

Title of paper, study objectives, number of participants enrolled, duration of follow-up post DVT and percentage lost to follow-up.

Population characteristic

Age, gender, ethnicity and location of study

DVT details

Location of DVT, provoked/unprovoked DVT, any co-existing medical conditions, measures of DVT, duration of oral anticoagulation, other DVT treatments besides oral anticoagulation, adverse events associated with treatment factors

Outcome details

The details on measure of outcome and number of outcome events in the population

Potential prognostic factor details

Type of potential prognostic factor (treatment or non-treatment), measures of potential prognostic factor, amount/dose of exposure to potential prognostic factor, potential prognostic factor/time of exposure post DVT, length of exposure to potential prognostic factor, time points recorded post DVT, type of data and thresholds were applicable.

Prognostic model study details

Data mentioned above were extracted were applicable. In addition, the equation of the model, the potential prognostic factors considered, their weight in the model, details on validation of the model study and statistics for discrimination of the model (such as area under the curve as well as their corresponding confidence intervals) were reported.

Effect measures details

The effect sizes such as relative risks, odds ratios, risk reduction and hazard ratios as well as corresponding standard errors, confidence intervals and p-values of these measures were extracted. Where reported, the unadjusted and adjusted effect sizes, and factors adjusted for were also extracted. Where relevant statistical information was missing form papers the authors were contacted and requested to supply the missing information. If a response was not received after one week, a reminder was sent. If there was still no response after a further week, the study was noted.

3.4.5 Quality assessment

The Altman checklist[139] was used to assess the quality of prognostic model studies. The quality of prospective cohort studies with multivariate analysis but no model

development was assessed using a hybrid table combining comprising of all components from the Hayden et al checklist[140] and an additional component ("blinding to outcome assessment") from the Cochrane risk of bias tool.[92] The assessment was carried out by two reviewers independently (HO and AY). All disagreements were resolved by discussion between them.

3.4.6 Analysis

Qualitative synthesis was used to analyse findings of identified studies. It was anticipated that a meta-analysis of findings would not be done because of the following problems that are often encountered in performing a systematic review of studies on prognosis[141] such as; different patient inclusion criteria between primary studies, different methods of measuring potential prognostic factors across studies, inadequate reporting of outcome difference, differences in effect estimates reported and differences in factors adjusted for by primary studies.

Analysis was grouped into factors that required updating of the evidence from a previous review and factors that were newly identified by this review.

The following elements were considered during analysis;

The study designs and method of analysis – Studies were categorised according to study designs. Prospective cohort studies were categorised into prognostic model studies and whether a multivariate analysis was carried out or not. It is only in the absence of the ideal study designs for gathering prognostic information (prognostic model studies and prospective cohort studies with multivariate analysis) should other study designs such as retrospective cohort studies, clinical trials and case control studies

be considered for gathering prognostic information[96,142,143] (see Appendix 2, Section 2.6.1 for hierarchy of evidence for studies on prognosis according to the Oxford centre for evidence based medicine).[96] Potential prognostic factors identified from prognostic model studies and prospective cohort studies with multivariate analysis were analysed in more detail. Potential prognostic factors assessed from other study designs and prospective cohort studies with univariate analysis only were noted.

The direction of effect size – this took into account the measure of effect, the differences and or similarities in effect sizes across studies and their significance.

Follow up and measurements of the outcome (PTS) and potential prognostic factor – The length of follow up, time points of outcome and potential prognostic factor measurements was described and compared across studies to determine their impact on any identified difference in effect size reported.

Factors adjusted for – Included studies adjusted for different factors in their multivariate analysis. These factors were reported and it was noted whether they had any effect on effect sizes compared to unadjusted values.

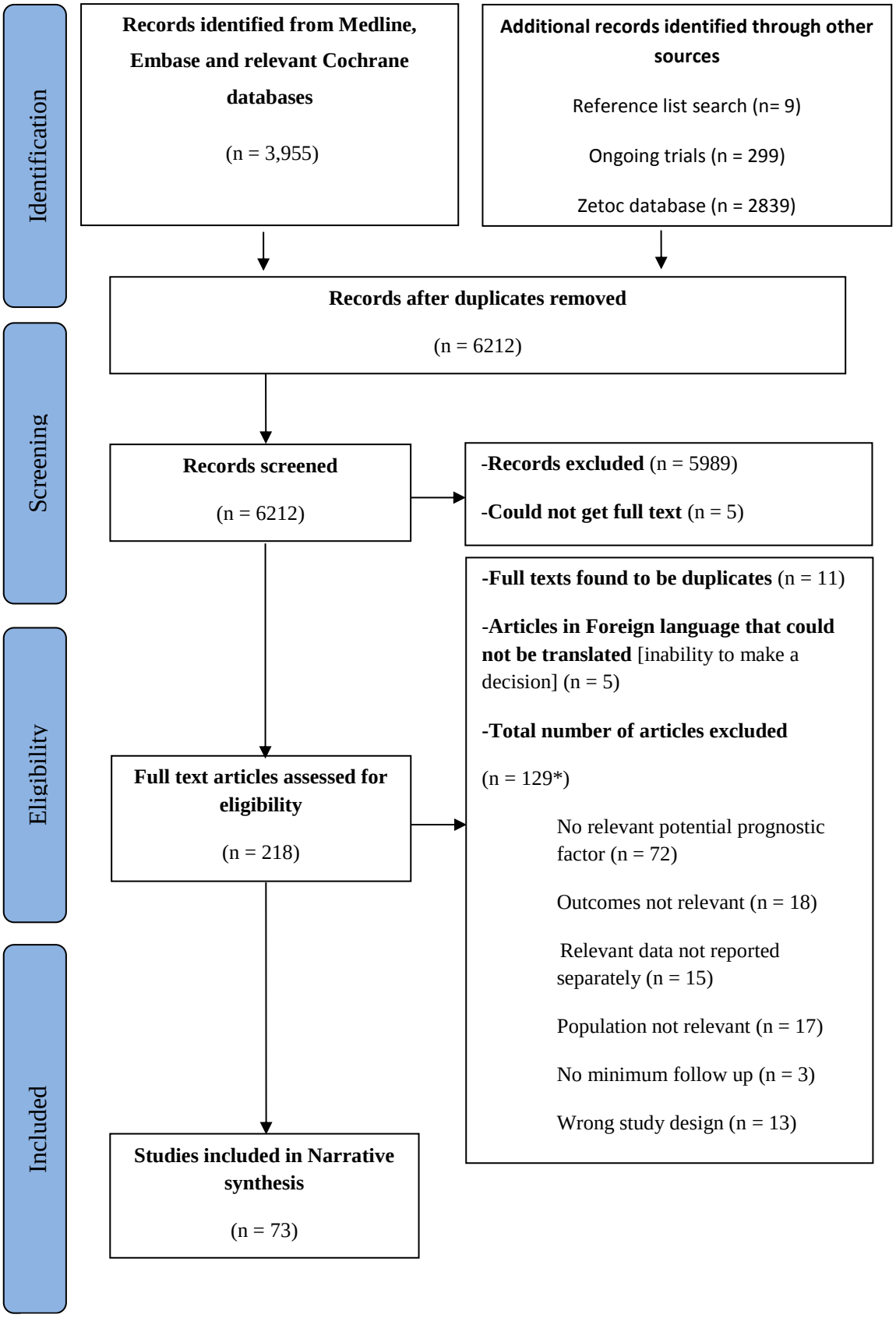
The risk of bias of included studies – Details of the measures of outcomes and the measures of potential prognostic factors were described including whether there was blinding to PTS assessment (where possible). The potential impacts of identified biases during quality assessments on final findings were reported. Publication bias was not assessed because no meta-analysis was carried out in this review.

3.5 Results

Six thousand two hundred and twelve records were identified by the search strategy. After screening of title and abstracts, 218 records were identified as potentially relevant. The full inclusion criteria were applied to the full texts of these articles and subsequently, 73 studies were included in this systematic review. Studies not included and reasons for not including them are outlined in Appendix 3, Section 3.6. Decisions could not be made on five full texts[144-148] due to inability to translate to English language (see Appendix 3, Section 3.7). Articles translated and subsequently excluded are listed in Appendix 3 section 3.8.

Please see the PRISMA flow diagram (Figure 7) for an illustration of the study screening and selection process.

Figure 7: PRISMA flow diagram of study screening and selection

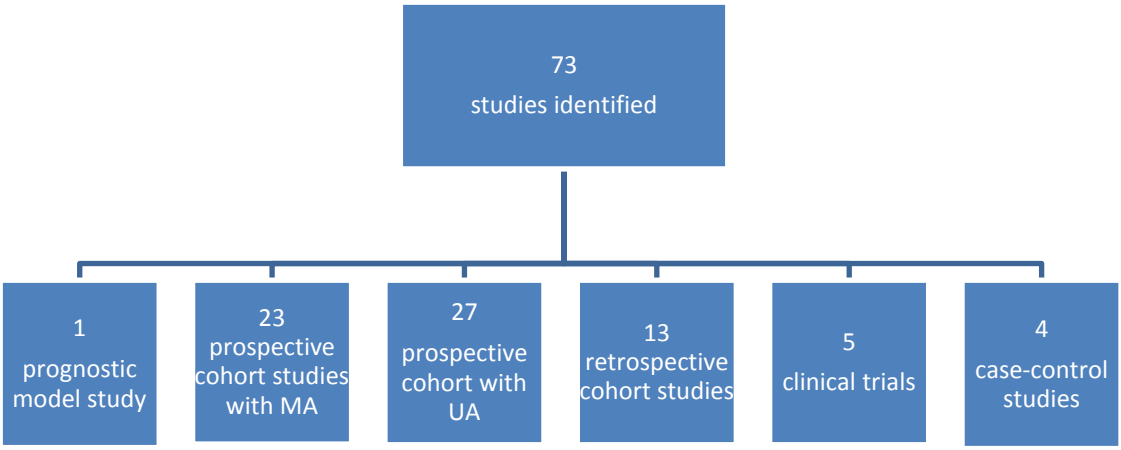


* – Nine studies had more than one reason for exclusion

3.5.1 Grouping of studies according to best evidence

The 73 studies included studies were subsequently grouped by study designs. Prospective cohort studies were grouped into whether they conducted a multivariate analysis or not. One prognostic model study,[149] 23 prospective cohort studies with multivariate analysis but no prognostic model development,[13,33,34,150-169] 27 prospective cohort studies with univariate analysis,[20,26,170-194] five clinical trials,[195-199] 13 retrospective cohort studies[200,201,49,202-204,205-211] and four case-control studies[81,212-214] were identified (see Appendix 3, Section 3.9).

Figure 8: Grouping of studies



Key: MA – Multivariate analysis UA – Univariate analysis

The prognostic model study and prospective cohort studies with multivariate analysis were analysed in more detail as these types of studies are preferable for getting the best prognostic information.[2,143,215] Novel potential prognostic factors not explored in the prognostic model study or prospective cohort studies with multivariate analysis but explored in other study designs were noted and reported. This was done to avoid loss of information regarding these potential prognostic factors.

3.5.2 Quality assessments

Presented in this section are the results of applying quality assessment tools to the identified model study and prospective cohort studies with multivariate analysis.

3.5.2.1 Quality of the model study

As there was only one model study identified[149], all the details of the model study including quality assessment are presented together for ease of reference.

3.5.2.2 Quality of prospective cohort studies with multivariate analysis

The quality of prospective cohort studies with multivariate analysis but no model development (23 studies) was assessed using a hybrid table combining all components from the Hayden et al checklist[140] and an additional component (blinding) from the Cochrane risk of bias tool[92] (see Appendix 3, Section 3.11).

Studies gave a clear description of their source population, sampling frame and recruitment procedure except one study.[153] In this study, patients were contacted from a register. It was not clear why out of 1388 eligible patients for the study only 488 patients were contacted for inclusion in the study.

Excluded patients and reasons for exclusion were well described in all studies.

Baseline characteristics were well described in all included studies. The population in two studies[13,166] were mainly younger patients while the population in another study comprised mainly of older patients.[161]

Most of the studies had small sample sizes with five studies[33,154,157,158,161] having a sample size that was less than 100. However two of the studies had a large sample size of 725 patients[168] and 1668 patients.[13]

In 14 studies,[13,28,33,151,152,154,156,157,160,162,163,167-169] greater than 80% of patients included in their study completed follow up. Expectedly, the percentage of patients that completed follow up dropped with increasing length of follow up across studies. No important differences in baseline characteristics of patient were reported in patients lost to follow up across studies. One study[13] made additional attempts to reduce loss to follow up by conducting over the phone assessments of PTS in patients not available for assessment in person.

Blinding in research on PTS can be quite challenging as the patient and clinician are aware that PTS is being assessed for. However, when PTS diagnostic methods have a clinician implemented and a patient reported component, blinding of the clinician to patient reported symptoms and vice versa is possible. It was not reported in nine studies[151-153,157,158,160,166-168] whether any kind of blinding was carried out. Two of these studies[151,152] were part of a larger study[47] that had reported that blinding was done. This finding suggests that assessing quality of studies entirely from what is reported in articles may not always be reliable. It was reported in the other studies that some form of blinding was done. In some cases, PTS assessors were blinded to the subjective part of the PTS diagnostic method used (where applicable).[28,47,156,165] Other times, PTS assessors were blinded to potential confounders for example, a patient's previous PTS score[47] (this is possible when a study requires the threshold for PTS diagnosis to be crossed on two occasions before making a diagnosis of PTS). In other studies, PTS assessors were blinded to results of radiologic investigations such as Doppler

ultrasound,[33,150,154,163,169] DVT treatment used,[13] ipsilateral recurrent DVT, extent of thrombosis and thrombophilia status.[155] A detailed description of how PTS was measured was clearly described in all studies. In five studies,[150,156,159,164,165] a diagnosis of PTS was made only after the threshold for diagnosis of PTS had been crossed on more than two consecutive occasions on the PTS diagnostic method used. In one study[13] an atypical method for PTS diagnoses (an adaptation of the Villalta scale for use over the phone) was used.

A clear and adequate description of potential prognostic factors and described method of potential prognostic factor measurement was given in all studies where applicable.

As a multivariate analysis had been conducted in all these studies, at least one potential confounding factor had been adjusted for. However, in four studies[150,157,159,167] factors adjusted for were not always reported.

In majority of the studies, analysis seemed to be appropriate. However, significant details to complement the interpretation of effect sizes such as p-Values or confidence intervals was not always reported in 10 studies.[33,13,151,153,158,159,162,163,165,166] The magnitude of effect size or effect estimates was not reported in two studies.[154,169] While it was reported in one study[161] that a logistic regression analysis had been done but the findings of the logistic regression was not reported.

It is important to note here that the majority of studies were sub-studies of a single large prospective study or carried out on the same population and were therefore mostly conducted by the same team of researchers. This gives room for bias although sub-studies usually investigated different potential prognostic factors from the other sub-studies. For example six studies[28,47,151,152,156,165] out of the 23 prospective cohort studies

were sub-studies of the same larger prospective study based in Canada that had included 387 patients originally. One study[168] although from a different cohort was conducted by mostly the same set of researchers from the other six studies. Two studies were on the same population of 86 patients[33,154] followed up in the Netherlands and another two studies (also from the Netherlands) were on the same population of 113 patients.[162,163]

Overall, nine studies[28,33,152,156,160,162,163,168,169] were deemed to be good quality studies with a low risk of bias. Ten studies[47,150,151,154,155,159,161,165-167] were deemed to be fair quality studies with a moderate risk of bias and four studies[13,153,157,158] were of poor quality with a high risk of bias (see Appendix 3, Section 3.11.1).

3.5.3 Findings

The findings on potential prognostic factors presented in this section are detailed and lengthy. For a summary of findings please see section 3.6.

Detailed information from included studies on factors assessed for their association with the development of PTS after DVT is summarised and detailed below.

3.5.3.1 Update of the evidence

In the systematic review of systematic reviews, three potential prognostic factors were identified as requiring an update of the evidence (inferior vena cava filter, loco-regional thrombolysis and physical activity).

There were no new studies since the conclusion of the previous systematic reviews in which the associations between PTS and loco-regional thrombolysis or inferior vena

cava filters were explored. Therefore the findings of the existing reviews on these factors remained unchanged.

3.5.3.1.1 Physical activity

Only one study that had assessed the relationship between physical activity and the development of PTS was identified.[165] It was a prospective cohort study that assessed the association between physical activity and development of PTS after DVT in a multivariate analysis. This study was of fair quality and had a sample size of 387 patients diagnosed with DVT. Follow up period of patients in the study was for 24 months.

The Villalta scale (scores had to have crossed the threshold for diagnosis on at least two consecutive occasions for a diagnosis of PTS to be made) was used to diagnose PTS. The reported incidence of PTS along the follow up period were, 48% at one month, 40% at four months, 38% at eight months, 39% at12 months and a cumulative incidence of 45.1% at 24 months.

Factors adjusted for included age, gender, BMI, pre-DVT physical activity, disease severity at one month.

Analysis of results was carried out based on categorising physical activity into mild to moderate activity and highly active at one month after DVT diagnosis using the Godin questionnaire.[216] Both categories of physical activity were assessed for an association with subsequent development of PTS two years after DVT diagnosis. Findings from the study demonstrated that mild to moderate activity may be associated with increased odds of developing PTS with odds ratio 1.64, 95% CI (0.85 to 3.15). The association

was not significant statistically although it appeared to decrease slightly in the highly active group 1.37, 95% C1 (0.68 to 2.79) (see Table 12).

In the previous systematic review of reviews, one study[130] that assessed the association between physical activity and PTS was identified (the RCT by Partsch et al in 2004). In this study, only a univariate analysis was carried out and a non-significant protective relationship was identified. This study[130] showed a different finding to that of the study identified in this review.[165] This may be due to the differences in sample size and study methodology employed by both studies (an RCT involving 37 patients[130] versus a prospective cohort study of 387 patients[165]) and the differences in the time period and definition of physical activity studied (nine days of immediate ambulation after DVT diagnosis[130] versus one month of self-reported physical activity after DVT diagnosis[165]).

In summary, this systematic review demonstrated that physical activity within one month of DVT diagnosis was weakly associated with an increased risk of developing PTS in a statistically non-significant association. This evidence was from one primary study of fair quality. Considering this evidence in conjunction with previous findings from Chapter 2 led the evidence on physical activity to determine if it is a prognostic factor for PTS to be deemed inconclusive.

Table 12: Physical activity

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential Prognostic Factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Shrier et al 2009[165]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months, 48% at 1 month, 40% at 4 months, 38% at 8months, 39% at12 months and 40% at 24 months	24	Mild – moderate activity (based on multiple imputations)	Age, Gender, BMI, pre-DVT physical activity, Disease severity at 1 month	OR 1.64 0.85 to 3.15	NR
						Mild – moderate activity (based on complete cases)	Age, Gender, BMI, Pre-DVT physical activity, Disease severity at 1 month	OR 1.82 0.90 to 3.65	NR
						Highly active (based on multiple imputations)	Age, Gender, BMI, Pre-DVT physical activity, Disease severity at 1 month	OR 1.33 0.68 to 2.60	NR
						Highly active (based on complete cases)	Age, Gender, BMI, Pre-DVT physical activity, disease severity at 1 month	OR 1.37 0.68 to 2.79	NR

Key: BMI – Body mass index DVT – Deep vein thrombosis NR – Not reported OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2 New findings on potential prognostic factors

Prognostic models and new potential prognostic factors assessed for an association with subsequent development of PTS after DVT were identified from studies included in this review.

Four potential prognostic models were identified from a prognostic model study

Twenty eight potential prognostic factors assessed for an association with PTS after DVT of the lower limb by prospective cohort studies with multivariate analysis were identified (see Table 13). Sixty seven other potential prognostic factors assessed for an association with PTS after DVT of the lower limb by other study designs and prospective cohort studies with no multivariate analysis were identified (see Table 13).

Table 13: Potential prognostic factors identified from included studies

Study design	Potential prognostic factors identified					
	Patient characteristics	**Risk factors for index DVT**	**Characteristics of index DVT**	**Biomarkers**	**DVT treatment factors**	**Venous function**
Prospective cohort studies with multivariate analysis	Age Body mass index Gender	Cancer Extent of DVT Location of DVT Hormonal factors Inherited thrombophilia Ipsilateral recurrent DVT Previous ipsilateral DVT Smoking Varicose veins	Calf swelling ≥ 3cm than contra lateral leg DVT symptoms duration Severity of the Villalta score Thrombi occlusion	Interleukin 6 Intracellular adhesion molecule 1 C-reactive protein Interleukin 10 D-dimer levels	Duration of warfarin therapy Sub-therapeutic anticoagulation	Venous outflow resistance Venous reflux Venous reflux velocity Venous blood retension index Calf muscle pump function
Other study designs/analysis	Race Lower income levels Mean of shortest distance from right iliac artery to fifth vertebral body Parity	Chronic venous insufficiency Central venous catheter placement Congenital heart failure Immobilisation Inflammatory bowel disease	DVT risk score (as calculated by the New York Heart Association protocol[217]) Contra-lateral recurrent DVT during follow up period Recurrent VTE during follow up Asymptomatic DVT	Activated protein C (APC) ratio Thrombin antithrombin complex Platelet count Factor VIII Interleukin 8	Multilayer compression bandaging in acute phase of DVT Percutaneous endovenous intervention used with oral anticoagulants	Recanalisation rate Venous blood ejection index Venous blood filling index

Study design	Potential prognostic factors identified					
	Patient characteristics	**Risk factors for index DVT**	**Characteristics of index DVT**	**Biomarkers**	**DVT treatment factors**	**Venous function**
	Use of non-steroidal anti-inflammatory drugs within 30 days prior to DVT diagnosis Use of statins within 30 days prior to DVT diagnosis Weight gain post DVT Visceral pattern of fat distribution	Postnatal DVT Trauma Renal failure Stroke Surgery Antithrombin III deficiency Antiphospholipid syndrome Protein C deficiency Protein S deficiency Hyperhomocystenaemia Caesarean section Antenatal DVT Previous VTE Hypercholesterolaemia Family history of VTE Travelling	Laterality of DVT (i.e. left or right leg affected by DVT) Provoked DVT Unprovoked DVT Presence of pulmonary embolism Tenderness along deep veins at presentation Entire leg swelling at presentation Pitting leg oedema at presentation Dilated superficial veins at presentation	Vascular adhesion molecule 1 (VCAM-1) Soluble vascular adhesion molecule (sVCAM-1) Prothrombin activatable fibrinolysis inhibitor (Pro TAFI) Tissue plasminogen activator Thrombomodulin, Monocyte chemoattractant protein 1 (MCP-1) Fibrinogen Tumour necrosis factor alpha Von williebrand factor	Power pulse spray in conjunction with angiojet thrombectomy and aspirin Regular follow up of patients post DVT	

Study design	Potential prognostic factors identified					
	Patient characteristics	**Risk factors for index DVT**	**Characteristics of index DVT**	**Biomarkers**	**DVT treatment factors**	**Venous function**
		Acute illness (not specified) Cardiovascular disease (not specified) Hypertension Presence of inflammatory disease Increased activity of plasminogen activator inhibitor – 1 (PAI-1) gene (evidenced by 4G/5G polymorphism)				

Key: DVT – Deep vein thrombosis VTE- Venous thromboembolism

3.5.3.2.1 Findings from prognostic model

In a model study[149] identified in this review, four prognostic models were developed. The quality assessment of the study and the findings from this study are presented below.

Quality assessment

Factors included in the prospective cohort study that led to the development of the prognostic models were identified from previous studies. Factors subsequently included in model development had to have p-value ≤ 0.10 in a univariate analysis before it was considered for inclusion in the development of the prognostic model. Clearly reported was the method of measurement of PTS and method of measurements of the prognostic variables.

No flow diagram illustrating the flow of patients through the study was presented. However, the flow of patients was described although only in part. The total number of patients at start and end of the study was given but there was no reporting of total number of patients available at each time point in the follow up process. Eighty five percent of participants completed the study which was more than the 80% required for a prognostic model study.[96] Missing values and how they were accounted for were also reported.

There was reporting bias identified in this study, as all data on summary of effect sizes were not reported, such as p-values of the area under the curve statistic of the models developed. Also the effect sizes of the performance of individual prognostic variables in the developed models were not reported. In addition there was no report of an internal or external validation of the reported models.

The study seemed to have been rigorously conducted, however, there was limited reporting of findings and absence of validation of findings which is essential to prognostic model studies.[96,139] Therefore the study was assessed as having a high risk of bias.

Findings

One hundred and eleven DVT patients were followed up over a period of two years. Ninety four patients completed the two year follow up. The prognostic models were developed based on data from patients that completed the follow up period. The cumulative incidence of PTS at three months as determined by the CEAP classification was 46% and this did not increase thereafter. Although number of patients included at start and finish of the study were reported, the number of patients at each follow up period (six weeks, three months, six months, one year and two years) was not reported. This made it difficult to know the precise flow of patients through the study. However, number of patients lost to follow up and reasons for loss to follow up were reported.

Prognostic variables selected for assessment in the study were identified from previous studies. Factors were assessed for an association with the development of PTS after DVT using univariate analysis. Only prognostic variables with a p-value of ≤ 0.10 in the univariate analysis were included in subsequently developed multivariate models. These prognostic variables consisted of a varied selection of baseline characteristics as well as results of non-invasive venous examinations measured at diagnosis of DVT, after six weeks, three months, six months, one year and two years post DVT, or when recurrent venous thrombosis occurred.

The only statistic of these models that was reported was the performance statistic – area under the curve. The area under the curve reflects the performance of the model in predicting PTS as an outcome after a DVT of the lower limb. The area under the curve ranges from 0.50 to one, with 0.5 depicting no apparent predictive value and one reflecting accurate prediction (that is, accurately predicting an outcome 100% of the time).[218]

The statistical significance (p-values and confidence intervals) of the performance indicator used (area under the curve) and equations for the models were not reported. Also not reported was the independent ability of each variable included in the models to predict PTS from multivariate analysis. Letters and emails were sent to the correspondence author of the study asking for access to this information. No response was received.

The components of the models and their performance statistic are reported below.

Model 1 – The following prognostic variables were included; proximal thrombosis score at six weeks measured on Doppler ultrasound, superficial valvular reflux at six weeks measured on Doppler ultrasound, gender, age and location of index DVT. The area under the curve of this model was 0.72 with 95% CI of 0.62 to 0.82. This suggests that this model will be able to discriminate between patients that will develop PTS and those that will not 72% of the time.

Model 2 – The following prognostic variables were included; proximal thrombosis score at six weeks on Doppler ultrasound, superficial valvular reflux at six weeks on Doppler ultrasound, gender, age, location of index DVT on Doppler ultrasound, venous outflow resistance on strain gauge plethysmography, and calf muscle pump function on

strain gauge plethysmography. The area under the curve of this model was 0.75 with 95% CI of 0.66 to 0.85. This suggests that this model will be able to discriminate between patients that will develop PTS and those that will not 75% of the time.

Model 3 – The following factors were included; overall thrombosis score on Doppler ultrasound, overall reflux score on Doppler ultrasound, gender, age, location of index DVT on Doppler ultrasound, venous outflow resistance on strain gauge plethysmography and calf muscle pump function on strain gauge plethysmography. The area under the curve of this model was 0.77 with 95% CI of 0.68 to 0.87. This suggests that this model will be able to discriminate between patients that will develop PTS and those that will not 77% of the time.

Model 4 – The following factors were included; overall thrombosis score on Doppler ultrasound, overall reflux score on Doppler ultrasound, gender, age, location of index DVT on Doppler ultrasound, venous outflow resistance on strain gauge plethysmography, calf muscle pump function on strain gauge plethysmography and provoked thrombosis. The area under the curve of this model was 0.79 with a 95% CI of 0.70 to 0.88. This model had the largest area under the curve and the narrowest confidence interval. The reported statistic suggests that this model will be able to discriminate between patients that will develop PTS and those that will not 79% of the time.

The reported performance statistics of the models demonstrated that all the models developed by this study have some accuracy in predicting risk of developing PTS. However, as earlier mentioned, there was a lot of poor reporting in this study so much that it was very difficult to decide if this study was indeed a prognostic model study or

just a study of predictive factors. The presence of reports that models were developed and the reporting of performance variable of developed models led to the classification of this study as a prognostic model study. The presence of poor reporting in addition to the absence of external and internal validation of the models limited the strength of conclusions that could be made from this study.

Table 14: Prognostic models

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Model	Variables included in model	Effect measure and sizes (95% confidence intervals) if reported
Tick et al 2010[149]	The Netherlands	111	CEAP	46% at 3 months	24	Model 1	Proximal TS, Superficial valvular reflux, gender, age, location of DVT	AUC 0.72 (0.62 to 0.82)
						Model 2	Proximal TS, superficial valvular reflux, gender, age, location of DVT, VOR, and CMP function	AUC 0.75 (0.66 to 0.85)
						Model 3	Overall TS, overall reflux score, gender, age, location of DVT, VOR and CMP function	AUC 0.77 (0.68 to 0.87)
						Model 4	Overall TS, overall reflux score, gender, age, location of DVT, VOR, CMP function and provoked thrombosis	AUC 0.79 (0.70 to 0.88)

Key: AUC – Area under the curve CMP – Calf muscle pump function DVT – Deep venous thrombosis NR – Not reported

PTS – Post-thrombotic syndrome TS – Thrombosis score VOR – Venous outflow resistance

3.5.3.2.2 Findings from potential prognostic factors assessed in multivariate analysis only

Details on prospective cohort studies that assessed associations between potential prognostic factors and PTS after DVT of the lower limb in a multivariate analysis are summarised and presented below. The studies are discussed under each potential prognostic factor identified. Details presented include, the description and measure of the potential prognostic factor where relevant, the sample size of the study, the follow up duration of patients, the PTS diagnostic methods used, the incidence of PTS as well as the variables and results of the multivariate analysis done.

3.5.3.2.2.1 Location of DVT

The term "location of DVT" describes the site of DVT for example "popliteal DVT", "calf DVT" or "ilio-femoral DVT".

Location of DVT was included in the prognostic model study as a potential prognostic variable[149] (see Section 3.5.3.2.1). The effect sizes quantifying the performance of the location of DVT in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of location of DVT or to quantify the weight of location of DVT in the models.

In five prospective cohort studies[13,158,159,166,167] the association between location of index DVT and the subsequent development of PTS from a multivariate analysis was reported (see Table 15). The sample sizes of the studies were 84 patients,[158] 121 patients,[167] 355 patients,[159] 406 patients[166] and 1668 patients.[13] The minimum follow up

period across the studies was 12 months[13] and the maximum follow up period was 96 months.[159]

The location of DVT was determined by ultrasonography,[13,166,167] venography,[158,159,166] impedance plethysmography[13] or computed tomography of the abdomen.[13]

PTS diagnostic methods used across studies included an adaptation of the Villalta scale for interviews conducted in person or over the phone.[13] This adaptation consisted of a combination of clinical signs and symptoms which were similar but not encompassing of all the criteria on the Villalta scale. In one study the Villalta scale was used,[159] while the CEAP classification was used in two studies[166,167] In one study[158] PTS was diagnosed using an unnamed scale developed for diagnosing chronic venous insufficiency by Kakkar and Lawrence in their study.[43] In one study[159] diagnosis of PTS was made only when patient scores crossed the threshold for diagnosis of PTS on the Villalta scale on at least two consecutive occasions. In the other four studies a diagnosis of PTS was made when the threshold for diagnosing PTS was crossed on one occasion.

The incidence of PTS across four of the studies was reported as 17.3% to 25% at 12 months,[13,159] 22.8% at 24 months,[159] 56% at 36 months,[158] 21% at 66 months[167] and 29.1% at 96 months.[159] It was more difficult to deduce the specific incidence of PTS across the years in the fifth study[166] as an incidence level of 43% was reported for a follow up period between 21 months and 67 months. The differences in timing of PTS assessment across studies made it difficult to extensively compare studies with a view to detect if diagnosing PTS after two consecutive occasions as was done in one study,[159] could affect the reported incidence of PTS. However at 12 months follow up in the study (in which PTS was diagnosed only after two consecutive occasions of crossing the

threshold), a comparatively lower incidence of PTS was reported compared to another study[13] that assessed PTS at a similar time point. In this study[13] an adaptation of the Villalta scale for over the phone use was employed for PTS diagnosis. As this method of PTS diagnosis comprised of only patient reported components unlike the unadapted Villalta scale that includes both patient reported and clinician implemented components, it was not ideal to compare incidence of PTS diagnosed by these methods.

In one study,[167] factors adjusted for in the multivariate analysis conducted were not reported. Meanwhile, the reported factors adjusted for in the multivariate analysis by the other studies were varied. They included, age,[13,154,158,166] gender,[13,158,166] cancer,[13,154] D-dimer >500ng/ml,[166] BMI,[13,166] factor V Leiden,[166] factor VIII,[166] factor II G20210A,[166] duration of index DVT symptoms,[13] recurrent ipsilateral DVT[159] and varicose veins,[13]

One study of poor quality[13] demonstrated that the presence of a clot in the popliteal vein made no difference when determining the risk of developing PTS with a relative risk of one (confidence intervals and p-value not reported). Another study of poor quality[158] and one of fair quality[159] demonstrated that the presence of a clot in the popliteal vein may increase the risk of developing PTS with a hazard ratio of 1.2 (confidence intervals and p-value not reported),[159] and an odds ratio of 13.30, 95% CI (2.49 to 71.15).[158] Four studies with varied quality (two poor quality[158, 13] and two fair quality studies[167,166]) demonstrated that proximal location of DVT at presentation was associated with an increased risk of PTS when compared to calf DVT (see Table 15). The finding was statistically significant in three of the studies[166,13,167] and was not statistically significant in the fourth study.[158]

These studies suggest that a proximally located DVT (in the knee and above) may be strongly associated with an increased risk of PTS afterwards. However conclusion that can be made from the evidence is limited because it is mostly from fair to poor quality studies.

Table 15: Location of DVT

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factor	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Monreal et al 1993[158]	Spain	84	Scale by Kakkar and Lawrence	56% at 36 months	36	Tibial DVT	Age and gender	OR 0.98 0.20 to 4.9	NR
						Popliteal DVT	Age and gender	OR 13.30 2.49 to 71.15	NR
						Femoral DVT	Age and gender	OR 2.96 0.50 to 17.33	NR
						Iliac DVT	Age and gender	OR 1.24 0.28 to 5.57	NR
Prandoni et al 1996 [159]	Italy	355	Villalta	17.3% at 12 months, 22.8% at 24 months, and 28% at 60 months, 29.1% at 96 months	96	Popliteal vein DVT	Ipsilateral recurrence	HR 1.2 NR	NS
Stain et al 2005[166]	Austria	406	CEAP	43.3% at 44±23 months	44±23	Proximal DVT	Age, gender, D-dimer >500ng/ml, BMI, Factor V Leiden, Factor VIII, Factor II G20210A	OR 2.1 1.3 to 3.7	NR

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factor	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Calf vein DVT	Gender, age, BMI, symptoms duration before DVT diagnosis, varicose veins at diagnosis, cancer	RR 0.9 0.6 to 1.3	NR
						Popliteal vein DVT	As above	RR 1 na	NR
						Femoral and iliac vein DVT	As above	RR 1.4 1.1 to 1.8	NR
Yamaki et al 2010[167]	Japan	121	CEAP	21% at 66months	66	Prognostic factors at initial presentation			
						Ilio-femoral DVT	NR	OR 3.44 1.38 to 8.58	0.008
						Calf DVT	NR	OR 0.10 0.01 to 0.79	0.028

Key: BMI – Body mass index CEAP – Clinical anatomical aetiological and pathophysiological DVT – Deep venous thrombosis

HR – Hazard ratio na – Not applicable NR – Not reported NS – Not significant

OR – Odds ratio PTS – Post-thrombotic syndrome RR – Relative risk

3.5.3.2.2.2 Extent of DVT

The term "extent of DVT" is used to describe the size of a thrombus. Sometimes it is described in simple terms for example "calf DVT with extension to ilio-femoral region". Other times it is presented in numerals when clot grading measures such as the thrombosis score[36] or the Marder score[219] have been used to describe the extent of DVT. The "extent of DVT" lends itself to providing more information about the characteristic of the thrombus by giving quantitative information on the size of the thrombus when compared to "location of DVT". Though, the size of DVT may be inferred from the site of DVT (as a clot in proximal veins is expected to be larger than a clot in the distal veins because of the size of the veins), this is not always the case, so that the site of DVT is not an accurate measure of extent of DVT.

The extent of DVT as measured by the thrombosis score was included as a potential prognostic variable in four prognostic models[149] (see Section 3.5.3.2.1). The effect sizes quantifying the performance of the extent of DVT in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of extent of DVT or to quantify the weight of extent of DVT in the models.

Six prospective cohort studies with multivariate analysis assessing the relationship between PTS and the extent of DVT were identified[34,154,158,159,161,162] (see Table 16). These studies had sample sizes of 84 patients,[158] 86 patients,[154] 93 patients,[161] 113 patients,[162] 355 patients[159] and 387 patients.[34] The minimum follow up period of these studies was 12 months[161,162] and the maximum follow up period was 96 months.[159]

In two of the studies[34,159] extent of DVT was measured by ultrasonography or venography to determine if there was a proximal DVT in addition to a calf DVT or a calf DVT only. In the other three studies clot grading scores on venography were used to measure extent of DVT. In one study[158] the Marder score was used,[219] and extent of thrombosis was classified into dummy variables, while in three studies[154,161,162] the thrombosis score[36] was used. The recordings of extent of DVT were carried out at one time point (at diagnosis of DVT) in three studies.[34,158,159] In the other three studies, extent of DVT was measured at seven days,[162] one month,[154,161,162] three month,[154,161,162] six months,[154] 12 months[154] and 24 months.[154]

PTS diagnostic methods used across studies include the Villalta scale,[34,159,162] CEAP classification[154, 161,162] and an unnamed scale[158] (developed for diagnosing chronic venous insufficiency by Kakkar and Lawrence in their study[43]). One study[159] made a diagnosis of PTS only when patient scores crossed the threshold for diagnosis of PTS on the Villalta scale on at least two consecutive occasions while other studies made a diagnosis of PTS when the threshold was crossed on one occasion.

The incidence of PTS was variable across studies. It was between 17.3% to 49% at 12 months,[159,161,162] 17.8% to 71% at 24 months,[34,154,159,161] 56% at 36 months,[158] 22.8% at 60 months,[159] 56% at 72 months[161] and 29.1% at 96 months.[159] At 12 months and 24 months there was a difference in incidence of PTS reported by the study that diagnosed PTS after the threshold for diagnosis on the Villalta had been crossed on two occasions (17.3% and 17.8%)[159] and the studies that made a diagnosis on one occasion on the Villalta (45.1%)[34] scale and CEAP classification (49% to 71%).[154,161,162]

Factors adjusted for in the studies include age,[34,154,158] gender,[34,158,162] BMI,[34,162] recurrent ipsilateral DVT,[34,159] severity of Villalta score at one month,[34] duration of warfarin therapy,[34] use of compression stockings,[34] previous ipsilateral DVT,[34] C-reactive protein,[162] interleukin 6[162] and D-dimers.[162]

The pattern across four of the studies was that the extent of DVT was associated with an increased risk of developing PTS,[34,154,161,162] with one of the studies demonstrating an increased risk of developing PTS by up to two times with relative risk 2.1, 95% CI (1.1 to 4.1).[162] These studies were all high quality studies except one study[47] which was of fair quality. The two remaining studies which were of poor[158] and fair quality,[159] showed a different trend when the extent of DVT was not shown to be associated with an increased risk of PTS from their multivariate analysis.[158,159]

It was evident across two good quality studies where extent of thrombosis was measured at more than one time point[161,162] that extent of thrombosis scores measured later after DVT diagnosis was more strongly associated with the development of PTS, relative risk 2.1, 95% CI (1.1 to 4.1) compared to scores obtained earlier, relative risk 2.5, 95% CI (0.5 to 12.9). This may explain the different findings from the two studies that found that extent of thrombosis was not associated with the development of PTS, as both studies had used only one measurement of extent of thrombosis from an earlier time point (at DVT diagnosis). A fair quality study that measured extent of thrombosis scores at three months post DVT[154] supported this finding, as it was associated with the development of PTS (see Table 16).

This evidence which was mainly from fair to good quality studies suggests that large extent of thrombosis at one month or greater than one month after a DVT diagnosis (residual thrombosis) may be strongly associated with the risk of developing PTS.

Table 16: Extent of DVT

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Haenen et al 2001[154]	The Netherlands	86	CEAP	71% at 24 months	24	High proximal TS at 3 months	Age	Pearson's *r* NR NR	0.008
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months	24	Extent of index DVT (Multivariate analysis 1[#)]	Age, BMI, Gender, Previous ipsilateral DVT	+2.23 proximal vs. distal +1.29 to +3.16	<0.001
						Extent of index DVT (Multivariate analysis 2[#)]	Age, BMI, Previous ipsilateral DVT, Severity of 1month Villalta score	+1.75 in proximal DVT vs. distal DVT +0.80 to +2.70	<0.001
						Extent of index DVT (Multivariate analysis 3[#])	Age, BMI, Previous ipsilateral DVT, Duration of warfarin use, Severity of 1month Villalta score, CS use, Recurrent ipsilateral DVT	+1.35 in proximal DVT vs. distal DVT +0.36 to +2.34	0.007

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Monreal et al 1993[158]	Spain	84	Scale by Kakkar and Lawrence	56% at 36 months	36	Extent of DVT			
						Dum 1	Age and gender	OR 0.50 0.09 to 2.76	NR
						Dum 2	Age and gender	OR 0.13 0.12 to 1.49	NR
						Dum 3	Age and gender	OR 0.72 0.05 to 10.98	NR
Prandoni et al 1996 [159]	Italy	355	Villalta	17.3% at 12 months, 22.8% at 24 months, and 28% at 60 months, 29.1% at 96 months	96	Extent of thrombosis	Ipsilateral recurrence	HR 1.1 NR	NS

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Roumen-Klappe et al 2005[161]	The Netherlands	93	CEAP	49% at 12 month, 55% at 24 month and 56% at72 month	72	Predictors of PTS at 1 month			
						TS	NA	AUC 0.57 0.41 to 0.70	NS
						VOR and TS	NA	AUC 0.68 0.53 to 0.81	<0.05
						Predictors of PTS at 3 months			
						TS	NA	AUC 0.70 0.52 to 0.79	<0.01
						VOR and TS	NA	AUC 0.72 0.54 to 0.80	<0.01
						TS and reflux	NA	AUC 0.75 0.56 to 0.82	<0.01
						VOR, TS and CMP	NA	AUC 0.75 0.55 to 0.82	<0.01
						VOR, TS and reflux	NA	AUC 0.77 0.56 to 0.82	<0.01
						TS, reflux and CMP	NA	AUC 0.76 0.54 to 0.81	<0.01
						VOR, TS, CMP and reflux	NA	AUC 0.76 0.55 to 0.82	<0.01

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals if reported	p-Value
Roumen-Klappe et al 2009[162]	The Netherlands	113	CEAP and Villalta	36.7% with CEAP at 12 months, 35.4% using Villalta at 12 months	12	TS day 7 (CEAP)	Gender, BMI, IL 6, CRP, D-dimers	RR 2.5 0.5 to 12.9	NR
						TS day 30 (CEAP)	As above	RR 2.0 0.8 to 5.4	NR
						TS day 90 (CEAP)	As above	RR 2.0 1.1 to 3.7	NR
						TS day 7 (Villalta)	As above	RR 6.0 0.9 to 41.1	NR
						TS day 30 (Villalta)	As above	RR 3.4 1.1 to 10.1	NR
						TS day 90 (Villalta)	As above	RR 2.1 1.1 to 4.1	NR

Key : [#] – Effect sizes are reported as mean change in Villalta scores

AUC – Area under the curve

BMI – Body mass index

CEAP – Clinical anatomical aetiological and pathophysiological

CMP – Calf muscle function

Dum – Dummy variable to categorise extent of thrombosis

DVT – Deep venous thrombosis

CRP – C-reactive protein

CS – Compression stockingsIL-6 – Interleukin 6

INR – International normalised ratio

MA – Multivariate analysis

MRV – Mean reflux velocity

NR – Not reported

NS – Not significant

PTS – Post-thrombotic syndrome

vs. – Versus

TS – Thrombosis score

VTE – Venous thromboembolism

VOR – Venous outflow resistance

3.5.3.2.2.3 Severity of Villalta score

The Villalta score is a diagnostic tool for PTS (see Appendix 1, Section 1.1 for description). PTS is diagnosed in patients only after three months post DVT, to avoid confusion with signs and symptoms of an underlying DVT as both conditions can present similarly. Therefore, even if the threshold for PTS diagnosis was fulfilled on the Villalta scale, a diagnosis of PTS cannot be made until three months post DVT. Use of the Villalta scale before three months could therefore be considered as a potential prognostic indicator.

The association between the scores of the Villalta scale before three months and the subsequent development of PTS was assessed in a multivariate analysis by two prospective cohort studies,[34,160] (see Table 17). The sample sizes of the studies were 122 patients[160] and 387 patients.[34]

PTS diagnostic methods used by studies include the Villalta scale[34,160] and the CEAP classification.[160] So that, Villalta scores before three months were used as a potential prognostic factor for future (three months post DVT and above) Villalta and CEAP scores. The incidence of PTS was 51.6% at 12 months from one study.[160] Only one of the studies had followed patients beyond 12 months and the reported incidence of PTS at the end of the follow up period at 24 months in that study was 45.1%.[34]

In one study, the severity of the Villalta score at one month was assessed in two of three multivariate analysis which adjusted for different factors.[34] The factors adjusted for in the first multivariate analysis that included the severity of Villalta score at one month include, age, BMI, previous ipsilateral DVT and extent of index DVT. In the second multivariate analysis all the factors in the first multivariate analysis were adjusted for in

addition to duration of warfarin use, use of compression stockings and recurrent ipsilateral DVT. The factors adjusted for in the second study[160] included age, gender, BMI, common femoral vein involvement, and use of compression stockings.

Findings from both studies showed a consistent pattern that an increase in severity of Villalta score at one month after diagnosis of DVT was significantly associated with an increased risk of developing PTS. The effect size reported by one fair quality study[34] was a mean change in Villalta score. In this study, severity of Villalta scores at one month was strongly predictive of PTS and was reported by the one of their multivariate analysis as mean change in Villalta score of: +1.97, 95% CI (+1.28 to +2.77); +5.03, 95% CI (+3.05 to +7.01); and +7.02, 95% CI (+5.03 to +8.98) for mild, moderate and severe categories of PTS on the Villalta scale at 1 month respectively. A second multivariate analysis (adjusting for different factors) by the same study reported similar findings with a mean change in Villalta score of +1.87, 95% CI (+1.05 to +1.25) for mild PTS; +4.95, 95% CI (+2.84 to +7.06) for moderate PTS; and +6.69, 95% CI (+4.59 to +8.80) for severe PTS. These findings were statistically significant (see Table 17). The second study[160] which was of good quality reported in odds ratios, there was a 1.78 increased odds of developing PTS with every unit increase of the Villalta score at one month post DVT (95% CI (1.19 to 2.64)).

The findings from identified studies can be considered valid because of the fair to good quality of studies that reported these findings. However these findings need to be considered with the fact that the Villalta scale is used for PTS diagnosis which means that these findings are expected. Although findings indicate that the severity of an initial DVT may be associated with an increased risk of PTS.

Table 17: Severity of the Villalta score

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months	24	Severity of 1month Villalta score (Multivariate analysis 1)[#]	Age, BMI, Extent of index DVT, Previous ipsilateral DVT	+1.97 for mild, +5.03 for moderate, +7 for severe vs. none +1.28 to 2.77 for mild, +3.05 to +7.01 for moderate, +5.03 to +8.98 for severe	<0.001 for mild, moderate and severe
						Severity of 1month Villalta score (Multivariate analysis 2)[#]	Age, BMI, Duration of warfarin use, Previous ipsilateral DVT, Extent of index DVT , CS use, Recurrent ipsilateral DVT	+1.87 for mild, +4.95 for moderate, +6.69 for severe +1.05 to +2.57 for mild, +2.84 to +7.06 for moderate, +4.59 to +8.80 for severe	<0.001 for mild, moderate and severe
Roberts et al 2013[160]	The United Kingdom	122	Villalta or CEAP	51.6% at 12 month	6	Villalta scale (per 1 unit increase)	Age, gender, BMI, common femoral vein involvement, and CS use	OR 1.78 1.19 to 2.64	0.005

Key: [#] - Reported as mean change in Villalta score BMI – Body mass index DVT – Deep vein thrombosis

CS – Compression stockings NR – Not reported OR – Odds ratio

PTS – Post-thrombotic syndrome vs. - versus

3.5.3.2.2.4 Previous ipsilateral DVT

Previous ipsilateral DVT is the term used to describe the history of a previous clot in the same leg being assessed.

The association between previous ipsilateral DVT and the risk of developing PTS was assessed in a multivariate analysis by three prospective cohort studies.[34,150,157] Sample sizes were 87 patients,[157] 228 patients[150] and 387 patients.[34] The minimum follow up periods of studies was 12 months[157] and the maximum follow up period was 24 months.[34,150]

Information on previous ipsilateral DVT was recorded at baseline in all studies. None of the studies specified the criteria to be met for a DVT to be termed previous ipsilateral DVT.

PTS diagnostic measure used across studies include the Villalta scale in two studies[34,150] and the Brandjes score in one study.[157] In two of these studies[150,34] for PTS to be diagnosed, individual patient scores had to have crossed the threshold for diagnosis of PTS on the Villalta scale on at least two consecutive occasions. Incidence of PTS across studies was 54% at 12 months[157] and 19% to 45.1% at 24 months.[150,34] The difference in timing of PTS assessment across studies made it difficult to detect if diagnosing PTS after two consecutive occasions made a difference to the reported incidence across studies.

Factors adjusted for was not reported by two studies.[150,157] In the third study an association between a previous ipsilateral DVT and PTS was assessed in three multivariate analysis multivariate analysis which adjusted for different factors.[34] The first multivariate analysis adjusted for age, BMI, gender and extent of DVT. The second

multivariate analysis adjusted for severity of Villalta score at one month and all of the factors in the first multivariate analysis except gender. While the third multivariate analysis adjusted for duration of warfarin therapy, compression use and recurrent ipsilateral DVT in addition to all factors in the second multivariate analysis.

There was consistency in findings across studies that a previous history of ipsilateral DVT was associated with the development of PTS in the same limb 12 to 24 months after an index DVT. The odds of developing PTS was increased by up to six to eight times more than in a patient with no history of a previous ipsilateral DVT. One study of fair quality[150] reported an odds ratio of 6.3, 95% CI (1.5 to 26.9), a second study which was of poor quality[157] reported an odds ratio of 8.8, 95% CI (1.6 to 49). While the third study[34] which was of fair quality reported mean change in Villalta score from three multivariate analysis. The first multivariate analysis reported the mean change in Villalta score as +1.78, 95% (CI +0.69 to +2.87), the second multivariate analysis reported similar findings to the first as +1.83, 95% (CI +0.73 to +2.90) while the third multivariate analysis reported a mean change in Villalta score of +1.43, 95% (+0.31 to +2.53). The findings across studies were statistically significant.

Findings from all three studies suggest that a previous ipsilateral DVT was strongly associated with the development of PTS after a DVT of the lower limb. There are limitations to the conclusions that can be made from this evidence as it is from only fair to poor quality studies.

Table 18: Previous ipsilateral DVT

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Bouman et al 2012 [150]	The Netherlands	228	Villalta	19% at 24 months	24	Previous ipsilateral DVT	NR	OR 6.3 1.5 to 26.9	0.012
Kahn et al 2008[34]	Canada	387	VILALLTA	Cumulative incidence 45.1% at 24 months	24	Multivariate analysis 1 (Previous ipsilateral DVT)[#]	Age, BMI, Gender, Extent of index DVT	+1.78 in previous ipsilateral DVT vs. no previous ipsilateral DVT +0.69 to +2.87	0.001
						Multivariate analysis 2 (Previous ipsilateral DVT) [#]	Age, BMI, Extent of index DVT, Severity of 1month Villalta score	+1.83 in previous ipsilateral DVT vs. no previous ipsilateral DVT +0.73 to +2.90	0.001
						Multivariate analysis 3 (Previous ipsilateral DVT) [#]	Age, BMI, Duration of warfarin use, Recurrent ipsilateral DVT, Extent of index DVT , CS use, Severity of 1month Villalta score	+1.43 in previous ipsilateral DVT vs. no previous ipsilateral DVT +0.31 to +2.53	0.012
Lopez-Azkarreta et al 2004[157]	Spain	87	Brandjes	54% at 12 months	12	Previous ipsilateral DVT	NR	OR 8.8 1.6 to 49	0.01

Key: [#] - Reported as mean change in Villalta score BMI – Body mass index DVT – Deep vein thrombosis CS – Compression stockings

HR – Hazard ratio NR – Not reported OR – Odds ratio PTS – Post-thrombotic syndrome vs. - versus

3.5.3.2.2.5 Ipsilateral recurrent DVT

Ipsilateral recurrent DVT was said to occur when DVT recurred in the same limb being assessed during study follow up.

Two prospective cohort studies[34,159] with multivariate analysis exploring the association between ipsilateral recurrent DVT and the development of PTS after DVT of the lower limb was identified. The sample sizes of the studies were 355 patients[159] and 387 patients.[34] The minimum follow up period across studies was 24 months[34] and the maximum follow up period was 96 months.[159]

The criterion for recurrent venous thrombosis in one of the studies[159] was the occurrence of a new intraluminal filling defect on venogram or in the absence of a definite diagnosis on venogram, an abnormal 125I-fibrinogen leg scan or results of non-invasive tests that had changed from normal to abnormal. In the second study,[34] the criterion for recurrent venous thrombosis was an objective diagnostic work up on suspecting a recurrence. This study[34] reported that the objective criteria consisted of algorithms and criteria by Wells et al[220] and Kearon et al.[221]

The Villalta scale was used in both studies to diagnose PTS. For PTS to be diagnosed across both studies, individual patient scores had to have crossed the threshold for diagnosis of PTS on at least two consecutive occasions.

The incidence of PTS was reported as 40% at 4 months,[34] 38% at 8 months,[34] 17.3 to 39% at 12 months,[34,159] 22.8 to 40% at 24 months,[34,159] 28% at approximately 60 months[159] and 29.1% at 96 months.[159]

One of the studies[159] did not report on the factors adjusted for in their multivariate analysis. The second study[34] reported that they adjusted for the following factors, age, BMI, gender, previous ipsilateral DVT, severity of Villalta score at one month, duration of warfarin therapy, extent of index DVT and use of compression stockings.

Both studies were of fair quality. There was consistency in the results across both studies as they both demonstrated that ipsilateral recurrent DVT was associated with an increased risk of developing PTS. This association was strong in one study with a hazards ratio of 6.4, 95% CI (3.1 to 13.3)[159] and weak in the second study with a mean change in Villalta score of +0.26, 96% CI (-1.40 to +1.91).[34]

This evidence from two fair quality studies suggests that ipsilateral recurrent DVT may be associated with an increased risk of PTS after DVT.

Table 19: Ipsilateral recurrent DVT

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Kahn et al 2008[34]	Canada	387	VILALLTA	Cumulative incidence 45.1% at 24 months (40% at 4 months, 38% at 8 months, 39% at12 months and 40% at 24months)	24	Recurrent ipsilateral DVT	Age, BMI, Duration of warfarin use, Previous ipsilateral DVT, Extent of index DVT , CS use, Severity of 1month Villalta score	+0.26 in recurrent ipsilateral DVT vs. no recurrent ipsilateral DVT -1.40 to +1.91	0.76
Prandoni et al 1996[159]	Italy	355	Villalta	17.3% at 12 months, 22.8% at 24 months, and 28% at 60 months, 29.1% at 96 months	96	Ipsilateral recurrence	NR	HR 6.4 3.1 to 13.3	NR

Key: BMI – Body mass index DVT – Deep vein thrombosis CS – Compression stockings HR – Hazard ratio NR – Not reported

OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.6 Venous parameters

As explained in Chapter 1, the pathophysiology of PTS is poorly understood, however a combination of factors including venous reflux, venous occlusion and calf muscle dysfunction have been identified as contributors to the pathogenesis of PTS. This hypothesis led some authors[167,194] to assess the function of the calf venous system after a patient has had a DVT and the relationship it has with the subsequent development of PTS in a multivariate analysis. The parameters assessed include thrombi occlusion of the venous system, venous reflux, venous outflow resistance, venous reflux velocity and venous retension index. The methods and findings of studies that have explored the relationship between these venous parameters and subsequent development of PTS in a multivariate analysis are detailed in this section.

3.5.3.2.2.6.1 Thrombi occlusion of the vein

Thrombi occlusion of the vein is a term that describes the occlusion of the venous system by the thrombus at presentation of the index DVT.

Two prospective cohort studies with multivariate analysis[159,167] exploring the association between thrombi occlusion and the risk of developing PTS after DVT was identified. However, only one of the studies looked at an independent relationship between thrombi occlusion and the risk of developing PTS.[159] The second study looked at the relationship between the venous reflux and thrombi occlusion in association with the development of PTS.[167] The sample size of the studies were 121 patients[167] and 355 patients.[159] The minimum follow up of the studies was 66 months[167] and the maximum follow up period was 96 months.[159]

Thrombi occlusion was determined at initial presentation by duplex ultrasound in one study[167] and venogram in the second study.[159]

PTS diagnostic methods used in the studies were the Villalta scale[159] and the CEAP classification.[167] The study that used the Villalta scale made a diagnosis of PTS after patients had crossed the threshold for diagnosis of PTS on at least two consecutive occasions.

The incidence of PTS was 17.3% at 12 months,[159] 22.8% at 24 months,[159] 28% at 60 months,[159] 21% at 66 months[167] and 29.1% at 96 months.[159]

Factors adjusted for was not reported by one study.[167] The second study[159] reported factors adjusted for as extent of thrombosis, thrombi in the popliteal vein and ipsilateral recurrent DVT.

Both studies were of fair quality. One of the studies demonstrated that there was no association between the development of PTS and thrombi occlusion at initial presentation (hazard ratio 0.8, confidence intervals and p-values not reported but "no association" stated).[159] However, the second study[167] found that the combination of thrombi occlusion and venous reflux measured at initial presentation was associated with an increased odds of developing PTS by about four times with an odds ratio of 4.4, 95% CI (2.82 – 20.72).

Both studies did not have sufficient homogeneity for their results to be compared. Therefore, although both studies seemed to demonstrate conflicting reports on the association between thrombi occlusion and the risk of PTS after DVT of the lower limb, it is in fact not possible to compare reported data on thrombi occlusion from both studies as they measured different things. What the evidence suggests from a study of

fair quality is that thrombi occlusion on its own is not associated with the development of PTS after DVT however when combined with venous reflux, it may be associated with the development of PTS after DVT.

Table 20: Thrombi occlusion

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Prandoni et al 1996[159]	Italy	355	Villalta	17.3% at 12 months, 22.8% at 24 months, and 28% at 60 months, 29.1% at 96 months	96	Venous occlusion	Ipsilateral recurrence	HR 0.8 NR	NS
Yamaki et al 2010[167]	Japan	121	CEAP	21% at 66 months	66	Venous occlusion and venous reflux	NR	OR 4.40 2.87 to 20.72	<0.0001

Key: DVT – Deep vein thrombosis HR – Hazard ratio NR – Not reported NS – Not significant

OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.6.2 Venous reflux

Venous reflux is the term used to describe the backflow of blood in the venous system. When this occurs in the superficial veins it is called superficial venous reflux and when it occurs in the deep veins it is called deep venous reflux.

Venous reflux was included as a potential prognostic variable in four prognostic models[149] (see Section 3.5.3.2.1). The effect sizes quantifying the performance of venous reflux in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of venous reflux or to quantify the weight of venous reflux in the models.

The association between venous reflux and the development of PTS was assessed in five prospective cohort studies[33,156,161,167,169] in a multivariate analysis. Sample size of the studies were 86 patients,[33] 93 patients,[161] 121 patients,[38] 125 patients[169] and 387 patients.[156] The minimum follow up was 24 months[33,156,169] and the maximum follow up period was 72 months.[161]

Venous reflux was determined at baseline (DVT diagnosis) with the aid of duplex ultrasound by two studies,[161,167] at six months post DVT with duplex ultrasound by one study,[169] at 12 months post DVT with compression ultrasonography by one study[156] and at three months, six months, 12 months and 24 months post DVT by duplex ultrasound in a fifth study.[33] One study explored the relationship between superficial venous reflux as well as deep venous reflux after DVT and subsequent development of PTS independently.[33] Another study explored the relationship between combined superficial reflux and deep venous reflux and subsequent development of PTS after DVT.[169] The remaining three studies[156,161,167] assessed only deep venous reflux after DVT in relation

to the development of PTS, although one of these studies[161] also assessed deep venous reflux combined with thrombosis score, venous outflow resistance and or calf muscle pump function.

The Villalta scale was used as a PTS diagnostic measure in two of the studies.[156,169] These studies only made a diagnosis of PTS if the threshold of making a diagnosis of PTS on the Villalta scale was crossed on two consecutive occasions. The other three studies used the CEAP classification[33,161,167] to make a diagnosis of PTS.

The incidence of PTS across included studies was 49% at 12 months,[161] 21.1% to 71% at 24 months,[33,156,169] 21% at 66 months[167] and 56% at 72 months.[161] The reported incidence of PTS was lower at 24 months in studies that made a diagnosis of PTS after the threshold for diagnosis had been crossed on two consecutive occasions (21% to 45.1%)[156,169] compared to a study that made a diagnosis on one occasion (71%).[33] It was not clear if this difference was due to the difference in number of assessments before diagnosis or due to the different PTS diagnostic method used.

In two studies[161,167] the relationship between the development of PTS and venous reflux was assessed in combination with other factors; thrombi occlusion,[167] venous outflow resistance,[161] extent of thrombosis as determined by the thrombosis score[161] and calf muscle pump function.[161] The other three studies only assessed venous reflux as an independent factor in relation to the development of PTS.

In two studies the factors adjusted for in their multivariate analysis was not specified.[161,167] A second study reported that varicose veins/venous insufficiencies and three month duration of anticoagulation was adjusted for. Another study reported that age was adjusted for[38] while a fourth study[155] reported that the following factors were

adjusted for; age, BMI, gender, previous ipsilateral DVT, type of DVT (cancer related, other provoked DVT or unprovoked DVT), extent of DVT and use of compression stockings.

One study of fair quality[167] found that the combination of venous reflux and thrombi occlusion at initial presentation was associated with an increased odds of developing PTS by about four times with an odds ratio of 4.4, 95% CI (2.82 to 20.72). A second study[161] also of fair quality found that venous reflux measured at three months post DVT, was a potentially predictive of the development of PTS after DVT of the lower limb (area under the curve 0.69, 95% CI (0.53 to 0.80)). The area under the curve increased when venous reflux was combined with extent of thrombosis (area under the curve 0.75, 95% (CI 0.56 to 0.82)) and venous outflow resistance (area under the curve 0.72, 95% (CI 0.54 to 0.82)). The combination of venous reflux with venous outflow resistance and extent of thrombosis gave an area under the curve of 0.77, 95% CI (0.56 to 0.82). The replacement of venous outflow resistance with calf muscle pump function did not make a difference and neither did the combination of all four factors (see Table 21). A third study[33] which was of good quality found that superficial reflux measured at three months, six months and 12 months post DVT was associated with the development of PTS. No association between deep venous reflux and the development of PTS was found in the same study (see Table 21). A fourth study[156] also of good quality, demonstrated that venous reflux was associated with the development of moderate-severe PTS compared to no or mild PTS with an odds ratio of 2.72, 95% CI (1.25 to 5.9) in a statistically significant relationship. While a fifth study which was also of good quality found no association between combined venous reflux and PTS,[169] effect estimate and size was not reported in this study.

There seemed to be conflict in the evidence including those from the three good quality studies, with two of them showing a significant association and one showing no association. The heterogeneity among the studies with regards to the actual combination of the factor assessed for and the effect size calculated can account for this. This evidence from mainly fair to good quality studies suggest that any kind of venous reflux or superficial venous reflux or venous reflux that occurs with venous occlusion may be a potential prognostic factor associated with the development of PTS after a DVT of the lower limb.

Table 21: Venous reflux

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Haenen et al 2002[33]	The Netherlands	86	CEAP	71% at 24 months	24	Superficial reflux at 3 months	Age	Pearson's *r* 0.37 NR	≤0.02
						Superficial reflux at 6 months	Age	Pearson's *r* 0.36 NR	≤0.02
						Superficial reflux at 12 months	Age	Pearson's *r* 0.32 NR	≤0.02
						Deep venous reflux at 3 months	Age	Pearson's *r* -0.08 NR	0.5
						Deep venous reflux at 6 months	Age	Pearson's *r* 0.06 NR	0.6
						Deep venous reflux at 12 months	Age	Pearson's *r* 0.17 NR	0.2
Latella et al 2010[156]	Canada	387	Villalta	45.1% at 24 months	24	Deep venous reflux at 12 months	Age, Gender, BMI, Previous ipsilateral DVT, Type of DVT(cancer related, other provoked DVT or unprovoked DVT), Extent of DVT, CS use	OR 2.72 1.25 to 5.9	0.01

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Roumen-Klappe et al 2005[161]	The Netherlands	93	CEAP	49% at 12 months, 55% at 24 months and 56% at72 months	72	Deep venous reflux at 3 months	NA	AUC 0.69 0.53 to 0.80	<0.05
						Deep venous reflux and VOR at 3 months	NA	AUC 0.72 0.54 to 0.82	<0.01
						Deep venous reflux and TS at 3 months	NA	AUC 0.75 0.56 to 0.82	<0.01
						Deep venous reflux, VOR and TS at 3 months	NA	AUC 0.77 0.56 to 0.82	<0.01
						Deep venous reflux, TS and CMP at 3 months	NA	AUC 0.76 0.54 to 0.81	<0.01
						Deep venous reflux, VOR, TS and CMP at 3 months	NA	AUC 0.76 0.55 to 0.82	<0.01
Ten Cate-Hoek et al 2010[169]	The Netherlands	125	Villalta	13.3% at 6 months, 17% at 12 months and 21.1% at 24 months	24	Superficial and deep venous reflux at 6 months	Varicose veins/ venous insufficiencies, 3month duration of anticoagulation	NR NR	NR

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Yamaki et al 2010[167]	Japan	121	CEAP	21% at 66 months	66	Deep venous reflux and Occlusion	NR	OR 4.40 2.87 to 20.72	<0.0001

Key: AUC – Area under the curve BMI – Body mass index CMP – Calf muscle pump function DVT – Deep vein thrombosis

NA – Not applicable NR – Not reported OR – Odds ratio PTS – Post-thrombotic syndrome

TS – Thrombosis score VOR – Venous outflow resistance

3.5.3.2.2.6.3 Venous outflow resistance

Venous outflow resistance was included as a potential prognostic variable in three prognostic models[149] (see Section 3.5.3.2.1). The effect sizes quantifying the performance of venous outflow resistance in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of venous outflow resistance or to quantify the weight of venous outflow resistance in the models.

Three prospective cohort studies with multivariate analysis[154,161,162] exploring the association between venous outflow resistance and the development of PTS after DVT was identified (see Table 22). The sample sizes were 93 patients,[161] 86 patients[154] and 113 patients.[162] The minimum follow up was 12 months[162] and the maximum follow up was 72 months.[161]

All studies used the strain gauge plethysmography to determine venous outflow resistance at different time points post the index DVT. These time points include seven days,[162] one month,[154,161,162] three months[154,161,162] and 12 months.[154]

Two studies used only the CEAP classification for PTS diagnosis[154,161] while, one study used both the Villalta score and the CEAP classification to make a diagnosis of PTS[162] (there was close similarity in the reported incidence of PTS at 12 months using the CEAP classification and Villalta scale; 36.7% and 35.4% respectively).

The incidence of PTS across the studies was 35.4 to 49% at 12 months,[161,162] 55 to 71% at 24 months[154,161] and 56% at 72 months.[161]

Factors adjusted for in two studies include; age,[162] gender,[162] BMI,[162] interleukin 6,[162] C-reactive protein[162] and D-dimers.[162]

High venous outflow resistance at one month and 12 months post DVT was shown by one study of fair quality[154] to be associated with the development of PTS, effect measure used was the Pearson's r, however the effect size was not reported, only the p-values were reported as ≤0.001 and ≤0.002 respectively. Findings from the other two studies which were both of good quality supported these results as their findings also demonstrated that high venous outflow resistance at one month and three months post DVT was significantly associated with the development of PTS[161,162] (see Table 22). There was a slight difference in strength of association when venous outflow resistance was measured earlier as demonstrated by one of the studies.[162] The venous outflow resistance on day seven was weakly associated with the development of PTS when the Villalta score was used for PTS diagnosis as opposed to when the CEAP was used[162] (see Table 22). There was also a strong association with an increased risk of PTS when venous outflow resistance was combined with extent of thrombosis (determined by the thrombosis score) and or venous reflux and or calf muscle pump function.[161] The combination of venous outflow resistance, venous reflux, extent of thrombosis and calf muscle pump function gave an area under the curve of 0.76, 95% CI (0.55 to 0.82).[161]There was no association when venous outflow resistance was combined with calf muscle pump function only.[161]

This evidence from good quality studies suggests that a high venous outflow resistance (a venous function test not routinely measured in practice) maybe associated with the development of PTS and this association is strengthened by the addition of other venous

parameters. This finding can be considered valid because of the good quality of studies that reported these findings.

Table 22: Venous outflow resistance

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Haenen et al 2001[154]	The Netherlands	86	CEAP	71% at 24 months	24	High VOR at 1 month	Age	Pearson's *r* NR NR	0.001
						High VOR at 12 month	Age	Pearson's *r* NR NR	0.002
Roumen-Klappe et al 2005[161]	The Netherlands	93	CEAP	49% at 12 months, 55% at 24 months and 56% at72 months	72	Predictors of PTS 1 month post DVT			
						VOR	NA	AUC 0.70 0.56 to 0.83	<0.01
						VOR and TS	NA	AUC 0.68 0.53 to 0.81	<0.05
						Predictors of PTS 3 months post DVT			
						VOR	NA	AUC 0.60 0.49 to 0.77	NS
						VOR and TS	NA	AUC 0.72 0.54 to 0.80	<0.01
						VOR and venous reflux	NA	AUC 0.72 0.54 to 0.82	<0.01
						VOR and CMP	NA	AUC 0.63 0.50 to 0.79	NS
						VOR, TS and CMP	NA	AUC 0.75 0.55 to 0.82	<0.01

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
						VOR, TS and venous reflux	NA	AUC 0.77 0.56 to 0.82	<0.01
						VOR, TS, CMP and venous reflux	NA	AUC 0.76 0.55 to 0.82	<0.01
Roumen-Klappe et al 2009[162]	The Netherlands	113	CEAP and Villalta	36.7% with CEAP at 12 months, 35.4% using Villalta at 12 months	12	VOR day 7 >0.8 (CEAP)	Age, gender, BMI >25, IL-6, CRP, D-dimer	RR 2.1 0.9 to 5.1	NR
						VOR day 30 >0.8 (CEAP)	As above	RR 2.2 1.2 to 4.0	NR
						VOR day 90 >0.8 (CEAP)	As above	RR 2.1 1.2 to 3.7	NR
						VOR day 7 >0.8 (Villalta)	As above	RR 3.6 1.7 to 7.5	NR
						VOR day 30 >0.8 (Villalta)	As above	RR 2.2 1.2 to 4.1	NR
						VOR day 90 >0.8 (Villalta)	As above	RR 2.1 1.2 to 3.8	NR

Key: AUC – Area under the curve CMP – Calf muscle pump function DVT – Deep vein thrombosis na – Not applicable

NR – Not reported NS – Not significant PTS – Post-thrombotic syndrome RR – Relative risk

TS – Thrombosis score VOR – venous outflow resistance

3.5.3.2.2.6.4 Venous reflux velocity

Venous reflux velocity describes the speed of the backflow of blood. It can either be reported as an average (mean) reflux velocity or as a peak (maximal) reflux velocity.

One prospective cohort study with multivariate analysis[167] exploring the association between venous reflux velocity and the development of PTS after DVT was identified. The sample size of this study was 121 patients. The length of follow up was 66 months.

The mean, peak and total reflux velocity was measured at six months post DVT in the femoral and popliteal veins using a duplex ultrasound.

PTS diagnosis was made with the CEAP classification and the incidence of PTS at the end of the follow up period was 21%.

Factors adjusted for in the multivariate analysis were not clearly reported.

This study was of fair quality and it showed that high mean reflux velocity and peak reflux velocity in the popliteal vein at six months was associated with an increased risk of developing PTS. Mean reflux velocity (8.6cm/s) in the popliteal vein was associated with increased odds of PTS by up to 13 times (odds ratio 13.67, 95% CI (4.09 to 45.65)) while peak reflux velocity (>29.7cm/s) was associated with an increased odds of PTS by about four times (odds ratio 4.36, 95% (CI 1.53 to 12.89)).

This study suggests that high venous reflux velocity in the calf veins is strongly associated with the development of PTS after DVT of the lower limb. This evidence was from a fair quality study with a sample size of 121.

Table 23: Venous reflux velocity

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Yamaki et al 2010[167]	Japan	121	CEAP	21% at 66 months	66	POPV PRV cut off >29.7	Not clear	OR 13.67 4.09 to 45.65	<0.0001
						POPV MRV cut off >8.6	Not clear	OR 4.36 1.53 to 12.89	0.006

Key: DVT – Deep vein thrombosis MRV – Mean reflux velocity NR – Not reported OR – Odds ratio

POPV – Popliteal vein PTS – Post-thrombotic syndrome PRV – Peak reflux velocity

3.5.3.2.2.6.5 Venous blood retension index

The association between venous blood retension index six months after DVT and PTS was explored in the same prospective cohort study[167] that assessed venous reflux velocity (described in the preceding section). The PTS diagnostic method used and incidence of PTS reported with respect to venous blood retension are the same.

In the study, measurement of the calf venous blood retension index was carried out six months after DVT diagnosis using near-infrared spectroscopy which is a non-invasive method for assessing venous function (by monitoring of tissue oxygenation). Calf venous blood retension index was calculated from venous expulsion and subsequent retention parameters achieved after a pre-defined muscular activity of the calf. The venous retention volume was divided by the venous expulsion volume to calculate the venous retension index.

Receiver operator characteristic analysis was conducted and the optimal cut off point with the highest accuracy, minimal false negativity and minimal false positivity for discrimination between the group of patients that developed PTS and group of patient that did not develop PTS at the end of the follow up period was identified. A cut off point 3.5 was used. The study reported the area under the curve estimate and tried to account for cofounders. The study is of fair quality and it reported that a high retension index at six months was predictive of PTS after DVT of the lower limb with an area under the curve of 0.91 and 0.95. It was found to be a strong prognostic factor associated with the development of PTS after DVT even

after potential confounders were accounted for with an odds ratio of 67.36, 95% CI (14.26 to 318.06).

This study of fair quality suggests that a high venous blood retension index at six months post DVT is strongly associated with the development of PTS five and half years after DVT. It is important to note that measurement of venous blood retension index is a highly specialised test that is not routinely assessed in practice. Therefore applicability of findings in reality may be faced with challenges.

Table 24: Venous blood retension Index

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Yamaki et al 2010[167]	Japan	121	CEAP	21% at 66 months	66	Venous blood retension index (cut off -3.5)	NR	OR 67.36 14.26 to 318.06	<0.0001

Key: AUC – Area under the curve DVT – Deep vein thrombosis NR – Not reported OR – Odds ratio

PTS – Post-thrombotic syndrome

3.5.3.2.2.7 Calf muscle pump function

Calf muscle pump function was included as a potential prognostic variable in three prognostic models[149] (see Section 3.5.3.2.1). The effect sizes quantifying the performance of calf muscle pump function in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of calf muscle pump function or to quantify the weight of calf muscle pump function in the models.

One prospective cohort study with multivariate analysis[161] exploring the association between calf muscle pump function and the development of PTS after DVT was identified. The sample size of the study was 93 patients. These patients were followed up for 72 months.

Calf muscle pump function was measured at one month and three months post DVT using the supine venous pump function test performed by a strain gauge plethysmography.

The CEAP classification was used for PTS diagnosis. The incidence of PTS reported by the study was 49% at 12 months, 55% at 24 months and 56% at72 months.

The factors adjusted for in the analysis carried out by the study were not reported.

The study which was of fair quality showed that poor calf muscle pump function at three months post DVT was predictive of subsequent development of PTS [area under the curve was 0.58, 95% CI (0.43 to 0.73)]. When venous outflow resistance was combined with calf muscle pump function as a single test, the area under the curve increased to 0.63, 95% CI (0.50 to 0.79). This increased to 0.75, 95% CI (0.55 to 0.82)

when thrombosis score was added. The area under the curve did not change substantially when venous outflow resistance was replaced by venous reflux or when all four factors were combined together.

This study of fair quality with a sample size of 93 patients demonstrates that poor calf muscle pump function at three months post DVT was associated with the development of PTS. However, calf muscle pump function is a highly specialised test that is not routinely measured in practice. Therefore application of these findings in practice may be faced with challenges.

Table 25: Calf muscle pump function

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Roumen-Klappe et al 2005[161]	The Netherlands	93	CEAP	49% at 12 months, 55% at 24 months and 56% at72 months	72	CMP	NA	AUC 0.58 0.43 to 0.73	NS
						CMP and VOR	NA	AUC 0.63 0.50 to 0.79	NS
						CMP, VOR and TS	NA	AUC 0.75 0.55 to 0.82	<0.01
						CMP, TS and venous reflux	NA	AUC 0.76 0.54 to 0.81	<0.01
						CMP, VOR, TS, and venous reflux	NA	AUC 0.76 0.55 to 0.82	<0.01

Key: AUC – Area under the curve CMP – Calf muscle pump function NA – Not applicable NR – Not reported

NS – Not significant TS – Thrombosis score VOR – Venous outflow resistance

3.5.3.2.2.8 Gender

Gender was included in four prognostic models[149] as a potential prognostic variable (see Section 3.5.4.2.1). The effect sizes quantifying the performance of gender in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of gender or to quantify the weight of gender in the models.

Five prospective cohort studies with multivariate analysis[34, 158, 152,166,13] exploring the association between gender and the development of PTS after DVT were identified (see Table 26). Sample size across the studies were, 84 patients,[158] 328 patients,[152] 387 patients,[34] 406 patients[166] and 1668 patients.[13] Minimum follow up period across studies was five months[152] and maximum follow up period was 67 months.[166]

The following PTS diagnostic methods were used across studies; the Villalta score,[34,152] an adaptation of the Villalta score for over the phone use,[13] the CEAP classification[166] and an unnamed scale (developed for diagnosing chronic venous insufficiency by Kakkar and Lawrence in their study[43]).[158]

The incidence of PTS were reported as 40% at four months,[34] 27.1% at about six months,[152] 38% at eight months,[34] 25% to 39% at 12 months,[34,13] 40% at 24 months[34] and 56% at 36 months.[158] It was difficult to deduce the specific incidence of PTS across the years in one of the studies[166] as an incidence level of 43% was reported for a follow up period between 21 months and 67 months. The time point which the reported incidence belonged to could not be determined. Neither was it clear whether it was the cumulative incidence that was reported or not.

The factors adjusted for include age,[13,34,152,158,166] BMI,[13,34,152,166] previous ipsilateral DVT,[34] extent of index DVT,[34,158] cancer, [13] location of DVT,[13,166] D-dimer levels,[166] factor V Leiden,[166] factor VIII,[166] factor II G20210A,[166] mild venous ectasia,[152] varicose veins,[13] duration of DVT symptoms,[13] use of compression stockings[152] and poor international normalised ratio control.[152]

There was no consistency in results across studies as some studies found that gender of a patient could impact on whether a patient develops PTS or not, while others did not find a similar relationship. Two studies, one of fair quality[34] and one of poor quality[13] found that female gender was associated with an increased risk of PTS by up to 1.5 times. A poor quality study found that male gender had no impact on whether a patient developed PTS after DVT of the lower limb or not.[13] Two studies, one of good quality[152] and one of poor quality,[158] found that gender was not associated with an increased odds of developing PTS. While one study of fair quality[166] found that male gender was strongly associated with increased odds of PTS (see Table 26). There was heterogeneity in timing of assessment of PTS, measure of PTS used and effect sizes reported across studies. It was not clear whether this contributed to the conflicting reports. There was also heterogeneity in the quality of studies.

Overall, the evidence on the association between gender and development of PTS after DVT is conflicting even between fair to good quality studies. This limits the conclusions that can be made from this evidence.

Table 26: Gender

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Galanaud et al 2013[152]	Multicenter (Canada, France, Switzerland, and the USA)	328	Villalta	27.1% at 5-7 months	5 – 7	Gender	Age, poor INR control^, CS, BMI, mild venous ectasia	OR 1.596 0.890 to 2.862	NS
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months (40% at 4 months, 38% at 8 months, 39% at 12 months and 40% at 24 months)	24	Gender	BMI, Age, Previous ipsilateral DVT, Extent of index DVT	+0.79 in women +0.13 to +1.46	0.020
Monreal et al 1993[158]	Spain	84	Scale by Kakkar and Lawrence	56% at 36 months	36	Gender	Age, Extent of thrombosis	OR 0.34 0.10 to 1.15	NR
Stain et al 2005[166]	Austria	406	CEAP	43.3% at 44±23 months	44 ± 23	Gender	Age, proximal DVT, D-dimer >500ng/ml, BMI, Factor V Leiden, Factor VIII, Factor II G20210A	OR 1.6 1.0 to 2.8	NR
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Gender	Gender, BMI, Symptoms duration before DVT diagnosis, Varicose veins at DVT diagnosis, Location of DVT, cancer	RR 1.5 1.1 to 1.9	NR

Key: [#] – Effect sizes are mean change in Villalta scores BMI – Body mass index DVT – Deep venous thrombosis CS – Compression stockings

INR – International normalising ratio NR – Not reported OR – odds ratio PTS – Post-thrombotic syndrome

RR – Relative risk VTE – Venous thromboembolism

3.5.3.2.2.9 Age

Age was included in four prognostic models[149] as a potential prognostic variable (see Section 3.5.3.2.1). The effect sizes quantifying the performance of age in the models were not provided. In addition, the equation of this model was not reported. It was therefore not possible to estimate the individual predictive value of age or to quantify the weight of age in the models.

The association between age and the development of PTS was assessed by five prospective cohort studies[13,34,152,153,158] in a multivariate analysis. The sample sizes were 84 patients,[158] 135 patients,[153] 328 patients,[152] 387 patients[34] and 1668 patients.[13]

Minimum follow up period across studies was five months[152] and maximum follow up was 36 months.[158]

The following PTS diagnostic methods were used across studies; the Villalta score,[34,152,153] an adaptation of the Villalta score for over the phone use[13] and an unnamed scale (developed for diagnosing chronic venous insufficiency by Kakkar and Lawrence in their study[43]).[158]

The incidence of PTS was reported as 40% at four months,[34] 27.1% at about six months,[152] 38% at eight months,[34] 25% to 39% at 12 months,[13,34] 40% at 24 months[34] and 24.4% to 56% at 36 months.[153,158]

One of the studies fitted age in three multivariate analysis which adjusted for different factors.[34] The first multivariate analysis adjusted for BMI, gender, previous ipsilateral DVT and extent of DVT. The second multivariate analysis adjusted for severity of Villalta score at one month and all of the factors in the first multivariate analysis besides

gender. While the third multivariate analysis adjusted for duration of warfarin therapy, compression use and recurrent ipsilateral DVT in addition to all factors in the second multivariate analysis. Factors adjusted for in other studies include gender, [13,152,158] BMI,[13,152] extent of index DVT,[158] cancer,[13] location of DVT,[13] mild venous ectasia,[152] varicose veins,[13] duration of DVT symptoms,[13] use of compression stockings,[152] calf swelling larger than three cm than asymptomatic leg[153] and poor international normalised ratio control.[152]

There was conflicting results across studies. Two studies, one of fair quality[34] and one of poor quality[153] demonstrated that older age was associated with an increased risk of developing PTS. Three studies, one of good quality[152] and two of poor quality[13,158] demonstrated results contradictory to the other two studies as older age was not shown to be associated with an increased risk of PTS (see Table 27). There was heterogeneity in time of assessment of PTS, measure of PTS and effect sizes reported across studies. These could have contributed to the conflicting reports.

Overall, the evidence on the association between age and development of PTS after DVT is conflicting therefore conclusions on findings are limited.

Table 27: Age

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Galanaud et al 2013[152]	Multicenter (Canada, France, Switzerland, and the USA)	328	Villalta	27.1% at 5-7 months	5 – 7	Age	Gender, Poor INR control, CS, BMI, Mild venous ectasia	OR 1.004 0.987 to 1.022	NS
Hach-Wunderle et al 2013[153]	Germany	135	Villalta	24.4% at 36 months	36	Age	Calf swelling ≥3cm larger than asymptomatic leg	OR 1.05 1.01 to 1.09	NR
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months (40% at 4 months, 38% at 8 months, 39% at 12 months and 40% at 24 months)	24	Age (Multivariate analysis 1)[#]	BMI, Gender, Previous ipsilateral DVT, Extent of index DVT	+0.30 per +10yr +0.07 to +0.53	0.011
						Age (Multivariate analysis 2)[#]	BMI, Gender, Previous ipsilateral DVT, Extent of index DVT, Severity of 1 month Villalta score	+0.34 per +10yr +0.10 to +0.56	0.004
						Age (Multivariate analysis 3)[#]	BMI, Previous ipsilateral DVT, Extent of index DVT, Severity of 1 month Villalta score, CS use, Recurrent ipsilateral DVT, Duration of warfarin use	+0.31 per 10yr +0.08 to +0.54	0.009

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Monreal et al 1993[158]	Spain	84	Scale by Kakkar and Lawrence	56% at 36 months	36	Age	Gender, Extent of thrombosis	OR 0.98 0.94 to 1.02	NR
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	18 - 29 years	Gender, BMI, Symptoms duration before DVT diagnosis, Varicose veins at DVT diagnosis, Location of DVT, cancer	RR 1 na	NR
						30 - 39 years	As above	RR 0.8 0.5 to 1.2	NR
						40 - 49 years	As above	RR 1.1 0.8 to 1.6	NR
						50 - 59 years	As above	RR 0.7 0.4 to 1.1	NR
						60 - 69 years	As above	RR 0.4 0.2 to 0.7	NR

Key: [#] – Effect sizes are mean change in Villalta scores BMI – Body mass index DVT – Deep venous thrombosis

CS – Compression stockings INR – International normalising ratio na – Not applicable NR – Not reported

OR – odds ratio PTS – Post-thrombotic syndrome RR – Relative risk VTE – Venous thromboembolism

3.5.3.2.2.10 Body mass index

The body mass index (BMI) also known as the Quetelet's index[222] is a tool that uses height and weight parameter (weight /height^2) to estimate body fat in adults. The WHO has used this tool to define a cut off for being underweight (BMI of ≤ 18), normal weight (BMI of 18 to 24), overweight (BMI of ≥ 25) and obesity (BMI of ≥ 30).[223]

Five prospective cohort studies[13,34,152,155,163] investigated BMI as a potential prognostic factor associated with the development of PTS after DVT of the lower limb in a multivariate analysis. The studies had samples sizes of 387 patients,[34] 328 patients,[152]145 patients,[155] 110 patients[163] and 1668 patients.[13] Follow up period across studies was a minimum of five months[152] and 26 months.[155]

Four of the studies used the Villalta scale for PTS diagnoses.[34,152,155,163] One study used an adaptation of the Villalta scale (in-person or telephone interview based on the Villalta scale)[13] and another study used the CEAP classification in addition to the Villalta scale.[163] Only one study[34] made a diagnosis of PTS when patient scores crossed the cut off for diagnosing PTS on two consecutive occasions on the Villalta scale. The other scales diagnosed PTS based on one episode of crossing the threshold on their respective scales.

The incidence of PTS was 40% at four months,[34] 27.1% at approximately six months,[152] 38% at eight months,[34] 25% to 39% at 12 months,[13,163] 26.4% at 37 months[155] and 40% at 24 months.[34] The incidence of PTS measured at a similar time point (12 months) did not vary much between the Villalta score (37%) and the CEAP classification (35.4%) in the study that used both diagnostic methods.[163]

The incidence of PTS in the study that made a diagnosis of PTS after two occasions on the Villalta scale could not be compared to the incidence reported by other studies because different time points were reported. However, for a similar time point (12 months) the study that used an adapted Villalta scale over the phone reported a lower incidence of PTS compared to another study that applied the standard Villalta scale (25% versus 39%). This was most likely because the Villalta scale includes a clinician observer component which might have been under reported by patients over the phone because they did not know the signs.

Factors adjusted for in varied combinations include gender,[13,34,152,155,163] age,[13,34,152,155,163] poor international normalised ratio control,[152] compression therapy,[34,152] mild venous ectasia,[152] intensity of warfarin therapy,[155] previous VTE,[155] duration of follow up,[155] inherited thrombophilia,[155] residual DVT,[155] previous ipsilateral DVT,[34] extent of index DVT,[34] severity of one month Villalta score,[34] recurrent ipsilateral DVT,[34] duration of warfarin use,[34] symptoms duration,[13] varicose veins at presentation of DVT,[13] location of DVT[13] and cancer.[13]

Two studies, one of fair quality[155] and another of poor quality[13] assessed the relationship between risk of developing PTS and a BMI of 25. These studies found that a BMI $\geq$ 25 was weakly associated with an increased risk of PTS. Effect sizes reported include an odds ratio of 1.06, 95% CI (0.99 to 1.13)[155] and a relative risk of 1.2, 95% CI (0.9 to 1.6).[13] Three studies, two of good quality[152,163] and one of poor quality[13] found that BMI of $\geq$ 30 may be associated with a two to two and a half fold increased odds of developing PTS. Effect sizes reported by these studies include an odds ratio of 2.627, 95% CI (1.469 to 4.699)[152] and a relative risk of 1.9, 95% (CI of 1.4 to 2.4).[13] One study[163] did not show much difference in the association reported when the Villalta

scale and the CEAP classification was used [Relative risk of 2.4, 95% CI (1.3 to 4.2) when Villalta scale was used and relative risk of 2.3, 95% CI (1.4 to 4.0) when CEAP classification was used]. One study of fair quality,[34] included BMI in three different multivariate analysis and a mean increase in Villalta score of between 0.07 to 0.14 was seen per 1kg/m^2 increase in BMI (see Table 28).

Overall, regardless of differences in sample size, PTS diagnostic methods and quality of studies, the evidence suggests that an increased BMI is associated with an increased risk of developing PTS after DVT of the lower limb. The increase in effect size reported across studies with increasing BMI also suggests that the greater the BMI of patients, the greater the risk of PTS. As evidenced by the weak association with increased risk of PTS in overweight patients which became a strong association with increased risk of PTS in obese patients. These findings can be considered valid because of the fair to good quality of studies that are among studies that reported these findings.

Table 28: Body mass index

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Prognostic Factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Galanaud et al 2013[152]	Multicenter (Canada, France, Switzerland, and the USA)	328	Villalta	27.1% at 5-7 months	5 – 7	BMI≥30	Gender, Age, Poor INR control 25% of the time, CS, Mild venous ectasia	OR 2.627 1.469 to 4.699	≤0.05
Kahn et al 2005[155]	Canada	145	Villalta	37% at 26.4 months	26.4	BMI >25	Age, Gender, Intensity of warfarin therapy, Previous VTE, Duration of follow up, Inherited thrombophilia and Residual DVT at time of randomisation	OR 1.06 0.99 to 1.13	0.085
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months	24	BMI (Multivariate analysis 1)[#]	Age, Gender, Previous ipsilateral DVT, Extent of index DVT	+0.14 per +1kg/m^2 +0.08 to +0.21	<0.001
						BMI (Multivariate analysis 2)[#]	Age, Gender, Previous ipsilateral DVT, Extent of index DVT, Severity of 1 month Villalta score	+0.09 per +1kg/m^2 +0.02 to 0.15	0.007
						BMI (Multivariate analysis 3)[#]	Age, Previous ipsilateral DVT, Extent of index DVT, Severity of 1 month Villalta score, CS use, Recurrent ipsilateral DVT, Duration of warfarin use	+0.07 per 1kg/m^2 +0.02 to +0.14	0.020

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Prognostic Factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Roumen-Klappe et al 2010[163]	The Netherlands	110	CEAP Villalta	37% at 12 months (CEAP) 35.4% at 12 months (Villalta)	12	BMI >30 (CEAP)	Age and Gender	RR 2.3 1.4 to 4.0	NR
						BMI >30 (Villalta)	Age and Gender	RR 2.4 1.3 to 4.2	NR
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Underweight	Gender, Age, Symptoms duration before DVT diagnosis, Varicose veins at DVT diagnosis, Location of DVT, Cancer	RR 1.3 0.4 to 3.6	NR
						Overweight	As above	RR 1.2 0.9 to 1.6	NR
						Obese	As above	RR 1.9 1.4 to 2.4	NR

Key: [#] – Effect sizes are mean change in Villalta scores

BMI – Body mass index

DVT – Deep venous thrombosis

CS – Compression stockings

INR – International normalising ratio

NR – Not reported

OR – odds ratio

PTS – Post-thrombotic syndrome

RR – Relative risk

VTE – Venous thromboembolism

3.5.3.2.2.11 DVT symptoms duration

One prospective cohort study with multivariate analysis[13] exploring the association between the duration of symptoms before DVT and the risk of developing PTS after a DVT of the lower limb was identified. The length of duration of symptoms was self-reported by patients. A cut off point of two weeks was used, so that patients that had symptoms of DVT ≥ 2 weeks before DVT diagnosis were compared with patients that had symptoms of DVT ≤ 2 weeks in relation to the development of PTS after DVT.

The sample size of the study was 1668 and the follow up period was for 12 months.

The PTS diagnostic measure used in this study was an adaptation of the Villalta scale. This adaptation of the Villalta scale involved an in-person or telephone interview where patients were asked if some components of the Villalta scale was present.

The incidence of PTS was 25% at 12 months.

Factors adjusted for in the multivariate analysis carried out by the study include gender, BMI, age, varicose veins present at DVT diagnosis, location of DVT and cancer.

The study was of poor quality and it demonstrated that when symptoms of DVT were ≤ 2 weeks before diagnosis there was no association with PTS development after 12 months, whereas DVT symptoms duration ≥ 2 weeks prior to presentation may be associated with an increased risk of developing PTS 12 months after DVT (RR 1.2, 95% CI (0.9 to 1.6)). The conclusion that can be made from this finding is limited as it likely not a valid finding due to the poor quality of the study.

Table 29: DVT symptoms duration

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Symptoms duration ≥2wks before diagnosis	Gender, BMI, age, varicose veins at DVT diagnosis, location of DVT, cancer	RR 1.2 0.9 to 1.6	NR
						Symptoms duration ≤2wks before diagnosis	As above	RR 1 na	NR

Key: BMI – Body mass index DVT – Deep vein thrombosis na – Not applicable NR – Not reported

PTS – Post-thrombotic syndrome RR – Relative risk

3.5.3.2.2.12 Varicose veins

Varicose veins occur when veins bulge and appear twisted in the skin due to pooling of blood in the veins. They are easily visible to the eye as thick bluish strings over the skin predominantly in the lower limbs and presence of varicose veins is therefore usually determined on physical examination.

Three prospective cohort studies with multivariate analysis[13,150,169] exploring the association between presence of varicose veins in the lower limbs at DVT diagnosis and the risk of developing PTS after DVT was identified. One of these studies combined varicose veins with other signs and symptoms of venous insufficiencies.[169]

The sample size of the studies were 125,[169] 228[150] and1668.[13]

Follow up period in the studies was 24 months[150,169] and 58.8 months.[13]

PTS diagnostic methods used included an adaptation of the Villalta scale by one study[13] and the standard Villalta scale in two of the studies[150,169] (scores had to have crossed the threshold for diagnosis on at least two consecutive occasions in both studies). The incidence of PTS was 25% at 12 months[13] and 19% to 21.1% at 24 months.[150,169]

Factors adjusted for in multivariate analysis were not reported by one study. One study[13] reported that the following factors were adjusted for; gender, age, BMI, symptoms duration before DVT diagnosis, location of DVT, cancer while the third study[169] reported that they adjusted for duration of anticoagulation and venous reflux in their study.

All three studies demonstrated an increased risk of PTS after DVT of the lower limb if varicose veins were present at diagnosis of DVT. One study of fair quality[150] reported

an odds ratio of 13.4, 95% CI (3 to 59.1). Another study which was of poor quality reported a relative risk of 1.5, 95% CI (1.2 to 1.9)[13] and the third study which was of good quality[169] reported a hazard ratio of 3.2, 95% CI (1.2 to 9.1). The two studies that reported effect using odds ratio reported a larger effect size compared to the other two studies that used other effect measures (odds ratio of 13.4[150] versus hazards ratio of 3.2[169] and relative risk of 1.5[13]). This difference can be attributed to the disparity in effect estimates and disparity in sample size, as small sample sizes have been shown to overestimate odds ratios[224] (this study had a small sample size and reported in odds ratio). The effect of the small sample size can also be seen as the studies with smaller sample sizes reported wider confidence intervals (less precision) compared to the larger study that had a smaller confidence interval (more precise) in comparison.

The findings of the study that lumped varicose veins with venous insufficiency is similar to findings from the other two studies that assessed varicose veins independently. Therefore, it is possible that not differentiating varicose veins from venous insufficiency did not have a huge impact on the study's findings.

Whether varicose veins directly contribute to the pathophysiology of PTS is not clear although some PTS diagnostic methods such as CEAP classification have included varicose veins as a criterion in the diagnosis of PTS. Overall, it is evident that the presence of varicose veins at diagnosis of DVT is associated with an increased risk of PTS and is a potential prognostic factor in the determination of the risk of developing PTS after a patient has suffered DVT of the lower limb. This finding is probably valid because of fair to good quality studies that reported these findings.

Table 30: Varicose veins

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Bouman et al 2012[150]	The Netherlands	228	Villalta	19% at 24 months	24	Varicose veins present at DVT diagnosis	NR	OR 13.4 3.0 to 59.1	0.001
Ten Cate-Hoek et al 2010[169]	The Netherlands	125	Villalta	13.3% at 6 months, 17% at 12 months and 21.1% at 24 months	24	Varicose veins/venous insufficiency at DVT diagnosis	Venous reflux, 3 months duration of anticoagulation	OR 7.5 2.3 to 24.5	0.001
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Varicose veins present at DVT diagnosis	Gender, age, BMI, symptoms duration before DVT diagnosis, location of DVT, cancer	RR 1.5 1.2 to 1.9	NR
						Varicose veins absent at DVT diagnosis	As above	RR 1 na	NR

Key: BMI – Body Mass index DVT – deep vein thrombosis na – Not applicable NR – Not reported

OR – Odds ratio PTS – post –thrombotic syndrome RR – Relative risk

3.5.3.2.2.13 Cancer

The association between the presence of cancer at the time of DVT diagnosis and the risk of developing PTS after a DVT was investigated in one prospective cohort study in a multivariate analysis.[13] The sample size of the study was 1668 patients and the follow up period was 12 months. The presence of cancer was self-reported by patients in the study.

The PTS diagnostic measure used in the study was an adaptation of the Villalta scale based on in-person or over the telephone interview.

The incidence of PTS was 25% at 12 months.

Factors adjusted in the study's multivariate analysis include; gender, age, symptoms duration before DVT diagnosis, varicose veins present at diagnosis and location of DVT.

The study's findings suggest that the presence of cancer may reduce the risk of developing PTS in a weak relationship. This study is of poor quality although it consisted of a large sample size that can be said to reflect the population to a large extent. It is possible that there might have been an underestimation of PTS diagnosis in this study because the Villalta scale which has a clinical observer component was adapted for over the phone use in some patients that could not be examined in person. So that it is possible that patients were missing signs that they should be reporting leading to an underestimation of PTS diagnosis.

Overall this study shows that cancer may be a favourable prognostic factor in DVT patients with respect to subsequent development of PTS. However because of the study's limitations, the strength of conclusion that can be drawn is limited hence, more studies are needed to clarify this association.

Table 31: Cancer

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Tick et al 2008[13]	The Netherlands	1668	Adaptation of Villalta	25% at 12 months	12	Cancer present	Gender, Age, Symptoms duration before DVT diagnosis, Varicose veins present at diagnosis, Location of DVT	RR 0.8 0.4 to 1.4	NR

Key: BMI – Body mass index DVT – Deep vein thrombosis OR – Odds ratio PTS – post-thrombotic syndrome

RR – Relative risk

3.5.3.2.2.14 Duration of warfarin therapy

Warfarin is an anticoagulation agent used in the treatment of DVT usually for short periods of three months to six months.[225] The duration of warfarin therapy may be longer in other conditions for example it can be for life in cases of recurrent VTE or when used for stroke prophylaxis in patients with atrial fibrillation.[226] The duration of warfarin therapy after DVT diagnosis was assessed for an association with risk of developing PTS after DVT by one prospective cohort study in a multivariate analysis.[34]

The sample size of the study was 387 patients diagnosed with DVT and the follow up period was for 24 months.

The Villalta scale was used to diagnose PTS. The incidence of PTS was 40% at four months, 38% at eight months, 39% at 12 months and 40% at 24 months with a cumulative incidence of 45.1% at the end of the follow up period.

Factors adjusted for in the multivariate analysis included age, BMI, previous ipsilateral DVT, severity of one month Villalta score, extent of index DVT, use of compression stockings and recurrent ipsilateral DVT.

Results showed that for every month of warfarin therapy, there was a slight increase in Villalta score over time of +0.09 per month, 95% CI (+0.04 to +0.13), p-value 0.001. Therefore, hypothetically if a patient was required to use warfarin for 24 months, the mean increase in Villalta score would be 2.16. This score is not sufficient to make a diagnosis of PTS in a patient with a baseline Villalta score of zero. A diagnosis of PTS is made when the Villalta score is equal to or greater than four. Therefore, in patients that will require warfarin for longer periods, this study has demonstrated that on the

average, 44.4 months of warfarin use can potentially predispose a patient to developing PTS after DVT diagnosis.

In summary, the evidence suggests that duration of warfarin therapy was strongly associated with the development of PTS in the first 24 months after DVT diagnosis. This finding was from a study of fair quality.

Table 32: Duration of warfarin therapy

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Kahn et al 2008[34]	Canada	387	Villalta	Cumulative incidence 45.1% at 24 months (40% at 4 months, 38% at 8 months, 39% at 12 months and 40% at 24 months)	24	Duration of warfarin use	Age, BMI, Previous ipsilateral DVT, Severity of 1 month Villalta score, Extent of index DVT, CS use, Recurrent ipsilateral DVT	+0.09 per month[#] +0.04 to +0.13	<0.001

Key: [#] – Effect size is reported as mean change in Villalta scores BMI – Body mass index DVT – Deep vein thrombosis

CS – Compression stockings PTS – Post-thrombotic syndrome

3.5.3.2.2.15 Sub-therapeutic anticoagulation

The international normalised ratio is a standardised laboratory measure used to determine the adequacy of anticoagulation of a patient on an anticoagulant.[66] A range of two to three is considered therapeutic when a patient is on anticoagulants for the treatment of DVT any value below this range is considered sub-therapeutic.[66]

The association between sub-therapeutic anticoagulation and the risk of developing PTS after DVT was assessed by two prospective cohort studies in a multivariate analysis analysis,[151,152] (see Table 33). Both were sub-studies of a larger REVERSE multicentre study. The sample sizes of the studies were 328 patients[152] and 349 patients.[151] Both studies had slight differences in their population.[151,152] The population of both studies consisted of patients who had a first episode of unprovoked DVT. The presence of a primary chronic venous insufficiency in patients was an exclusion criteria for one of studies[152] so that only data on patients without signs of a primary chronic venous insufficiency were included, unlike the second study[151] where all patients with a first unprovoked DVT were included.[151,152] Patients were treated with vitamin K antagonists for six months after an initial treatment with low molecular weight heparin in both studies.

As expected, the same PTS diagnostic method (the Villalta scale) was the same in both studies.[151,152]

The incidence of PTS at five to seven months was also similar in both studies (27.1%[152] and 27.8%[151]).

In addition to the slight difference in population between the studies as described above, there were also differences in the factors adjusted for. Age, gender, BMI, concurrent pulmonary embolism and previous secondary VTE was adjusted for in one of the studies[151] and gender, age, compression stockings, BMI and mild venous ectasia were adjusted for in the second study.[152]

The pattern of result generally tended towards an increased risk of PTS with sub-therapeutic anticoagulation. The study that did not limit their analysis to those without an underlying primary chronic venous insufficiency showed an increased risk[151] compared to the study that limited its population to patients without an underlying primary chronic venous insufficiency.[152] The increased risk of PTS associated with sub-therapeutic anticoagulation did not seem to make a difference whether it there was sub-therapeutic anticoagulation for the first three months of anticoagulation or for the entire period of the anticoagulation in patients that received anticoagulation for six months[151] (see Table 33 for effect sizes).

In summary, both studies suggested that there was an increased risk of PTS when anticoagulation is not adequate in the treatment of DVT. Both studies had similar findings which was not unexpected as they were sub-studies of the same larger prospective cohort study. Their finding is likely valid as they were both studies of fair to good quality.

Table 33: Sub-therapeutic anticoagulation

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Chitsike et al 2012[151]	Multicenter (Canada, France, Switzerland, and the USA)	349	Villalta	27.8% at 5 – 7 months	5 – 7	Sub-therapeutic anticoagulation during first 3 months of anticoagulation	Age, Gender, BMI, Concurrent PE and Previous secondary VTE	OR 1.84 1.13 to 3.01	NR
						Sub-therapeutic anticoagulation for entire period of anticoagulation (5 – 7months)	Age, Gender, BMI, Concurrent PE and Previous secondary VTE	OR 1.88 1.15 to 3.07	NR
Galanaud et al 2013[152]	Multicenter (Canada, France, Switzerland, and the USA)	328	Villalta	27.1% at 5 – 7 months	5 – 7	Sub-therapeutic anticoagulation for entire period of anticoagulation (5 – 7 months)	Gender, Age, CS, BMI, Mild venous ectasia	OR 1.018 1.003 to 1.034	≤0.05

Key: BMI – Body mass index CS – Compression stockings DVT – Deep vein thrombosis INR – International normalised ratio

NR – Not reported OR – Odds ratio PE – Pulmonary embolism PTS – post-thrombotic syndrome

3.5.3.2.2.16 Inherited thrombophilia

The association between inherited thrombophilia and the development of PTS was explored by one prospective cohort study in a multivariate analysis.[155] Inherited thrombophilia in simple terms means genetic predisposition to having an abnormally increased tendency to form clots. There are various genetic mutations that may be described as inherited thrombophilia. However only factor V Leiden and pro-thrombin gene mutation were assessed in this study.

The sample size of the study was 145 patients[155] and the follow up period was for 26.4 months. Diagnosis of PTS was made with the use of the Villalta scale. The incidence of PTS at the end of the follow up period was 37%.

The factors adjusted for in multivariate analysis were age, gender, BMI, intensity of warfarin therapy, previous VTE, duration of follow up and residual DVT at time of randomisation.

This study was of fair quality and it suggests that inherited thrombophilia showed a protective effect against the risk of developing PTS after DVT with an odds ratio of 0.33, 95% CI (0.15 to 0.73).

This is an interesting finding as the presence of a thrombophilia indicates a prothrombotic state. One could presume that these group of patients therefore had an increased risk of recurrent clot formation and consequently an increased risk of PTS, as venous occlusion due to clots is one of the entities identified in the still poorly understood aetiology of PTS. It is important to note that only factor V Leiden and pro-thrombin mutation was assessed in this study. This evidence is from a fair quality study.

Further studies are required to explore this relationship as well as explore other causes of thrombophilia in relation to the development of PTS.

Table 34: Inherited thrombophilia (factor V Leiden or prothrombin mutation)

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Kahn et al 2005[155]	Canada	145	Villalta	37% at 26.4 months	26.4	Inherited thrombophilia	Age, Gender, BMI, Intensity of warfarin therapy, Previous VTE, Duration of follow up and Residual DVT at time of randomisation	OR 0.33 0.15 to 0.73	0.006

Key: BMI – Body mass index DVT – deep vein thrombosis OR – Odds ratio PTS – Post-thrombotic syndrome

VTE – Venous thromboembolism

3.5.3.2.2.17 Smoking

The association between smoking and the risk of developing PTS after DVT of the lower limb was assessed by one prospective cohort study in a multivariate analysis study.[157] In the study 87 patients were followed up for 12 months (see Table 35).

PTS was diagnosed with the use of the Brandjes tool and the incidence of PTS at the end of the follow up period was 54%.

The study reported that a multivariate analysis of the study was done however the factors adjusted for in the multivariate analysis were not reported. The study was of poor quality. Findings from the study suggest that smoking was associated with increased odds of developing PTS after DVT of the lower limb. This relationship however was a non-significant relationship. An odds ratio of 3.5, 95% CI (0.8 to 14) and p-Value of 0.09 was reported.

Conclusion on the effect of smoking as a potential prognostic factor is likely unreliable because of the poor quality of the study and the wide confidence interval reported. The study however consisted of a small sample size which may account for the wide confidence interval and weak effect reported.

Table 35: Smoking

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Lopez-Azkarreta et al 2004[157]	Spain	87	Brandjes	54% at 12 months	12	Smoking	NR	OR 3.5 0.8 to 14	0.09

Key: DVT – Deep vein thrombosis OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.18 Hormonal factors

The association between hormonal factors and the risk of developing PTS after DVT of the lower limb was assessed by one prospective cohort study in a multivariate analysis.[157] In the study 87 patients were followed up for 12 months.

In the study, hormonal factors were determined by patients who were pregnant, in the puerperium period, were on tamoxifen or oral contraceptive pills at study baseline.

The Brandjes tool was used to diagnose PTS. At the end of the follow up period, the reported incidence of PTS was 54%.

The study reported that a multivariate analysis of the study was done however the factors adjusted for in the multivariate analysis were not reported. Their multivariate analysis suggested that female hormones may be associated with an increased risk of PTS. This was however a non-statistically significant finding.

Conclusion on the effect of hormones as a potential prognostic factor associated with the development of PTS after a DVT of the lower limb is likely unreliable because of the poor quality of the study and the wide confidence interval reported indicating reduced precision. The study consisted of a small sample size which may account for the wide confidence interval and weak effect seen. Clarification on the association between hormonal factors assessed above and risk of developing PTS is required from further studies.

Table 36: Hormonal factors

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Lopez-Azkarreta et al 2004[157]	Spain	87	Brandjes	54% at 12 months	12	Hormones	NR	OR 5.7 0.9 to 3.6	0.06

Key: DVT – Deep vein thrombosis OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.19 Interleukin 6

Interleukin 6 is a cytokine secreted by macrophages and T-cells.[227] It has a role to play in the regulation of metabolic, regenerative, and neural processes as well as during the inflammatory response.[227]

Three prospective cohort studies with multivariate analysis[162,164,168] exploring the association between interleukin 6 and the risk of developing PTS after DVT were identified (see Table 37). The sample sizes of the studies were 113 patients,[162] 307 patients[164] and 725 patients.[168] The length of follow up of the studies was 12 months[162] and 24 months.[164,168]

Blood samples for interleukin 6 level measurements were taken from patients at various time points. For one study[162] blood was taken for interleukin 6 levels determination at DVT diagnosis and afterwards on day seven, day 30 and day 90. In a second study[168] blood samples were taken at DVT diagnosis and at one month and six months after DVT diagnosis. In the third study, blood sample for interleukin 6 levels was taken at four months post DVT.[164]

In one study[164] a diagnosis of PTS was made only after the threshold for PTS diagnosis had been crossed on at least two consecutive occasions on the Villalta scale. In the study, a PTS incidence of 45.9% at 24 months was reported. In a second study[168] the outcome of an assessment using the Villalta scale on only one occasion was required to make a diagnosis of PTS. The incidence of PTS in this study was 47.4% at 24 months. In the third study[162], both the CEAP classification and the Villalta scale was used to diagnose PTS, and there was only a slight difference in the incidence of PTS at the end of the follow up period (36.7% with CEAP and 35.4% with the Villalta scale at 12

months). The incidence of PTS reported by the study[164] in which PTS was diagnosed after two consecutive occasion of crossing the threshold for diagnosis was slightly lower (45.9%) compared to the study[168] in which PTS was diagnosed after the threshold for PTS diagnosis on the Villalta scale was crossed only on one occasion at similar time points (47.4%).

In one study[162] two multivariate analysis was conducted, in the first multivariate analysis, age, gender, BMI, C-reactive protein and D-dimers were included while in the second multivariate analysis, all factors in the first multivariate analysis were included except C-reactive protein and D-dimers. The second study[164] also conducted two multivariate analysis. The factors adjusted for in the first multivariate analysis were age, gender, extent of index DVT, recurrent DVT, cancer and cardiovascular co morbidities while the second multivariate analysis replaced age with BMI. The third study[119] adjusted for age, gender, BMI, compression stockings use, infectious or inflammatory conditions, congestive heart failure, stroke or myocardial infarction within a month of DVT diagnosis, smoking, type of DVT (provoked or unprovoked), extent of DVT, use of the following medications within 30 days of DVT diagnosis (antiplatelets, non steroidal anti-inflammatory drugs and statins).

All three studies were good quality studies. In the study where both the CEAP classification and Villalta scale for PTS diagnosis there was a difference in results.[162] A weak association between elevated levels of interleukin 6 was demonstrated when the CEAP classification was used to diagnose PTS, this association was absent when the Villalta scale was used (see Table 37 for effect sizes). The other two studies[164,168]also reported a weak association between elevated levels of interleukin 6 and risk of

developing PTS. The two studies that developed two multivariate analysis did not demonstrate a significant difference between them (see Table 37).

Overall, a weak association between elevated levels of interleukin 6 and the risk of developing PTS was demonstrated by all three studies. Interleukin 6 is therefore only weakly associated with an increased risk of PTS after a patient has suffered a DVT of the lower limb.

Table 37: Interleukin 6

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Rabinovich et al 2015[168]	Canada USA	725	Villalta	47.4% at 24 months	24	IL-6 (Baseline)	Age, Gender, BMI, CS use, Infectious/ Inflammatory conditions, CHF, Stroke or MI, Smoking, Type of DVT,Extent of DVT, Use of antiplatelets/ NSAIDs/statins	RR 1 0.85 to 1.18	NR
						IL-6 (1 month)	As above	RR 1.05 0.89 to 1.25	NR
						IL-6 (6 months)	As above	RR 1.07 0.90 to 1.28	NR
Roumen-Klappe et al 2009[162]	The Netherlands	113	CEAP and Villalta	36.7% with CEAP at 12 months, 35.4% using Villalta at 12 months	12	IL-6 (CEAP)	Age, Gender, BMI>25, CRP, D-dimer	RR 1.2 0.7 to 2.2	NR
							Age, Gender, BMI>25	RR 1.3 0.8 to 2.1	NR
						IL-6 (Villalta)	Age, Gender, BMI>25, CRP, D-dimer	RR 0.6 0.2 to 1.4	NR
							Age, Gender, BMI>25	RR 0.5 0.2 to 1.2	NR

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Shbaklo et al 2009[164]	Canada	307	Villalta	45.9% at 24 months	24	IL-6	Age, Gender, Extent of index DVT, Recurrent DVT, Cancer, Cardiovascular co morbidities	OR 1.55 0.97 to 2.47	0.064
						IL-6	BMI, Gender, Extent of index DVT, Recurrent DVT, Cancer, Cardiovascular co morbidities	OR 1.36 0.84 to 2.21	0.207

Key: BMI – Body mass index CHF – Congestive heart failure CRP – C-reactive protein DVT – Deep vein thrombosis

CS – Compression stockings IL-6 – Interleukin 6 MI - Myocardial infarction NR – Not reported

NSAIDs – Non-steroidal anti-inflammatory drugs OR – Odds ratio PTS – Post-thrombotic syndrome

RR – Relative risk

3.5.3.2.2.20 Intracellular adhesion molecule 1

Intercellular Adhesion Molecule 1 is a protein found on the surface of leucocytes and endothelial cells and has been found to play a role in the inflammatory process among other functions.[228]

An association between intracellular adhesion molecule 1 and risk of PTS was assessed by two prospective cohort studies in multivariate analysis.[164,168] Sample sizes of the studies were 307 patients[164] and 725 patients.[168] Both studies followed up patients post DVT for 24 months.

Blood samples for the measurement of intracellular adhesion molecule 1 levels were taken at DVT diagnosis, one month after DVT and six months after DVT in one study.[168] In the second study[164] blood samples for intracellular adhesion molecule 1 levels were taken at four months post DVT.

The Villalta scale was used to assess patients for PTS at the end of the follow up period in both studies. However, in one of the studies,[164] patients had to have crossed the threshold for PTS diagnosis on the scale on at least two consecutive occasions for a diagnosis to be made. The reported incidence of PTS at the end of the follow up period was 45.9%[164] and 47.4%[168] at the end of the 24 months period. The incidence of PTS reported by the study [164] that diagnosed PTS only after two consecutive occasions of crossing the threshold for diagnosis was slightly lower (45.9%) compared to the study[168] that diagnosed PTS only after one occasion on the same scale and at similar time points(47.4%).

Two multivariate analysis were conducted in one of the studies,[164] one of these adjusted for age, gender, extent of index DVT, recurrent DVT, cancer and cardiovascular co

morbidities while the second multivariate analysis adjusted for BMI, gender, extent of index DVT, recurrent DVT, cancer and cardiovascular co morbidities. The third study[168] adjusted for age, gender, BMI, compression stockings use, infectious or inflammatory conditions, congestive heart failure, stroke or myocardial infarction within a month of DVT diagnosis, smoking, type of DVT (provoked or unprovoked), extent of DVT, use of the following medications within 30 days of DVT diagnosis (antiplatelets, non steroidal anti-inflammatory drugs and statins).

Both studies were of good quality. In the study[164] that conducted two multivariate analysis, a weak association between elevated intracellular adhesion molecule 1 levels and the risk of developing PTS was demonstrated in one multivariate analysis, this became a strong association when age was replaced with BMI as was done in the second multivariate analysis (see Table 38 for effect sizes). The second study[168] demonstrated a strong association between PTS and elevated intracellular adhesion molecule 1 levels at one month and six months after DVT.

Both studies suggest that elevated intracellular adhesion molecule 1 level taken at one month, four months and six months post DVT is strongly associated with an increased risk of developing PTS at 24 months after DVT. Results are also suggestive of a slight progression in risk of PTS with time in the presence of elevated intracellular adhesion molecule 1 levels.

Table 38: Intracellular adhesion molecule 1

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Rabinovich et al 2015[168]	Canada USA	725	Villalta	47.4% at 24 months	24	ICAM-1 (Baseline)	Age, Gender, BMI, CS use, Infectious/ Inflammatory conditions, CHF, Stroke or MI, Smoking, Type of DVT,Extent of DVT, Use of antiplatelets/ NSAIDs/statins	RR 1.14 0.98 to 1.44	NR
						ICAM-1 (1 month)	As above	RR 1.23 1.05 to 1.45	NR
						ICAM-1 (6months)	As above	RR 1.25 1.05 to 1.48	NR
Shbaklo et al 2009[164]	Canada	307	Villalta	45.9% at 24 months	24	ICAM - 1	Age, Gender, Extent of index DVT, Recurrent DVT, Cancer, Cardiovascular co morbidities	OR 1.33 0.82 to 2.16	0.242
						ICAM - 1	BMI, Gender, Extent of index DVT, Recurrent DVT, Cancer, Cardiovascular co morbidities	OR 1.74 1.10 to 2.99	0.046

Key: BMI – Body mass index CHF – Congestive heart failure DVT – Deep vein thrombosis CS – Compression stockings

ICAM – 1 – Intercellular Adhesion Molecule 1 MI – Myocardial infarction NSAIDs – Non-steroidal anti-inflammatory drugs

OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.21 C-reactive protein

C-reactive protein is a protein synthesised by the liver.[229] It is important to the inflammatory process and is known to be one of the markers of inflammation.[229]

Three prospective cohort studies with multivariate analysis[150,162,168] assessed the association between C-reactive protein and the risk of developing PTS after DVT of the lower limb (see Table 39). The sample sizes of the studies were 113 patients,[162] 228 patients[150] and 725 patients.[168] Length of follow up was for 12 months and 24 months.[150,168]

For one study[162] blood was taken for C-reactive protein level determination at DVT diagnosis and afterwards on day seven, day 30 and day 90. In a second study,[168] blood samples for C-reactive protein level were taken at DVT diagnosis, at one month after DVT and at six months after DVT. In the third study blood was taken for C-reactive protein levels at four to seven months after DVT, 12 months after DVT and 24 months after DVT.[150]

Diagnosis of PTS was made using the CEAP classification[162] and the Villalta scale.[150,162,168] One study[150] made a diagnosis of PTS only after the threshold for PTS diagnosis had been crossed on at least two consecutive occasions on the Villalta scale. The incidence of PTS reported were 19% to 47.4%after 24 months[150,168] and 35.4% to 36.7% at 12 months depending on the diagnostic measure used[162] (see Table 39). At a similar time point (12 months), there was a lower incidence of PTS reported by the study that diagnosed PTS after two consecutive occasions of crossing the diagnostic threshold on the Villalta scale (19%)[150] compared to the study that diagnosed PTS after one occasion of crossing the diagnostic threshold on the Villalta scale (47.4%).[168]

In one study[162] two multivariate analysis was conducted. In the first multivariate analysis, age, gender, BMI, interleukin 6 and D-dimers were included in the analysis while in the second multivariate analysis all factors in the first multivariate analysis were included except interleukin 6 and D-dimers. A second study[150] did not report on the studies adjusted for in their multivariate analysis while the third study[168] adjusted for the following factors; age, gender, BMI, compression stockings use, infectious or inflammatory conditions, congestive heart failure, stroke or myocardial infarction within a month of DVT diagnosis, smoking, type of DVT (provoked or unprovoked), extent of DVT, use of the following medications within 30 days of DVT diagnosis (antiplatelets, non steroidal anti-inflammatory drugs and statins).

In one study of good quality[162] it was reported that there was a weak association between elevated levels of C-reactive protein in the first three months after DVT diagnosis (regardless of the PTS diagnostic measure used) and the risk of developing PTS 12 months post DVT when age, gender, BMI > 25, interleukin 6 and D-dimers were adjusted for . When only age, gender and BMI were adjusted for, a strong association with an increased risk of PTS was seen when the CEAP classification was used, this association disappeared with the use of the Villalta scale[162] (see Table 39 for details on effect sizes). The varied results may indicate a spurious result because there was little difference in incidence according to diagnostic measure as well as little difference in effect size when age, gender, BMI > 25, interleukin 6 and D-dimers were adjusted for. A second study of fair quality[150] reported a strong association between elevated C-reactive protein levels at 12 months post DVT and the risk of developing PTS at 24 months post DVT, no multivariate analysis for the other time points were reported. An eight fold increase in odds of developing PTS was reported by this study.

The third study also of good quality[168] reported no association between PTS and elevated levels of C-reactive protein at baseline, and a weak association between PTS and elevated C-reactive protein levels at one month and six months.

In summary results from these studies was likely varied because of the different time points that C-reactive protein was measured. However, overall evidence from these studies suggests that association between elevated levels of C-reactive protein and the incidence of PTS after DVT progressively gets stronger with time.

Table 39: C-reactive protein

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Bouman et al 2012 [150]	The Netherlands	228	Villalta	19% at 24 months	24	CRP (12 months)	NR	OR 8.0 2.4 to 26.4	0.001
Rabinovich et al 2015[168]	Canada USA	725	Villalta	47.4% at 24 months	24	CRP (Baseline)	Age, Gender, BMI, CS use, Infectious/ Inflammatory conditions, CHF, Stroke or MI, Smoking, Type of DVT,Extent of DVT, Use of antiplatelets/ NSAIDs/Statins	RR 0.95 0.81 to 1.11	NR
						CRP (1 month)	As above	RR 1.10 0.93 to 1.30	NR
						CRP (6 months)	As above	RR 1.06 0.89 to 1.26	NR
Roumen-Klappe et al 2009[162]	The Netherlands	113	CEAP and Villalta	36.7% with CEAP at 12 months, 35.4% using Villalta at 12 months	12	CRP (CEAP)	Age, Gender, BMI>25, IL-6, D-dimer	RR 1.8 0.9 to 3.3	NR
							Age, Gender, BMI>25	RR 1.8 1.0 to 3.0	NR
						CRP (Villalta)	Age, Gender, BMI>25, IL-6, D-dimer	RR 1.2 0.6 to 2.5	NR
							Age, Gender, BMI>25	RR 0.9 0.5 to 1.8	NR

Key: BMI – Body mass index CHF – Congestive heart failure CRP – C-reactive protein DVT – Deep vein thrombosis

CS – Compression stockings IL-6 – Interleukin 6 MI – Myocardial infarction NR – Not reported

NSAIDs – Non-steroidal anti-inflammatory drugs OR – Odds ratio PTS – Post-thrombotic syndrome

RR – Relative risk

3.5.3.2.2.22 Interleukin 10

Interleukin 10 is an anti-inflammatory cytokine produced by monocytes and lymphocytes.[230] It has an important function in the regulation of inflammation and immune processes.[230]

One prospective cohort study assessing the association between interleukin 10 and PTS after DVT in a multivariate analysis was identified[168] (see Table 40). The study consisted of 725 patients at baseline. These patients were followed up for 24 months.

Interleukin 10 levels were determined from blood samples taken at baseline, one month and at six months after DVT diagnosis.

PTS was determined in this group of patients with the Villalta scale and the incidence of PTS at the end of the follow up period was 47.4%.

Factors adjusted for in their multivariate analysis include age, gender, BMI, compression stockings use, infectious or inflammatory conditions, congestive heart failure, stroke or myocardial infarction within a month of DVT diagnosis, smoking, type of DVT (provoked or unprovoked), extent of DVT, use of the following medications within 30 days of DVT diagnosis (antiplatelets, non steroidal anti-inflammatory drugs and statins).

At study baseline and at one month after DVT, elevated interleukin 10 levels had a weak association with PTS with the same effect size reported (see Table 40). At six months post DVT, this association became strong. The study was of good quality.

In summary, elevated interleukin 10 levels at six months post DVT was demonstrated to be strongly associated with an increased risk of developing PTS 24 months after DVT. This conclusion can be considered valid because it was made from a good quality study.

Table 40: Interleukin 10

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Rabinovich et al 2015[168]	Canada USA	725	Villalta	47.4% at 24 months	24	IL-10 (Baseline)	Age, Gender, BMI, CS use, Infectious/ Inflammatory conditions, CHF, Stroke or MI, Smoking, Type of DVT,Extent of DVT, Use of antiplatelets/ NSAIDs/Statins	RR 1.08 0.92 to 1.27	NR
						IL-10 (1 month)	As above	RR 1.08 0.92 to 1.27	NR
						!L-10 (6 months)	As above	RR 1.27 1.07 to 1.51	NR

Key: BMI – Body mass index CHF – Congestive heart failure DVT – Deep vein thrombosis CS – Compression therapy

IL10 – Interleukin 10 MI – Myocardial infarction NR – Not reported

NSAIDs – Non-steroidal anti-inflammatory drugs PTS – Post-thrombotic syndrome RR – Relative risk

3.5.3.2.2.23 D-dimer levels

D-dimer is an antigen that can be found in the blood when there is breakdown of fibrin found in a thrombus.[231] It is therefore a marker of fibrin degradation and has been found to be very important clinically for the exclusion of VTE.[231]

Three prospective cohort studies [156,160,166] explored the association between D-dimer levels and the development of PTS after DVT in a multivariate analysis. The sample sizes were 387 patients,[156] 122 patients[160] and 406 patients.[166] Follow up period across studies was for a minimum of 11 months and a maximum of 44 months.[166]

D-dimer levels was measured from blood samples taken at presentation with DVT,[160] at four months post DVT[156] and at least three months after DVT diagnosis (measured after cessation of Vitamin K antagonists).[166]

The methods of PTS diagnosis used was the Villalta scale[156,160] and the CEAP classification.[166] One study made a diagnosis of PTS only when the criteria for PTS diagnosis was met on at least two consecutive occasions.[156]

The incidence of PTS in two of the studies was 51.6% at 12 months[160] and 45.1% at 24 months.[156] The third study reported an incidence of 43.3% after their follow up period which was between 11 months and 44 months.[166]

Factors adjusted for include age,[156,160,166] gender,[156,160,166] BMI,[156,160,166] common femoral vein involvement,[160] extent of DVT,[156] proximal DVT,[166] and daily use of stockings,[156,160] history of DVT,[156] warfarin use at time of taking blood,[156] factor V Leiden,[166] factor VIII[166] and factor II G20210A.[166]

Two studies, one of good quality[156] and one of fair quality[166] showed that elevated D-dimer levels (both used same levels of D-dimers - 500µg/L and 500ng/L) three to four months post DVT was strongly associated with PTS. In the third study which was also of good quality,[160] there was a weak association between D-dimer levels greater than the median value of the study population (above 1910ng/ml) at presentation and PTS. See Table 41 for effect sizes.

In summary, the evidence suggests that elevated D-dimer levels three to four months after DVT was associated with the risk of developing PTS.

Table 41: D-dimer levels

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Latella et al 2010[156]	Canada	387	Villalta	45.1% at 24 months	24	D-dimer >500µg/L (4 months)	Warfarin use at time of drawing blood, Age, Gender, BMI, Extent of DVT, CS use	OR 1.05 1.00 to 1.09	0.03
Roberts et al 2013[160]	The United Kingdom	122	Villalta or CEAP	51.6% at 12 month	6	D-dimer >1910ng/ml (Baseline)	Age, Gender, BMI, Common femoral vein involvement, and Daily use of stockings	OR 2.81 0.94 to 8.41	0.066
Stain et al 2005[166]	Austria	406	CEAP	43.3% at 44±23 months	44±23	Elevated D-dimer levels >500ng/ml (at least 3 months post DVT)	Age, Gender, Proximal DVT, BMI, Factor V Leiden, Factor VIII, Factor II G20210A	OR 1.9 1.0 to 3.9	NR

Key: BMI – Body mass index CRP – C-reactive protein DVT – Deep vein thrombosis CS – Compression stockings

NR – Not reported OR – Odds ratio PTS – Post-thrombotic syndrome

3.5.3.2.2.24 Calf swelling ≥ 3cm than contra lateral leg

Calf swelling is a prominent symptom of DVT. One prospective cohort study of poor quality[153] explored the association between calf swelling at DVT diagnosis and the development of PTS afterwards (see Table 42).

The sample size of the study was 135 patients. These patients had been followed up for 36 months after the diagnosis of DVT.

Measurement of calf swelling in both lower limbs was carried out at presentation with DVT.

The Villalta scale was used to measure PTS in these patients and the incidence of PTS at the end of the follow up period was 24.4%.

Only age was adjusted for in this multivariate analysis. The findings of the study was that calf swelling calf swelling ≥ 3cm than asymptomatic leg at the time of DVT presentation was associated with the development of PTS 36 months later. This was a weak association. See Table 42 for effect sizes.

The evidence demonstrates a weak association between calf swelling ≥3cm than asymptomatic leg at the time of DVT presentation and development of PTS after. This evidence is likely not reliable because it was made from findings of a poor quality study.

Table 42: Calf swelling ≥ 3cm larger than asymptomatic leg

Author(s) and year	Location of study	Sample size evaluated for PTS (n)	Measure of PTS	Incidence of PTS (%)	Length of follow up (months)	Potential prognostic factors	Factors adjusted for	Effect measure and sizes 95% confidence intervals	p-Value
Hach-Wunderle et al 2013[153]	Germany	135	Villalta	24.4% at 36 months	36	Calf swelling ≥3cm larger than asymptomatic leg	Age	OR 2.21 0.96 to 5.11	NR

Key: DVT – Deep vein thrombosis NR – Not reported OR – Odds ratio PTS – Post-thrombotic syndrome

3.6 Summary of results

3.6.1 The evidence from the prognostic model study

The four models developed by the prospective cohort study with multivariate analysis and prognostic model[149] (see Section 3.5.3.2.1 for details of variables included in the models) demonstrated that all four models may be able to fairly predict the risk of developing PTS. The overall reported receiver operator characteristic curves of these models were between 72% to 79%. However there are limitations to this conclusion due to the following;

1. Based on recommendations from simulation studies by Peduzzi et al,[232] the rule of thumb for prognostic model development is that for every factor included in a model, at least 10 patients should develop the event of interest (PTS). Therefore, for model 1 which included five prognostic variables, expected number of events per variable should be 50, for model 2 and model 3 with seven prognostic variables each, expected number of events per variable should be 70, and for model 4 with eight prognostic variables, events per variable should be at least 80. In this study there was a maximum of 46 PTS events during follow up. This falls short of the required event per variable to develop a valid prediction model.
2. An external validation of the models in a different set of population was not identified. This further limits the validity of the models, as a requirement of a valid prognostic model development, is to assess the functionality of the developed model in a different set of population.[233]

3. Reporting bias was identified in the study as no individual effect size of prognostic variables from the multivariate analysis was reported. Also no prognostic model equation was provided by the authors limiting transferability of their findings to a different population as well as creating no room for external validation studies of the model by other researchers.

Despite the poor quality of this evidence and hence the limitations to the conclusions that can be made, this evidence suggests that developing a prognostic model to identify patients at risk of PTS after DVT may be possible. However well conducted and well-presented prognostic model studies are required.

3.6.2 The evidence from prospective cohort studies with multivariate analysis

Twenty nine potential prognostic factors associated with the development of PTS after DVT of the lower limb were identified from the prospective cohort studies with multivariate analysis only. They include location of DVT, extent of DVT, severity of the Villalta scale one month after DVT, previous ipsilateral DVT, ipsilateral recurrent DVT, venous parameters (thrombi occlusion of the vein, venous reflux, venous outflow resistance, venous reflux velocity, and venous blood retension index), calf muscle pump function, gender, age, body mass index, DVT symptoms duration prior to presentation, varicose veins, cancer, physical activity, duration of warfarin therapy, sub-therapeutic anticoagulation, inherited thrombophilia, smoking, hormonal factors, inflammation parameters (interleukin 6, intracellular adhesion molecule 1, C-reactive protein and interleukin 10) D-dimer levels and calf swelling ≥ 3cm than asymptomatic leg.

3.6.2.1 Unfavourable potential prognostic factors (associated with an increased risk of PTS after DVT of the lower limb)

The evidence suggests that a DVT in the popliteal vein was strongly associated with an increased risk of PTS and that this risk could be as high as 13.3 times as when the clot was located in the calf vein (see Section 3.5.3.2.2.1). The evidence also suggests that ilio-femoral DVT was associated with an increased risk of PTS which could be as high as 3.44 times as when DVT was located in the calf veins. This evidence was from fair to

poor quality studies thus limiting the strength of conclusions that could be made. The finding however seems plausible because of the uniformity in direction of effect. In addition, these findings may be related to the likelihood that a clot in the relatively larger proximal veins (popliteal vein and above) will be generally bigger than clots in the calf veins and may therefore be associated with a wider surface area of damage. This was further buttressed with the findings from fair to good quality studies that the extent of clot at presentation may have an association with an increased risk of developing PTS. Though, residual clot after the acute phase of DVT appeared to have a stronger association with PTS and may increase the risk of PTS by up to six times (see Section 3.5.3.2.2.2). The suggested effect of residual clot in some ways signifies persistence of the underlying disease condition which in this case is DVT.

Two fair to good quality studies suggest that the higher the Villalta score at one month post DVT the higher the odds of developing PTS. With up to 1.78 increased odds with every increase in score on the Villalta scale (see Section 3.5.3.2.2.3). This finding is not unexpected as the Villalta is used to diagnose PTS. However, none of the patients' scores reached the threshold for PTS diagnosis on the scale. The findings was buttressed by results from a poor quality study which suggests that DVT symptoms lasting more than two weeks prior to presentation was weakly associated with an increased risk of PTS. These findings suggest that the severity of the index DVT was important in determining patients that will develop PTS later on. While the evidence on severity of the Villalta score at one month may be valid, the evidence on the association between PTS and the duration of DVT symptoms prior to presentation requires exploration by more studies.

Fair to poor quality studies suggested a strong association between a previous ipsilateral DVT and an increased risk of developing PTS after DVT. These studies suggest the odds may be as high as eight times as if there was no previous ipsilateral DVT (see Section 3.5.3.2.2.4). In addition, two fair quality studies have suggested that an ipsilateral recurrent DVT increased the risk of PTS by up to 9.57 times (see Section 3.5.3.2.2.5). These findings buttresses the points discussed in the earlier paragraphs that the more damage sustained to a vein, the higher the likelihood of PTS.

Some measures of venous function after DVT were found to be associated with the development of PTS after DVT of the lower limb. Four fair to good quality studies suggested that venous reflux may be associated with an increased risk of PTS (see Section 3.5.3.2.2.6.2). One of the studies suggests that when venous reflux was combined with thrombi occlusion the risk may be as high as 4.4 times. However one good quality study did not find a similar association. The finding by some studies that venous reflux may be associated with development of PTS after DVT was supported by findings from one fair quality study that a high venous reflux velocity may be associated with an increased risk of PTS and this risk could be as high as 13.5 times as in a patient with normal venous reflux velocity (see Section 3.5.3.2.2.6.4).

Findings from three good quality studies suggest that increased venous outflow resistance was associated with an increased risk of PTS and this risk could be as high as 3.6 times (see Section 3.5.3.2.2.6.3). Two fair quality studies suggest that a high venous blood retension index may be associated with an increased risk of PTS and this risk could be as high as 67 times (see Section 3.5.3.2.2.6.5). The association between some of the venous parameters and PTS such as venous reflux and venous reflux velocity was increased when they were combined with other venous function measures such as

venous occlusion, degree of calf muscle pump function and thrombosis score (see Section 3.5.3.2.2.6). These findings suggest that the measures of extent of damage to a vein caused by DVT may be predictive of whether a patient will develop PTS subsequently or not.

One fair quality study suggests that calf muscle pump function on its own was able to predict patients at risk of PTS 58% of the time and that this ability to predict risk of PTS was increased to up to 76% when venous outflow resistance, thrombosis score and venous reflux were added (see Section 3.5.3.2.2.7).

Overall the evidence suggests from studies with varied quality that abnormal venous parameters after DVT may be able to predict patients at risk of PTS subsequently. However, the ability to predict patients at increased risk seemed to be improved when two or more venous parameters were combined compared to only one venous parameter.

The evidence from studies of varied quality (two good, two fair and one poor quality studies) suggests that increased BMI was associated with an increased risk of developing PTS by all studies that explored this relationship (see Section 3.5.3.2.2.10). When the cut off was set to a BMI of 25, the association was weak. However, it appeared the strength of association increased with an increase in BMI as the weak association seen when threshold for BMI was ≥ 25 became stronger when BMI was ≥ 30.

The evidence from studies of varied quality (one good, one fair and one poor quality study) suggests that the presence of varicose veins at presentation was strongly associated with increased odds of developing PTS (up to 13.4 times – see Section

3.5.3.2.2.12). This is to be expected as this suggests some pre-existing poor venous function.

The evidence from two fair to good quality sub-studies of the same larger prospective cohort study suggests that sub-therapeutic anticoagulation was strongly associated with increased odds of developing PTS (up to 1.8 times - see Section 3.5.3.2.2.15). This finding corroborates findings from an earlier systematic review of systematic reviews that optimal DVT treatment at presentation was necessary to reduce the risk of PTS.

The evidence from one study of fair quality suggests that the duration of warfarin therapy was strongly associated with an increase in Villalta score over time (see Section 3.5.3.2.2.14). This finding is interesting because patients required to take warfarin for longer periods are usually patients with recurrent DVT, with extensive DVT and or older patients (at risk of chronic conditions requiring warfarin) and so are already at risk of DVT as already explained above. The study however adjusted for these possible cofounders suggesting that this effect is entirely due to warfarin alone. This finding therefore contradicts previous results that optimal treatment of DVT and optimal anticoagulation was necessary to reduce risk of PTS after DVT of the lower limb.

Good quality studies suggested that elevated levels of some inflammatory markers measured after DVT were associated with an increased risk of PTS. There appeared to be an associated increased risk of PTS when there were elevated inflammatory markers late after DVT. Elevated levels interleukin-10 and C-reactive protein levels were weakly associated with an increased risk of PTS in the immediate period after DVT (see Sections 3.5.3.2.2.22 and 3.5.3.2.2.21). This association became stronger the longer after DVT they were measured. There was a strong association with risk of PTS when

there were elevated levels of interleukin 10 at six months post DVT and elevated levels of C-reactive protein at 12 months post DVT. However, elevated levels of intracellular adhesion molecule 1 was strongly associated with an increased risk of PTS from as early as one month post DVT (see Section 3.5.3.2.2.20) while interleukin 6 was shown to be weakly associated with an increased risk of PTS in the majority of the evidence (see Section 3.5.3.2.2.19). Persistence of raised inflammatory markers demonstrates a persistence of the underlying disease when other conditions that may cause raised inflammatory markers are adjusted for; therefore this finding was not unexpected.

The evidence from one fair to two good quality studies suggests that there was an association between elevated levels of D-dimers and subsequent development of PTS (see Section 3.5.3.2.2.23). Across the studies it was suggested that elevated D-dimer levels at presentation was weakly associated with increased risk of PTS. This changed to a strong association when elevated D-dimer levels persisted after the acute phase of DVT.

One study of poor quality suggested that smoking as well as hormonal factors (pregnancy, in the puerperium period, use of tamoxifen or oral contraceptive pills at study baseline) were associated with an increased risk of developing PTS in a non-statistically significant relationship. Factors adjusted for in the only study that assessed both factors did not report on the variables in their multivariate analysis. The study consisted of a small sample size. Therefore larger studies are required to explore these relationships. Hormonal factors were restricted to the conditions described above which is limited to women, therefore this evidence accounted for only a fraction of hormones. Overall, valid conclusions cannot be made from this evidence because of the poor quality and other limitations.

The evidence from one poor quality study suggested that calf swelling ≥ 3cm than asymptomatic leg at presentation was shown to be associated with an increased risk of PTS in a weak relationship (see Section 3.5.3.2.2.24). The only factor adjusted for was age in the only study that explored this relationship. Confounders such as trauma to leg, lymphoedema were not adjusted for. Further studies are needed to assess this relationship, even though calf swelling ≥ 3cm than asymptomatic leg at presentation is a marker of disease severity and thus will be expected to be associated with an increased risk of PTS.

3.6.2.2 Favourable potential prognostic factors (associated with a reduced risk of PTS after DVT of the lower limb)

The evidence from one study of fair quality suggests that inherited thrombophilia (factor V Leiden and prothrombin mutations) was not associated with an increased risk of PTS. Rather it was found to be associated with a reduced risk of PTS (see Section 3.5.3.2.2.16). It was an unexpected finding because available evidence demonstrates that ipsilateral recurrent DVT was associated with an increased risk of PTS. Factor V Leiden and prothrombin mutations are pro-thrombotic conditions and therefore are likely to be associated with recurrent DVT and should hypothetically be associated with an increased risk of PTS and not a reduced risk. Further studies are required to confirm or debunk this finding.

The evidence from one study of poor quality suggests that underlying cancer at presentation of DVT was protective against subsequent development of PTS (see

Section 3.5.3.2.2.13). This finding may not be reliable as it was from a poor quality study.

3.6.2.3 Potential prognostic factors with conflicting evidence on their association with risk of PTS

There was conflicting reports from studies of varied quality (good, fair and poor quality studies) on the association between gender and the risk of PTS (see Section 3.5.3.2.2.8). The conflict in direction of effect size could not be accounted for by the quality of the studies. Some studies suggested that female gender may be associated with increased risk of developing PTS with one of the studies showing a weak relationship. Another study suggested it was male gender associated with increased odds of PTS while other studies suggested there was no association between gender and development of PTS after DVT. Further studies are required to explore this relationship in detail.

There were also varied reports on the association between older age and the risk of developing PTS after DVT of the lower limb (see Section 3.5.3.2.2.9). Same as the evidence on gender, there were studies of varied quality that investigated this relationship and there was conflict in their reports that could not be explained by a difference in quality of studies. Some studies showed an increased risk with older age. This finding buttressed evidence identified so far that damage to vein is associated with increased risk of PTS as normally there is a higher likelihood of progressive loss of elasticity and other venous function as patients get older. However the other studies showed that age was not associated with an increased risk of PTS.

Physical activity was found to be weakly associated with an increased risk of PTS by the only study identified to have explored this relationship in a multivariate analysis (see Section 3.5.3.1.1). This study was of fair quality. The findings of the study were in contrast to the findings from the systematic review of systematic reviews where physical activity was found to be associated with an increased risk of PTS after DVT from one RCT. Both studies had different study designs, different definitions for physical activity and variation in analysis (multivariate versus univariate). These differences may explain the differences in directions of effect reported by both studies.

Thrombi occlusion of the vein on venography carried out at DVT presentation on its own was not associated with the later development of PTS (see Section 3.5.3.2.2.6.1). However, when it was combined with venous reflux, there were increased odds of developing PTS by up to 4.4 times. This finding supports the understanding of pathophysiology of PTS as it is known today (see Chapter 1). However, only one study of fair quality demonstrated this while adjusting for only one factor (ipsilateral recurrence), further studies adjusting for more potential confounders such as paralysis and residual thrombosis are required.

3.6.3 Potential prognostic factors from the remaining evidence

To add robustness to the conclusions made from this systematic review, other factors investigated by included studies but had not been assessed in a multivariate analysis from prospective cohort studies are highlighted in this section.

Sixty seven additional factors had been explored for an association with subsequent development of PTS after a DVT of the lower limb in a univariate analysis. Thirteen of these factors were found to be potential unfavourable prognostic factors. Four were found to be potential favourable prognostic factors and another four were found to have conflict in the direction of effect. Forty six factors were found to have no association with the development of PTS following a DVT of the lower limb. These factors are presented in Table 43 together with references of studies that assessed them.

Table 43: Other factors assessed for an association with PTS from the remaining evidence

Other potential prognostic factors from the remaining evidence (n = 67)			
Unfavourable factors (n = 13)	**Favourable factors (n = 4)**	**Conflicting evidence (n = 4)**	**No association with PTS (n = 46)**
Risk factors for the index DVT: postnatal DVT,[81] chronic venous insufficiency,[150,152,169] presence of inflammatory disease[150] and increased activity of the plasminogen activator inhibitor – 1 (PAI-1) gene (evidenced by 4G/5G polymorphism)[191] **Use of some medications**: use of non-steroidal anti-inflammatory drugs and use of statins within 30 days prior to DVT diagnosis[152]); **Characteristics of index DVT**: DVT risk score[183] (as calculated by the New York Heart Association protocol[217]), contra-lateral recurrent DVT during follow up period,[181] venous blood filling index[194] and recurrent VTE during follow up[150]; **Increased levels of biomarkers**: Activated protein C (APC) ratio and thrombin antithrombin complex **Others:** Lower income levels[152]	**Characteristic of index DVT:** Provoked DVT[150] and asymptomatic DVT.[184]**DVT treatment:** Percutaneous endovenous intervention used with oral anticoagulants[193,199] and use of power pulse spray in conjunction with angiojet thrombectomy and aspirin[198]	**Characteristic of index DVT:** Unprovoked DVT **Post DVT factors:** elevated levels of biomarkers such as platelet count,[152,178] elevated levels of factor VIII,[152,166,174,192,212] elevated levels of interleukin 8[28,212,213] and unprovoked DVT[149,153,157,186,192]	**Characteristics of the patient**: Race,[151,152] mean of shortest distance from right iliac artery to fifth vertebral body,[183] visceral pattern of fat distribution[170] and parity.[81] **Risk factors for the index DVT:** Central venous catheter placement,[167] congenital heart failure,[167,194] immobilisation,[150,153,157,167,194,196,203] inflammatory bowel disease,[167,194] trauma,[150,153,194,196] surgery,[150,153,167,194] renal failure,[167,194] stroke,[167,194] protein C deficiency,[167,194] protein S deficiency,[167,194] antithrombin III deficiency,[167,194] antiphospholipid syndrome,[167,194] hyperhomocystenaemia,[152,167,194] caesarean section,[81] antenatal DVT,[81] previous VTE,[151,155,169] hypercholesterolaemia,[157,178] family history of VTE,[150,153,203] travelling,[150,153] acute illness,[153] cardiovascular disease[150] and hypertension.[157] **Characteristics of the index DVT:** Laterality of DVT (i.e. left or right leg affected by DVT),[81,153,167] presence of pulmonary embolism,[151-153] tenderness along deep veins at presentation, entire leg swelling at presentation, pitting leg oedema at presentation and dilated superficial veins at presentation.[153] **Post DVT factors:** Elevated levels of biomarkers such as; vascular adhesion molecule 1 (VCAM-1),[28] soluble vascular adhesion molecule (sVCAM-1),[214] prothrombin activatable fibrinolysis inhibitor (Pro TAFI),[214] tissue plasminogen activator,[214] thrombomodulin,[214] monocyte chemoattractant protein 1 (MCP-1),[28] fibrinogen,[178] tumour necrosis factor alpha,[212] and von williebrand factor.[213,214] Post DVT venous parameters such as recanalisation rate,[170,183] and venous blood ejection index.[194] Weight gain post DVT.[170] **DVT treatment:** Multilayer compression bandaging in acute phase of DVT[195] and regular follow up of patients post DVT.[155]

Key: DVT – Deep vein thrombosis PTS – Post-thrombotic syndrome

3.7 Discussion

The methods and findings of this systematic review have been reported in the previous sections. This section discusses the validity and the applicability of the evidence by considering the scope and content of the evidence and how it fits in a broader context. It will round up with a discussion on the strengths and limitations of included studies as well as those of this systematic review.

3.7.1 Consideration of evidence

The primary studies included in this review covered the time period from 1980 to 2015. There were comparatively more studies investigating factors associated with PTS in recent years than before. This suggests increasing interest in PTS research.

The majority of included studies were conducted in Canada, Italy and The Netherlands and most studies included patient groups between 18 years and 70 years. What this means is that findings from included studies may apply more to the adult western population than the rest of the world.

The studies included in this review varied in their follow up period, ranging from three months to eight years. The overall findings of this review are unlikely to be affected by this difference in follow up period because no meta-analysis was done and interpretation of results was put in context of the findings of individual studies.

Many studies did not report whether a DVT was provoked, unprovoked, a first time DVT or not a first time DVT. Therefore, this reviews findings could not be sub-analysed or interpreted with respect to this sub-groups. Rather this review's findings

apply to any kind of DVT. This means that findings can potentially be broadly applied to any DVT of the lower limb. However there may be subtle or huge differences between sub-groups that this review could not investigate due to the absence of classifying data according to types of DVT.

3.7.2 Strengths and limitations of the evidence

The included studies had the same limitations common in PTS research. They include a variation in length of follow up, variation in the timing of PTS assessment, variation in methods used to measure PTS and lack of blinding in the assessment of PTS in most of the studies. Other limitations identified from some of the included studies include the lack of uniformity in the effect sizes reported and lack of reporting of the results from univariate analysis in studies that also conducted a multivariate analysis. In addition, the aim of some of the studies was not primarily for the investigation of prognostic factors associated with the development of PTS so that this sometimes also led to insufficient reporting of relevant data.

An important limitation of included studies was the selective reporting by some studies where only effect sizes on factors found to be associated with the development of PTS in a multivariate analysis were reported in detail. Factors that were not found to be associated with the development of PTS were not reported in detail (for example no effect sizes reported) by these studies and were only mentioned. In addition some of these studies did not report on the factors adjusted for in their multivariate analysis.

Another limitation was that many of these primary studies were conducted by the same set of researchers. This could lead to bias such that the direction of PTS research could be dictated solely by interests of these researchers. However, if methods employed are

appropriate and interpretation of findings are transparent and robust, this would not be a concern.

These limitations restricted the conclusions that could be made from the findings of some studies.

3.7.3 Strengths and limitations of this systematic review

A robust systematic review method was used. An extensive search of three databases and areas of grey literature meant a low likelihood of missing relevant studies regardless of whether they had a positive finding or not, thereby potentially reducing publication bias in this review. In addition majority of studies not in English were translated to assess whether they were eligible for inclusion.

An identified strength of this review is the inclusion of only studies that had used an objective method for diagnosing DVT. This likely meant there was a reduced risk of selection bias in the patient recruitment process of included studies.

The review explored study designs that would represent the best evidence in a thorough and transparent manner so that potentially reliable conclusions could be made from this systematic review. Potential prognostic factors that were found to have an association with PTS from the remainder of the evidence were reported in this review although not explored in as much detail as factors identified from best evidence. This reduced the likelihood of missing information on potential prognostic factors in relation to the later development of PTS after DVT. Also, factors reported not to have an association with

the development of PTS were reported by this systematic review to give robustness to findings of this review and to reduce the gaps in current knowledge as much as possible.

Limitations of this systematic review include the lack of detailed analysis of potential prognostic factors assessed in univariate analysis only. This might mean some loss of information with regards to these factors.

A statistical summary of effect sizes on each factor was not carried out due to heterogeneity between studies including variation in time points of assessment of PTS, follow up periods, factors adjusted for and effect sizes reported.

Assessment for publication bias could not be done because no meta-analysis was conducted and there were less than ten studies that assessed each factor.

3.8 Conclusion

In this chapter, the potential prognostic factors associated with the development of PTS after DVT of the lower limb were further explored with the aid of a systematic review of primary studies thereby building on findings from the previous chapter.

In summary, this systematic review was able to identify new evidence on only one out of the three potential prognostic factors found to need updating from the previous systematic review of systematic reviews – physical activity. The evidence which was from a study of fair quality suggests that there was a weak association between levels of self-reported physical activity for one month after DVT and subsequent development of PTS. Putting this new evidence into perspective with the earlier findings from the systematic review of systematic reviews, the evidence on the three potential prognostic factors found to need updating remains inconclusive.

This systematic review identified four poor quality prognostic models and 28 new potential prognostic factors that may be associated with the development of PTS after DVT of the lower limb from the best evidence for prognostic studies.

The evidence suggests 16 potential prognostic factors were strongly associated with an increased risk of PTS after DVT of the lower limb and were potential unfavourable prognostic factors. The evidence on 10 of these factors was from good quality studies (residual thrombosis, venous reflux, increased venous outflow resistance, increased BMI, presence of varicose veins at DVT diagnosis, sub-therapeutic anticoagulation, elevated levels of D-dimer, elevated levels of interleukin 10, elevated levels of C-reactive protein and elevated levels of ICAM 1 after acute phase of DVT). The evidence

on six unfavourable potential prognostic factors were from studies of fair quality (proximal location of DVT, previous ipsilateral DVT, recurrent ipsilateral DVT, high venous reflux velocity, high venous blood retension index and long duration of warfarin therapy).

Seven additional unfavourable potential prognostic factors were identified, however they were found to be weakly associated with an increased risk of PTS after DVT. One was from good quality evidence (interleukin 6), three were from fair quality evidence (calf muscle pump function, physical activity and duration of DVT symptoms), while three were from evidence of poor quality (smoking, hormonal factors and calf swelling ≥ 3cm than asymptomatic leg at DVT presentation). Three potential prognostic factors had conflicting reports on them (gender, age and thrombi occlusion).

The evidence from studies of fair quality suggests that there were two potential prognostic factors that were associated with a reduced risk of development of PTS after DVT of the lower limb – potential favourable factors (cancer and inherited thrombophilia), however only the evidence on inherited thrombophilia was statistically significant.

This systematic review demonstrates that the risk of developing PTS after DVT is increased by venous test parameters depicting poor venous function, markers of persistent inflammation after DVT and inadequacy of anticoagulation. Hence, it is probable that employing an aggressive approach to recover venous function after DVT will lead to a reduction in the risk of PTS afterwards. The findings of this review seemed to corroborate the findings of the previously conducted systematic review of

systematic review which showed that the manner in which DVT is treated could impact on the risk PTS.

Though this systematic review has done a lot of work with regards to identifying prognostic factors associated with the development of PTS after DVT, a lot of factors were identified, with few of them being from high methodological studies that could lead to valid conclusions. Therefore, it was recognised that further research is needed to identify the most important factors from the array of factors identified from this review (see Chapter 6).

In addition, there seemed to be a huge variability in PTS diagnostic methods used across studies. The next chapter seeks to explore these variations in PTS diagnosis further.

Chapter 4: Identification and assessment of the utility of PTS diagnostic methods used in the previously conducted reviews

4.1 Introduction

There is a lack of a reference standard for diagnosing PTS (see Chapter 1). In this chapter the methods used to diagnose PTS are identified from the studies included in the systematic reviews conducted in the previous two chapters. The popularity of the use of identified PTS diagnostic methods is explored and reported.

4.2 Aims

To identify and elaborate on PTS diagnostic methods used by researchers from systematic reviews of the evidence on potential prognostic factors associated with the development of PTS after a DVT of the lower limb.

4.3 Objectives

- To assess the range of methods that have been used to diagnose PTS from the review of the evidence on potential prognostic factors associated with the development of PTS after a DVT of the lower limb
- To assess the frequency of use of methods used for PTS diagnosis identified from above

4.4 Methods

The methods employed in the review of the evidence on potential prognostic factors (see methods sections of Chapter 2 and Chapter 3) yielded the data used for this section. Therefore, no separate search strategy was conducted for the purpose of identifying PTS diagnostic methods used in the literature. The same articles remaining after the screening and selection phase of both systematic reviews were used in this chapter (see PRISMA flow charts of Chapter 2 and Chapter 3). The diagnostic criteria for PTS were extracted and the proportion of studies that used a particular PTS diagnostic method presented.

4.5 Results

PTS diagnostic methods identified from both reviews are presented in this section as well as the frequency of use of PTS diagnostic methods across identified evidence.

4.5.1 PTS diagnostic methods identified from systematic review of systematic reviews

Fourteen systematic reviews were found eligible for inclusion in the systematic review of systematic reviews (see result section of Chapter 2). The diagnostic methods reported in these systematic reviews are listed below. It was not possible to determine the exact proportion of primary studies that used an identified PTS diagnostic method. As primary studies could have been included in more than one review, using the proportion of reviews reporting on a PTS diagnostic method could be potentially misleading. Therefore, information on the type of PTS diagnostic methods reported by the reviews was concentrated on rather than the proportion of reviews that reported a particular PTS diagnostic method.

PTS diagnostic methods identified could be grouped into clinical assessment only methods, clinical assessment and radiological methods, radiological methods and patient reported outcome questionnaires. In total, two clinical assessment only methods, three radiological only methods and one method which combined both clinical assessment and radiological assessment were identified. The types of patient reported outcome questionnaires used were not reported.

Clinical assessment only methods: Six reviews[38,39,59,112,114,117] reported that subjective clinical assessment (did not give any details other than a clinical assessment was used for PTS diagnosis) were used by primary studies they had included in their review, four reviews[39,116,118,119] reported that the Villalta scale was used, one review[118] reported that the CEAP classification was used, one review[115] reported that standardised scales were used but the scales were not named.

Clinical assessment and radiological methods: One review[116] reported that the Ginsberg's criteria was used by included primary studies.

Radiological only methods: Two reviews[38,114] reported that venography was used, one review[38] reported that plethysmography was used.

Patient reported questionnaires: Two reviews[38,39] reported that patient reported outcome questionnaires were used.

PTS diagnostic method not reported: Three systematic reviews (21.4%) did not report on how primary studies included in their review diagnosed PTS.[109,111,113]

Table 44: PTS diagnostic methods identified from systematic review of systematic reviews

Authors	PTS diagnostic methods reported
Alesh 2007[109]	Not reported
Casey 2012[38]	Clinical assessments Doppler ultrasound Plethysmography Patient reported outcomes Venography
Fox and Kahn 2008[112]	Clinical assessment
Giannoukas et al 2006[111]	Not reported
Hull et al 2011[39]	Clinical assessment Patient reported outcomes Villalta scale
Kahn et al 2008[119]	Villalta scale
Kakkos et al 2006[116]	Villalta scale Ginsberg's criteria
Kolbach et al 2003[117]	Clinical assessment
Luo et al 2006[113]	Not reported
Musani et al 2010[118]	CEAP classification Villalta scale
Ng et al 1998[114]	Clinical assessment Venography
Segal et al 2007[110]	Not reported
Watson et al 2004[59]	Clinical assessment
Wells and Forster 2001[115]	Clinical scales used (not named)

Key: CEAP – Clinical etiological anatomical and pathophysiological classification

4.5.2 PTS diagnostic methods identified from systematic review of primary studies

Seventy three primary studies were found eligible for inclusion in the systematic review of primary studies (see results section of Chapter 3). The diagnostic methods reported in these primary studies are listed below along with the frequency with which these were used. They are grouped into clinical assessment only methods, clinical assessment and radiological methods, and radiological only methods. In total, nine clinical assessment only methods, three radiological only methods and two methods which combined both clinical assessment and radiological assessment for PTS diagnosis were identified.

Clinical assessment only methods: Five studies (6.8%)[20,49,176,185,206] used subjective clinical assessments (did not give any details other than a clinical assessment was used for PTS diagnosis). Sixty four primary studies (87.6%) reported that clinical assessment only methods with pre-defined criteria were used for PTS diagnosis. Thirty studies (41.1%)[13,34,81,151-153,155,156,159,160,162,164,165,168-170,178,179,184,186,187,192,195,200,203,204,208,212-214] used the Villalta scale (two of which used modified versions of the Villalta scale[204,13]), 22 studies (30.1%)[26,33,149,150,154,162,163,166,167,171-174,180-182,188,191,195,202,205,234] used CEAP classification (one of which used a modified version of the CEAP classification[182]), four studies (5.5%)[175,177,190,210] used the Widmer classification and one study (1.4%)[157] used the Brandjes score. Five studies (6.8%) used criteria that were first defined by their respective studies.[158,207,209,235,236] These five criteria are described in Appendix 4. The other PTS diagnostic methods are described in detail in Appendix 1, Section 1.1.

Clinical assessment and radiological methods: Six primary studies (8.2%) used a combination of clinical assessment and radiological findings to make a diagnosis of PTS. Two studies (2.7%)[168,183] used the Ginsberg's criteria (see Appendix 1, Section 1.1) and one study (1.4%)[196] used Doppler ultrasound with or without clinical assessment (see Appendix 1, Section 1.2.1). Three studies (4.1%)[193,198,199] used criteria that included both radiological and clinical assessment component defined by their studies (see Appendix 4).

Radiological only methods:

Four primary studies (5.5%) used radiological only methods for PTS diagnosis. Two studies (2.7%)[49,196] used Doppler ultrasound, two studies (2.7%)[49,178] used Venography and one study (1.4%) used plethysmography.[49]

Table 45: PTS diagnostic methods identified from systematic review of primary studies

PTS diagnostic method	Number of studies that used method (%)	Author(s), year and reference
Clinical assessment only methods		
Subjective clinical assessment	5 studies (6.8%)	Casella et al 2007,[176] Eichlisberger et al 1994,[206] Johnson et al 1995,[20] Mohr et al 2000,[49] Pinar Cabezos et al 2010[185]
Brandjes tool	1 study (1.4%)	Lopez-Azkareta et al 2004[157]
CEAP classification	22 studies (30.1%)	Andreozzi 2007,[171] Asbeutah at al 2004,[172] Bellmunt-Montoya et al 2006,[202] Biguzzi et al 1998,[173] Bittar 2012,[174] Bouman et al 2012,[150] Haenen et al 1999,[201] Haenen et al 2001,[154] Haenen et al 2002,[33] Janssen et al 1997,[26] Kreidy 2015,[205] Labropoulos et al 2008,[180] Labropoulos et al 2010,[181] Mc Coll et al 2000,[182] Roumen-Klappe et al 2005,[161] Roumen-Klappe et al 2009,[162] Roumen-Klappe et al 2009,[195] Roumen-Klappe et al 2010,[163] Schindler and Dalziel 2005,[188] Stain et al 2005,[166] Tick et al 2010[149] Yamaki et al 2009,[234] Yamaki et al 2011[167]
Clinical assessment only scales first used to diagnose PTS by individual studies	5 studies (6.8%)	Browse et al 1980,[207]Monreal et al 1993,[158] Singh and Masuda 2005,[209] Widmer et al 1985,[235] Widmer et al 1987,[236]
Villalta scale	30 studies (41.1%)	Ageno et al 2003,[170] Bittar 2015,[212] Bouman et al 2014,[214] Chitsike et al 2012,[151] Delluc et al 2010,[203] Gabriel et al 2004,[178] Galanaud et al 2013,[152] Gerlach et al 2010,[179] Hach-Wunderle 2013,[153] Kahn et al 2005,[155] Kahn et al 2008,[34] Latella et al 2010,[156] Mazetto 2012,[213] Persson et al 2009,[184] Prandoni et al 1996,[159] Rabinovich et al 2015,[168] Roberts et al 2011,[186] Roberts et al 2013,[160] Rosfors et al 2001,[208] Rosfors et al 2010,[187] Roumen-Klappe et al 2009,[162] Roumen-Klappe et al 2009,[195] Sartori et al 2014,[192] Shbaklo et al 2009,[164] Shrier et al 2009,[165] Spiezia et al 2009,[204] Ten Cate-Hoek et al 2010,[169] Tick et al 2008,[13] Van Dongen et al 2005,[200] Wik et al 2012[81]
Widmer classification	4 studies (5.5%)	Blattler 1991,[175] Franzeck et al 1997,[177] Kneimeyer et al 1990,[210] Ziegler et al 2001[190]

PTS diagnostic method	Number of studies that used method (%)	Author(s), year and reference
Clinical assessment and radiological assessments		
Ginsberg	2 studies (2.7%)	Park et al 2012,[183] Rabinovich et al 2015[168]
Doppler ultrasound ± clinical assessment	1 study (1.4%)	AbuRahma et al 1998[196]
Clinical and radiological assessment scale first used to diagnose PTS by individual studies	3 studies (4.1%)	Mehdipour et al 2009,[198] Sharifi et al 2010,[199] Sharifi et al 2015[193]
Radiological only methods		
Doppler ultrasound	2 studies (2.7%)	Mohr et al 2000,[49] Incalcaterra 2014[191]
Plethysmography	1 study (1.4%)	Mohr et al 2000[49]
Venography	2 studies (2.7%)	Gabriel et al 2004,[178] Mohr et al 2000[49]

Key: CEAP – Clinical aetiological anatomical and pathophysiological classification

VCSS- Venous clinical severity score

4.6 Discussion

The approach used in this section to identify PTS diagnostic methods from the evidence on potential prognostic factors associated with the development of PTS was done because studies on potential prognostic factors were more likely to specify the outcome measure than studies on treatment of PTS where outcome measures may not be stated. Therefore, this approach of identifying variation in PTS diagnosis and frequency of use of identified PTS methods was a more pragmatic and less time consuming approach to assessing variation in methods used to diagnose PTS. There is always the small risk of missing out on other methods that may have been used to diagnose PTS, this is however unlikely to have a huge impact on the results of this study which has already detected a wide variation in methods used to diagnose PTS.

From both systematic reviews the following PTS diagnostic methods were identified

1. Clinical assessment only methods – which include; subjective clinical assessments (no criteria for PTS diagnosis –based solely on the subjective assessment of clinician/researcher), standardised clinical assessments such as the Brandjes score, the CEAP classification, the Villalta scale (including modified versions of the Villalta scale) and the Widmer classification. Clinical assessment only criteria first developed or used for PTS diagnosis by respective primary studies including Browse et al,[207] Monreal et al,[158] Widmer et al,[189] and Singh and Masuda.[209]
2. Clinical assessment and radiological methods – which include the standardised Ginsberg's criteria, the criteria first developed by Mehdipour et al's study[198] and the criteria first developed by Sharifi et al's study[199]
3. Radiological methods – which include Doppler ultrasound, Plethysmography and Venography.
4. Patient reported outcome questionnaires.

Many challenges to PTS diagnosis were demonstrated in this chapter. These include the aforementioned wide variation in methods used for PTS diagnosis and the use of PTS diagnostic methods developed primarily by individual studies which had not been investigated before for their validity for PTS diagnosis.[189,198,207,209] It was also demonstrated that studies were using patient reported outcome questionnaires and subjective clinical assessments for PTS diagnosis.

4.7 Conclusion

In summary, this chapter demonstrates two aspects of the difficulties that face the diagnosis of PTS at the moment – too many varied methods being used for PTS

diagnosis and studies devising their own methods for PTS diagnoses likely due to the absence of a universally accepted reference diagnostic method. This means that conclusions from studies cannot reliably be grouped together and conclusions cannot reliably effect changes demonstrating the need for a reference standard for PTS diagnosis to be developed or selected from the methods available. Chapter 5 explored how PTS diagnostic methods compared in terms of diagnosing PTS.

It was demonstrated in this that the CEAP classification tool and the Villalta scale are currently the most widely used PTS diagnostic methods among researchers. There was no information on PTS diagnostic methods used in daily clinical practice. A summary of what experts in the UK are using for PTS diagnosis in their daily practice was gathered through an e-Delphi study. The methods and results of this e-Delphi study are described in Chapter 6.

Chapter 5: Correlation of PTS diagnostic methods in proportion of PTS diagnosed (systematic review of primary studies)

5.1 Introduction

As demonstrated in chapter 4, there is a wide variation in the methods being used for PTS diagnostic methods because there is no consensus on what the reference standard for PTS diagnosis should be. It is not surprising therefore that various methods are being used to diagnose PTS. It is however not clear if PTS diagnostic methods are detecting similar incidence of PTS in the same population. This chapter explored how existing PTS diagnostic methods compared to each other in detecting clinically relevant disease.

Ideally a test should be compared to a reference standard, however there is no recognised PTS diagnosis reference standard, even though the international society of thrombosis and haemostasis (ISTH) recommends use of the Villalta scale to encourage comparison across PTS research (despite its limitations).[237] Therefore, another method for assessing accuracy of diagnostic tests in the absence of a reference standard was used.[238] This method was by validating existing PTS diagnostic methods. Validation was achieved by assessing relationships between PTS diagnostic methods and detection of clinical characteristics of PTS (i.e. proportion of clinically relevant disease detected

by a PTS diagnostic method) and comparing these between diagnostic methods. This was achieved with a systematic review of the evidence.

5.2 Aim

To compare the proportion of PTS diagnosed by PTS diagnostic methods

5.3 Objectives

- To identify studies that have compared two or more PTS diagnostic methods at the same time point
- To assess correlation between PTS diagnostic measures in identifying clinically relevant disease

5.4 Method

5.4.1 Search strategy

A search of the following databases was conducted using keywords combined with an appropriate BOOLEAN operator; MEDLINE (Ovid) 1946 to August 2014 and EMBASE (Ovid) 1947 to August 2014. The search strategy was developed with the help of an information specialist (Sue Bayliss). Selected keywords were informed by relevant studies identified from a scoping search.

The keywords combined descriptors of the post-thrombotic syndrome and various terms that may be used for diagnostic criteria for example;

(‘Post-thrombotic syndrome’ OR ‘postthrombotic syndrome’ OR ‘PTS’ OR ‘Post phlebitic syndrome’) AND (‘scale’ OR ‘score’ OR ‘scoring’ OR ‘definition’ OR ‘classification’ OR ‘measures’ OR ‘questionnaire’ OR ‘Villalta’ OR ‘Ginsberg’ OR

‘Brandjes’ OR ‘Widmer’ OR ‘clinical etiological anatomical and pathophysiological classification’ OR ‘CEAP’ OR ‘venous clinical severity score’ OR ‘VCSS’).

References of identified studies were also checked to identify any potentially relevant review not already identified by the search strategies used.

The search results were then entered into reference management software (Endnote X4 version). An inbuilt algorithm in Endnote X4 was used to automatically remove duplicate records. Remaining duplicate records were searched for and removed manually.

Appendix 5, Section 5.1 shows the search strategies used in the databases.

5.4.2 Study screening and selection

Two reviewers HO and AY independently screened the titles and abstracts of records to identify those relevant to the review. Relevance was determined based on population, study designs, exposure, comparator and outcomes.

Hard copies of relevant articles were subsequently obtained and the full inclusion and exclusion criteria described below were applied to them by the same reviewers. Studies that met all the inclusion criteria were included in the review. Studies that did not meet the inclusion criteria were excluded.

Inclusion criteria

Patient group – Adults that have had at least one episode of objectively confirmed DVT of the lower limb.

Setting – Studies in all settings were considered.

Index method of PTS diagnosis and Comparator – Any PTS diagnostic method against which another PTS diagnostic method had been compared with was regarded as an index test and other test(s) compared with was regarded as the comparator PTS diagnostic method.

Outcomes – Similarities and differences between PTS diagnostic methods with regards to the proportion of PTS diagnosed at least three months after an initial DVT diagnosis. This minimum time interval between DVT and PTS assessment is important because a diagnosis of PTS cannot be reliably made earlier than three months post DVT.

Study design – Cross sectional studies, case-control studies, cohort studies (both retrospective and prospective cohort studies) and RCTs were considered for inclusion in this systematic review.

Language – Only studies in English were included in the systematic review

Time of PTS assessment – Patients must have been assessed for PTS at the same time using the PTS diagnostic tools to be compared.

5.4.3 Summary of screening and selection process

The Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram[91] was used to present a summary of the selection process

5.4.4 Data extraction

Full data extraction was carried out by OH and discrepancies checked by AY. The following details were extracted;

Study details:

Title of paper, study objectives, number of participants enrolled, duration of follow-up post DVT and percentage lost to follow-up.

Population characteristic:

Age, gender, ethnicity and location of study

PTS diagnostic method details:

Type of PTS diagnostic methods used, components of PTS diagnostic methods, threshold for PTS diagnosis for each identified PTS diagnostic method, details on diagnostic method accuracy such as specificity, sensitivity, predictive values, likelihood ratios and odds ratio. Effect measures used to measure correlation between two or more diagnostic methods like agreement kappa and gamma statistic were reported.

Outcome details:

Number of PTS events in the population based on the different diagnostic methods

5.4.5 Quality assessment

The quality of identified studies was appraised using a tool for quality assessment of diagnostic accuracy studies (QUADAS 2).[239] The components of the tool that referred to reference standard tests were omitted because there was no reference standard. The components of the tool referring to index tests were duplicated for each additional index test identified. The assessment was carried out by two reviewers independently (HO and AY). All disagreements were resolved by discussion between them.

5.4.6 Analysis

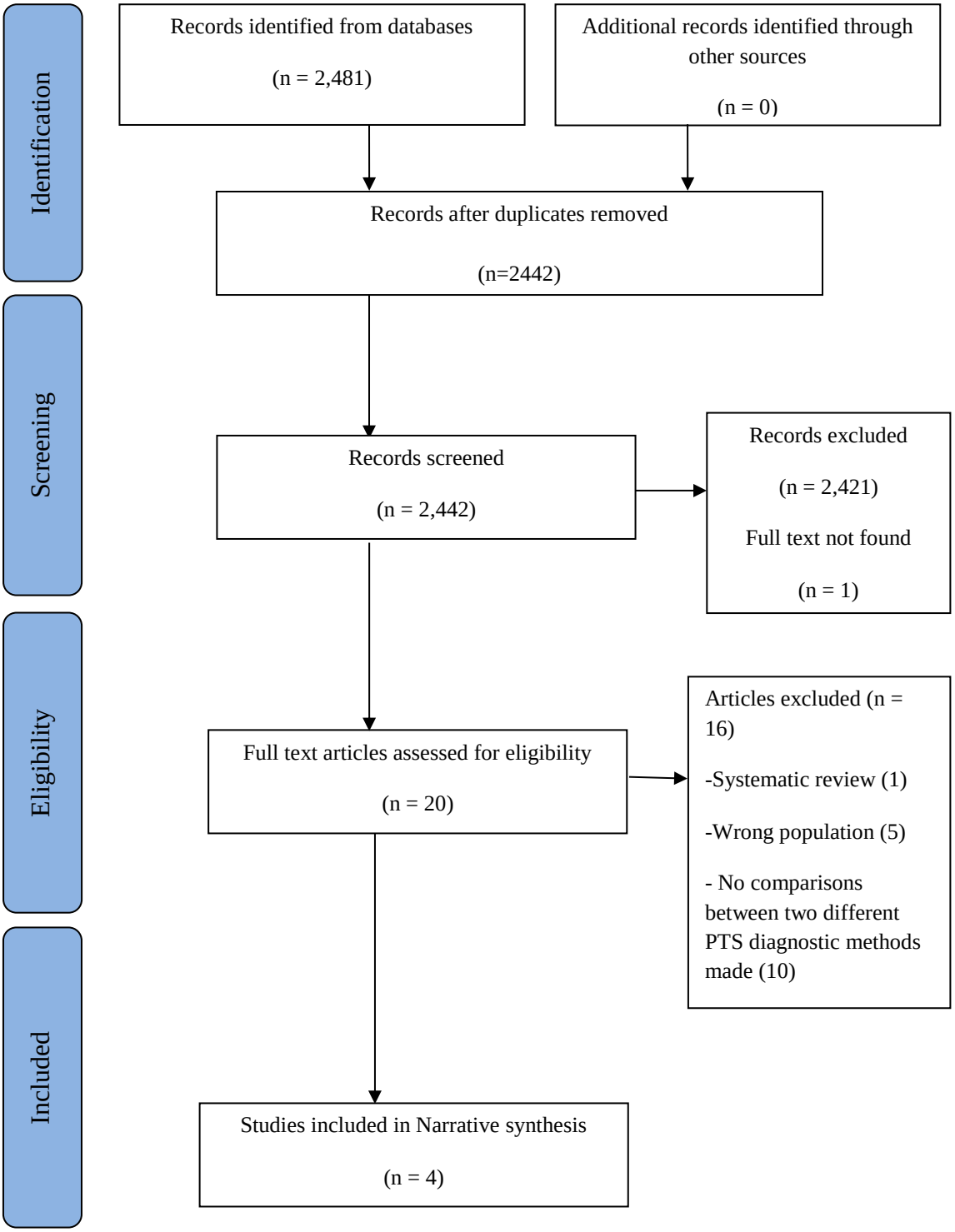
There is no reference standard to compare identified PTS diagnostic methods with, therefore it was not possible to calculate statistics such as sensitivity, specificity, positive predictive value, negative predictive value or to attempt a meta-analysis as would be ideal where these statistics could be computed. Therefore, a narrative analysis of findings was done. The measure of correlation reported by studies was noted and interpreted accordingly, for example where agreement Kappa was presented by studies, a correlation score of < 0.20 was rated as poor agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as good agreement and 0.81 to 1.00 as very good agreement.[240]

5.5 Results

Two thousand, four hundred and forty two records of titles and abstracts were identified and screened after removal of duplicates, 21 records were potentially relevant. The full text of one record[241] was not found despite attempts to contact the corresponding author and could not be assessed for eligibility for inclusion. The full texts of 20 studies were therefore assessed for their eligibility and four of these met the inclusion criteria. Reasons for exclusion of studies (see Appendix 5, Section 5.2) were, wrong population,[242-246] wrong study design[117] and no comparisons between at least two different PTS diagnostic methods.[158,160,162,163,168,187,195,247-249]

Please see the PRISMA flow diagram (Figure 9) for an illustration of the study screening and selection process.

Figure 9: PRISMA flow diagram of study screening and selection



5.5.1 Characteristics of included studies

Four studies that had assessed the correlation between at least two diagnostic methods with regards to proportions of PTS diagnosed were identified. They included three cohort studies (one retrospective[40] and two prospective cohort[178,250]) and one randomised controlled trial.[251] The publication years of the four studies ranged from 2004 up to the year 2014.

They all reported that the preceding DVT had been objectively confirmed. The length of follow up across studies was between three months and 72 months (see Table 46).

Sometimes included studies assessed correlation between PTS diagnostic methods in other areas besides the proportion of PTS diagnosed. Other areas assessed were, correlation with clinical characteristics of PTS and correlation with radiological evidence of PTS. However, for the purpose of this systematic review, only correlation in proportion of clinically relevant disease diagnosed by diagnostic methods was explored further.

See Table 46 for summary of characteristics of included studies.

Table 46: Characteristics of included studies

Author and year	Type of study	Population (n)	Country	PTS diagnostic methods compared	Domains assessed	Time points of assessment after DVT diagnosis	Diagnostic methods applied at same time or not
Gabriel et al 2004[178]	Prospective cohort	135 DVT patients	Spain	Phlebography and Villalta	Proportion of PTS diagnosed	12 months	Yes
Jayaraj et al 2014[251]	RCT	69 DVT patients	USA	VCSS and Villalta	Proportion of PTS diagnosed	3, 6, 12 and 24 months	Yes
Kahn et al 2006[250]	Prospective cohort	259 DVT patients	Canada	Ginsberg and Villalta	Proportion of PTS diagnosed Correlation with clinical characteristics of PTS Correlation with radiological evidence of PTS	12 months	Yes
Kolbach et al 2005[40]	Retrospective cohort	124 DVT patients (137 legs)	The Netherlands	Brandjes and CEAP	Proportion of PTS diagnosed Correlation with radiological evidence of PTS	Average of 72 months	Yes
				Brandjes and VCSS			
				Brandjes and Villalta			
				Brandjes and Widmer			
				CEAP and VCSS			
				CEAP and Villalta			
				CEAP and Widmer			
				VCSS and Villalta			
				VCSS and Widmer			
				Villalta and Widmer			

Key: CEAP – Clinical etiological and pathophysiological classification DVT – Deep vein thrombosis PTS – Post-thrombotic syndrome
RCT – Randomised controlled trial USA – United States of America VCSS – Venous clinical severity score

5.5.2 Quality assessment

All four included studies[40,178,250,251] reported that an aim/objective of their study was to compare at least two or more PTS diagnostic methods.

All four studies followed up patients with lower limb DVT. One out of the four studies followed up only patients with proximal DVT,[251] hence limiting the application of findings from that study to only patients with proximal lower limb DVT. In all four studies, selection criteria were clearly described. There was exclusion of patients that could potentially make the diagnosis of PTS difficult such as patients with pre-existing chronic venous insufficiency and or patients with pre-existing arterial insufficiency. Therefore the population in all four studies was not a true representation of patients that would normally be seen in clinical practice.

In all four studies, the description and application of the PTS diagnostic methods was reported in sufficient detail to allow for replication. Researchers applying a particular PTS diagnostic method were blinded to findings of other PTS diagnostic measures in one of the studies.[251] In two studies[178,250] it was not reported if researchers were blinded in this respect. In one study,[40] it was reported that the same researcher applied all PTS diagnostic methods to be compared.

In three studies[40,178,250] patients had the same DVT treatment regimen prior to application of PTS diagnostic methods. While in the fourth study[251] patients were randomised to receive either compression stockings or no stockings. In this study, assessment for PTS using the diagnostic methods to be compared was carried out in all patients regardless of the DVT treatment used. All four studies used similar time points

for PTS diagnostic measure application and made comparisons based on these time points.

In summary three of the studies[178,250,251] were deemed of fair quality while one study was deemed to be of poor quality[40] (see Appendix 5, Section 5.4).

5.5.3 Correlation between PTS diagnostic methods – Proportion of PTS diagnosed

All four studies had assessed correlation between at least two PTS diagnostic methods and the proportion of PTS that they diagnosed.

A total of 12 comparisons between PTS diagnostic methods were identified. The diagnostic methods compared include, Brandjes and CEAP, Brandjes and VCSS, Brandjes and Villalta, Brandjes and Widmer, CEAP and VCSS, CEAP and Villalta, CEAP and Widmer, Ginsberg and Villalta, VCSS and Villalta, VCSS and Widmer, Villalta and phlebography, Villalta and Widmer. The findings from these studies in this respect are detailed below and summarised in Table 47.

5.5.3.1 Brandjes and CEAP

One poor quality study[40] by Kolbach et al assessed the correlation between Brandjes and CEAP classification tool with regards to the proportion of PTS diagnosed in the same population after DVT. It was a cross sectional study who recalled 124 patients diagnosed with DVT an average of six years after diagnosis.

The unit of assessment used by this study were legs with DVT. The 124 patients included in the study contributed 137 legs with DVT because 13 out of 124 patients

(10.5%) had bilateral DVT. Therefore 137 legs with DVT were studied in total. In the 13 patients with bilateral DVT, it was not clear when the second DVT was diagnosed and if they had reached the minimum time period for an assessment and diagnosis of PTS to be made.

Both diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner by the same researcher.

The Brandjes tool identified 90 post DVT legs as having PTS (65.7%) while the CEAP identified 66 post DVT legs as having PTS (48.2%). Comparison of agreement kappa was 0.54, 95% CI (0.43 to 0.66).

In summary there was moderate agreement between both methods in diagnosing PTS.

5.5.3.2 Brandjes and VCSS

Kolbach et al[40] also assessed the correlation between Brandjes and VCSS in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The Brandjes tool identified 90 post DVT legs as having PTS (65.7%) while the VCSS identified 74 post DVT legs as having PTS (54%). Comparison of agreement kappa was 0.22, 95% CI (0.09 to 0.36).

In summary there was fair agreement between both methods in diagnosing PTS.

5.5.3.3 Brandjes and Villalta

Kolbach et al[40] also assessed the correlation between Brandjes and Villalta in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The Brandjes tool identified 90 post DVT legs as having PTS (65.7%) while Villalta identified 83 post DVT legs as having PTS (60.6%). Comparison of agreement kappa was 0.40, 95% CI (0.27 to 0.53).

In summary there was fair agreement between both methods in diagnosing PTS.

5.5.3.4 Brandjes and Widmer

Kolbach et al[40] also assessed the correlation between Brandjes and Widmer in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The Brandjes tool identified 90 post DVT legs as having PTS (65.7%) while Widmer identified 80 post DVT legs as having PTS (58.4%). Comparison of agreement kappa was 0.52, 95% CI (0.40 to 0.64).

In summary there was moderate agreement between both methods in diagnosing PTS.

5.5.3.5 CEAP and VCSS

Kolbach et al[40] also assessed the correlation between CEAP and VCSS in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The CEAP tool identified 66 post DVT legs as having PTS (48.2%) while VCSS identified 74 post DVT legs as having PTS (54%). Comparison of agreement kappa was 0.27, 95% CI (0.12 to 0.41).

In summary there was fair agreement between both methods in diagnosing PTS.

5.5.3.6 CEAP and Villalta

Kolbach et al[40] also assessed the correlation between CEAP and Villalta in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The CEAP identified 66 post DVT legs as having PTS (48.2%) while Villalta identified 83 post DVT legs as having PTS (60.6%). Comparison of agreement kappa was 0.42, 95% CI (0.29 to 0.56).

In summary there was moderate agreement between both methods in diagnosing PTS.

5.5.3.7 CEAP and Widmer

Kolbach et al[40] also assessed the correlation between CEAP and Widmer in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The CEAP identified 66 post DVT legs as having PTS (48.2%) while Widmer identified 80 post DVT legs as having PTS (58.4%). Comparison of agreement kappa was 0.53, 95% CI (0.40 to 0.65).

In summary there was moderate agreement between both methods in diagnosing PTS

5.5.3.8 Ginsberg and Villalta

One fair quality study[250] assessed the correlation between Ginsberg and Villalta scale with regards to the proportion of PTS diagnosed in the same population after DVT. This was a prospective cohort study that had followed up 259 patients for one year after their DVT diagnosis.

Both diagnostic methods were applied at the same time point (one year after DVT diagnosis) however it was not clear if researchers were blinded to findings of one diagnostic method before the application of the other.

The Ginsberg identified 21 post DVT legs as having PTS (8.1%) while Villalta identified 96 post DVT legs as having PTS (37%). Comparison of agreement kappa was 0.22, 95% CI (0.13 to 0.32).

In summary there was fair agreement between both methods in diagnosing PTS.

5.5.3.9 Phlebography and Villalta

One fair quality study[178] assessed the correlation between phlebography and Villalta scale with regards to the proportion of PTS diagnosed in the same population after DVT. This was a prospective cohort study that had followed up 169 patients for one year after a DVT diagnosis.

A diagnosis of PTS on phlebography was made one year post DVT when there was total venous occlusion in the affected venous segment or narrowing greater than 50% of at least half of the affected segment when compared to an initial phlebography done at DVT diagnosis. Only 135 patients successfully had phlebography at DVT diagnosis and phlebography one year post DVT. Only these 135 patients were included in the analysis. Both diagnostic methods were applied for PTS diagnosis at the same time point (one year after DVT diagnosis). In addition, researchers were blinded to findings of one diagnostic method before the application of the other.

Eighty four patients developed PTS as determined by phlebography (62.2%). None of the patients was diagnosed with PTS when the Villalta scale was used. No degree of correlation statistic was calculated in the study.

In summary, it appears that there is a low level of agreement between both diagnostic methods.

5.5.3.10 VCSS and Villalta

Two studies[40,251] one of fair quality[251] and one of poor quality[40] compared the correlation between the Villalta scale and the VCSS scale. The population of both

studies were 69[251] and 124[40] post-DVT patients. Patients were followed up for two years in one study[251] and an average of six years in the second study.[40]

The poor quality study was the same study by Kolbach et al mentioned previously,[40] the unit of assessment was legs affected by DVT. Thirteen out of 124 patients that were followed up by the study had bilateral DVT. Therefore 137 legs with DVT were assessed in total.

In both studies, both diagnostic methods were applied at the same time point in a non-blinded manner by the same researcher.

In one of the studies[251] the actual numbers of patients diagnosed with PTS according to the diagnostic methods were not reported. However, correlation between the two instruments was reported as 0.71 ($p < 0.05$) for mild to moderate disease and 0.50 ($p > 0.05$) for severe disease. In the second study,[40] VCSS identified 74 post DVT legs as having PTS (54%) while Villalta identified 96 post DVT legs as having PTS (37%). Comparison of agreement kappa was 0.41, 95% CI (0.28 to 0.55).

In summary there appeared to be a good level of agreement between both instruments for mild to moderate disease, moderate level of agreement for severe disease and moderate level of agreement where there was no differentiation in severity of PTS.

5.5.3.11 VCSS and Widmer

Kolbach et al[40] also assessed the correlation between VCSS and Widmer classification in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point

(median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The VCSS identified 74 post DVT legs as having PTS (54%) while Widmer identified 80 post DVT legs as having PTS (58.4%). Comparison of agreement kappa was 0.24, 95% CI (0.10 to 0.38).

In summary there was fair level of agreement between both methods in diagnosing PTS.

5.5.3.12 Villalta and Widmer

Kolbach et al[40] also assessed the correlation between Villalta and Widmer classification in relation to the proportion of PTS diagnosed. The unit of assessment was the same (137 DVT legs) and PTS diagnostic methods were applied at the same time point (median of six years after DVT diagnosis) in a non-blinded manner as described in section 5.5.3.1.

The Villalta identified 83 post DVT legs as having PTS (60.6%) while Widmer identified 80 post DVT legs as having PTS (58.4%) Comparison of agreement kappa was 0.44, 95% CI (0.29 to 0.58).

In summary there was a moderate level of agreement between both methods in diagnosing PTS.

Table 47: Summary of correlation between methods of PTS diagnosis

Author and year	PTS diagnostic methods compared	Correlation (Significance)
Gabriel et al 2004[178]	Phlebography and Villalta	84% diagnosed with PTS on phlebography, none on Villalta (correlation not reported)
Jayaraj et al 2014[251]	VCSS and Villalta	0.71 for mild to moderate disease ($p < 0.05$) 0.50 for severe disease ($p > 0.05$)
Kahn et al 2006[250]	Ginsberg and Villalta	0.22 95% CI (0.13 to 0.32).
Kolbach et al 2005[40]	Brandjes and CEAP	0.54 95% CI (0.43 to 0.66)
	Brandjes and VCSS	0.22 95% CI (0.09 to 0.36)
	Brandjes and Villalta	0.40 95% CI (0.27 to 0.53).
	Brandjes and Widmer	0.52 95% CI (0.40 to 0.64)
	CEAP and VCSS	0.27 95% CI (0.12 to 0.41)
	CEAP and Villalta	0.42 95% CI (0.29 to 0.56)
	CEAP and Widmer	0.53 95% CI (0.40 to 0.65)
	VCSS and Villalta	0.41 95% CI (0.28 to 0.55)
	VCSS and Widmer	0.24 95% CI (0.10 to 0.38)
	Villalta and Widmer	0.44 95% CI (0.29 to 0.58)

Key: CEAP – Clinical aetiological anatomical and pathophysiological classification VCSS – Venous clinical severity score

5.5.4 Findings from abstract with no full text

A study conducted in 2011,[241] reported on correlations between the VCSS and the venous segmental disease score (VSDS) as well as the VCSS and the venous disability score (VDS) in the assessment of PTS in 62 patients at six, 12 and 24 months after DVT. Only the abstract to this study was found. There was no full text available for this study so it was not analysed further.

5.6 Discussion

The methods and findings of this systematic review have been reported in the previous sections. This section discusses the validity and the applicability of the evidence by considering the scope and content of the evidence and how it fits in a broader context.

5.6.1 Summary of main results

In terms of proportion of PTS detected, one poor quality study[40] found that the Brandjes score had a moderate level of agreement with the CEAP and Widmer classifications. This was unexpected as both the CEAP and Widmer classification have static components unlike the Brandjes score which was developed with components that should potentially measure change in severity of PTS. The same study found a fair level of agreement between the Brandjes score and the VCSS and Villalta scale. It also found a fair level of agreement between the CEAP classification and the VCSS while it found a moderate level of agreement between the CEAP classification and both the Villalta and Widmer classification. There was a fair level of agreement between the VCSS and Widmer and a moderate level of agreement between the Villalta and Widmer

classification. A fair quality study[178] found a low level of agreement in proportion of PTS diagnosed between phlebography and Villalta scale. Two studies, one of poor quality[40] and one of fair quality[251] found that there was a moderate level of agreement between the Villalta and the VCSS scale although one of the studies[251] demonstrated that this level of agreement between both tools became good when they were used to diagnose mild to moderate PTS. This review demonstrated that there were additional PTS diagnostic methods not identified chapter 4 (see Section5.5.4). Further demonstrating the wide variation in methods used to assess PTS.

In summary, this review demonstrates that PTS diagnostic methods compared by included studies are quite different from each other in their ability to detect clinically relevant disease. This suggests that pooling of results across studies that have used different PTS diagnostic methods for PTS diagnosis is not valid. It exposes the difficulties surrounding PTS research.

5.6.2 Strength and limitations of included studies

Only four studies were identified and these studies covered only the western world (The Netherlands, Canada, Spain and the United States of America), meaning that results from these studies is related to patients from only these parts of the world.

At least one of the aims of all four studies was to compare PTS diagnostic methods so that their aims were directly attempting to answer the question asked by this review.

Limitations of included studies include the small sample sizes and varied follow up periods across studies. In addition, identified studies were of fair to poor quality, meaning that strong conclusions could not be made from them.

Included studies had patient selection bias so that patients were not a true representative of what will be seen in daily clinical practice for example patients with concurrent chronic venous insufficiency at time of DVT diagnosis were excluded from all four studies.

It was unclear in some of the studies whether blinding was carried out or not. It was also unclear in some studies whether the tests were assessed at the same time as the marker of validity. This limits the conclusions that could be made directly from these studies.

5.6.3 Strength and limitations of this systematic review

At every stage of the systematic review, efforts were made to make the process, transparent and easily reproducible by documentation of the whole process especially the screening and selection stage. The use of two reviewers also meant that loss of studies during the selection process though unavoidable due to human error would be minimal. The databases searched were limited to only two databases because of time constraints. However the databases used were large so that it was unlikely that relevant studies would be missed.

There was no reference standard used in this systematic review for reasons stated previously. However, the next best available method to aid comparison of diagnostic methods was done i.e. comparison of ability to detect the signs and symptoms of PTS.

This systematic review could not collate results in a meta-analysis due to heterogeneity of included studies and publication bias could not be assessed as no meta-analysis was done and due to the small number of included studies.

5.7 Conclusion

This systematic review demonstrates that pooling of results across studies on PTS that have used different PTS diagnostic methods is potentially not valid. It also demonstrates it is difficult to identify which of the PTS diagnostic methods was the most reliable in detecting PTS. This meant that an alternative source of evidence on the most reliable PTS diagnostic measure was required. It has been suggested that in the absence of reliable or conclusive research on diagnostic methods, clinical observation of the performance of a diagnostic tool can be used to determine the reliability of diagnostic methods.[252] The opinions of experts in PTS in the UK were therefore sought on which of these methods used for PTS diagnosis were reliable and had the potential of becoming the reference standard. A summary of expert opinion on what the reliable methods of PTS diagnoses are was gathered through an e-Delphi study. The methods and results of this e-Delphi study are described in Chapter 6.

Chapter 6: Expert opinion on potential prognostic factors and methods of PTS diagnosis (e-Delphi study)

6.1 Introduction

From previous work undertaken and described in preceding chapters, a wide range of potential prognostic factors associated with the development of PTS after DVT of the lower limb were identified. The evidence on some of these factors was not conclusive, either because there was conflict in the evidence or because of the poor quality of the studies. In addition, the studies that investigated these factors were mostly based on small population sizes, employed non-standardised diagnostic criteria for PTS, were varied with regards to PTS diagnostic methods, times of PTS assessments and lengths of follow up. Therefore in order to identify the most relevant and useful factors among this wide range of factors, the views of experts were sought via an e-Delphi study. Experts' views and assessments on the reliability of methods for diagnosing PTS were also sought as clinical observation is an alternative mode of determining the reliability of a diagnostic test where previous research findings are not conclusive.[252] This chapter introduces the Delphi method and explains the rationale for its use in this study before outlining its aims and objectives, methods and findings.

6.1.1 Introduction to the Delphi method

History has demonstrated that humans have used informed judgement to analyse, predict and prepare for future outcomes. A method that has been used to gather informed judgement in this way is the Delphi method. The Delphi method has been described by Delbecq et al as "a method for the systematic solicitation and collection of judgements on a particular topic through a set of carefully designed sequential questionnaires interspersed with summarised information and feedback of opinions derived from earlier responses"[253].

The Delphi method was first developed during the Cold war in the 1950s by the RAND corporation to predict the impact of technology on warfare so that counteractive measures could be prepared if needed.[254] This was done because there was an absence of scientific theories or models that could help predict the future of science and technology. The basis for the Delphi method is the assumption that judgements from a structured and informed group of people were more reliable and valid in predicting future occurrences than judgements from an individual or unstructured group of people.[255,254]

It has been demonstrated that results obtained from other study designs correlate well with results obtained via the Delphi method.[256,257] Therefore, the Delphi method has continued to be used to gather expert views on a range of topics to this day. It has been employed in business to make forecasts on market trends,[258] in education to set education models, in policy planning to determine pros and cons of potential policies and many other fields.[259] Relevant to this subject, the Delphi method has been employed in the field of medicine for reaching consensus among experts on guidelines in health

care, collating health quality indicators as well as identifying prognostic factors for clinical conditions.[260,261] More recently, the Delphi method has been used in determining relevant outcomes to measure in future clinical trials where there was absent or limited evidence on outcomes.[256]

In summary, there is scientific evidence that judgements of experts collated via the Delphi method have been used as an alternative method for answering questions in situations where there is absent, inconclusive or inadequate evidence. Therefore, it was anticipated that the Delphi study would be helpful in assessing available evidence on prognostic factors (some of which were inconclusive or inadequate) with an aim to identify factors considered important in clinical practice that may be used as a set of outcomes in future clinical trials. It was also anticipated that the Delphi study would help identify method(s) of PTS diagnosis that experts considered most reliable in daily clinical practice to potentially inform the development of a reference standard.

6.2 Aim

To seek the judgements of experts on potential prognostic factors associated with the development of PTS after DVT of the lower limb and to seek their judgement on the most reliable means of diagnosing PTS.

6.3 Objectives

- To set up a panel of experts in the field of PTS
- To develop questions for a three round Delphi study administered via the internet (e-Delphi) – these questions sought to explore the views of the panel of experts on potential prognostic factors for developing PTS after DVT of the lower limb. Questions sought to get expert judgement on the reliability of current PTS diagnostic measures. This included questions that sought to;
    A. Identify potential prognostic factors associated with the development of PTS after a DVT of the lower limb from expert judgement,
    B. Prioritise prognostic factors,
    C. Identify the methods employed by experts in the diagnosis of PTS.
    D. Prioritise PTS diagnostic methods according to their reliability from expert views.
- To conduct a three round e-Delphi study
- To analyse results of the rounds with a view to collate guidance from experts

6.4 Method

6.4.1 Study design

As stated previously, the study design employed was the Delphi method.

Participants

The e-Delphi study included the following key participants;

I. The respondents – experts on PTS in the United Kingdom
II. The facilitator – the person who summarises and analysed responses received from the experts (myself)

Method of application of the Delphi method

The Delphi method was delivered electronically with the use of emails. Studies that apply the Delphi method via the internet are called electronic Delphi (e-Delphi) studies.[262] A decision to use the e-Delphi method was made as it allows experts to contribute to the study regardless of where they are, in their own time as long as they have an internet connection. In addition, it facilitates anonymity, thereby reducing the potential bias that could occur in a face to face Delphi as discussed previously. It was also identified as a less costly option compared to the face to face method.

Therefore, for each round of the e-Delphi, an email containing a hyperlink to the questionnaire was sent to experts. The hyperlink would direct the expert to a web based questionnaire powered by "Survey Monkey" (https://www.surveymonkey.com/).

6.4.2 How experts were identified and sampling

The success of the Delphi method relies on the selection of credible experts. Experts are the source of informed judgement that is sought. The identification of experts should therefore be a rigorous process as the outcome of applying the method relies heavily on the input from identified experts. An expert has been defined as "any individual with relevant knowledge and experience of a particular topic".[263] However, Olaf, one of the co-founding fathers of the Delphi method acknowledged that measuring or defining an expert or expertise can be a tasking process as expertise is not exactly measurable.[254] But many researchers agree that the definition of an expert should depend on the subject area and the objectives of the study.[254,263,264]

6.4.2.1 Determination of an expert in PTS

The process of determining an objective method to identify experts in PTS was not straightforward because in addition to PTS being a lesser recognised complication of DVT, it was expected that few people involved in DVT management would be interested in PTS. Therefore for the purpose of this study, an expert in PTS was defined as a person who had to be;

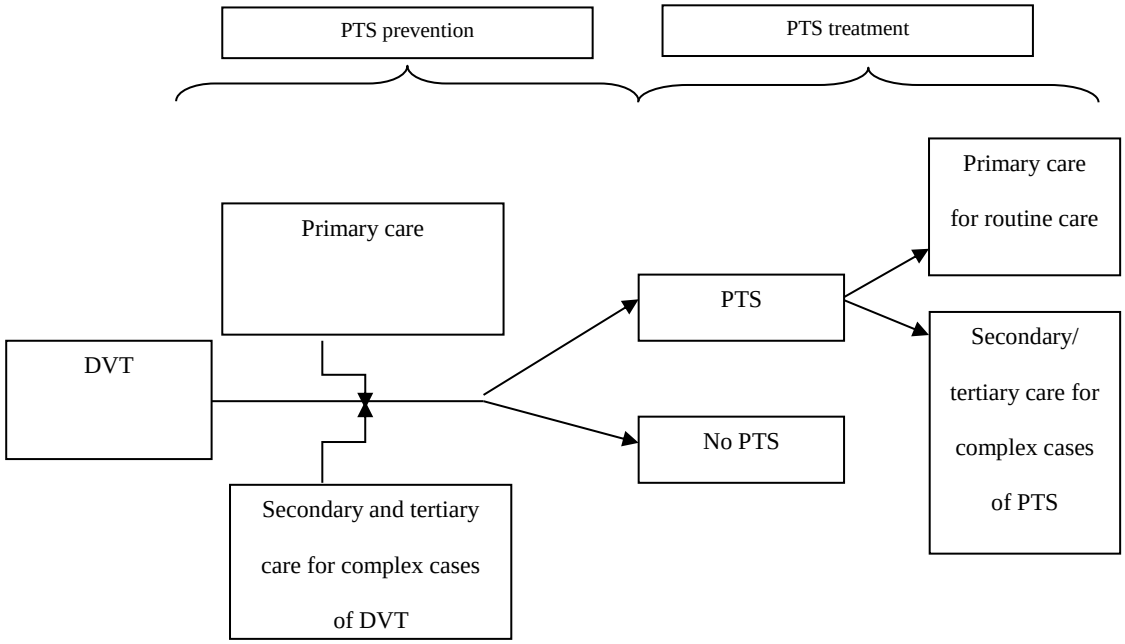
1. Involved in the management and or research in the area of DVT and or the long term complications of DVT AND
2. Recommended by identified key persons in the area of PTS (the key informants) – This was to confirm the interest and expertise of the person in PTS

Staff involved in the management and or research on DVT

Specialists involved in the long term management of DVT at primary secondary and tertiary levels of care were considered because they are more likely to have followed patients from the beginning of DVT to the development of PTS. These specialists were expected to be equipped to give experience-based views on factors that may be associated with the development of PTS after DVT.

The diagram below illustrates the progression of patients from DVT to PTS and the care they receive at every stage.

Figure 10: Levels of care in the management of patients from DVT to PTS



Key: DVT – Deep vein thrombosis PTS – Post-thrombotic syndrome

The above diagram demonstrates that there are various specialists at different levels of care who are involved in the management of DVT and potentially PTS and whose inputs may provide a better insight into the factors that may predispose an individual to develop PTS after DVT.

In view of the above, experts on PTS were expected to include the following groups of people;

- Clinicians managing DVT and PTS in primary care

    I. General practitioners – some general practitioners provide anticoagulation services for patients after DVT of the lower limb. They may also prescribe or re-prescribe compression stockings for patients with DVT. They are usually the point of contact when patients develop symptoms of PTS such as leg swelling, leg pain and leg ulcers.

    II. Clinical nurse specialists – clinical nurse specialists affiliated with consultant haematologists follow up patients with DVT in the community. Together with the general practitioners, clinical nurse specialists perform the role of providing anticoagulation services and advice in the community as well as compression stockings prescribing. They also provide care for patient with venous ulcers.

- Clinicians managing DVT and PTS in secondary and tertiary care

    I. Vascular surgeons –vascular surgeons work to provide complex treatment options for DVT such as surgical embolectomy and catheter directed thrombolysis. They may also provide care for complicated cases of DVT and PTS.

    II. Haematologists – they are responsible for the development of the anticoagulation guidelines for each hospital. They work with

complicated patients (patients with co-morbidities that require complex anticoagulation arrangements after DVT) and also work with clinical nurse specialists in haematology clinics to provide care for patients with DVT and PTS.

III. Interventional radiologists – they may work with vascular surgeons to provide complex treatment options for patients with DVT or PTS.

IV. Clinical nurse specialists – they provide DVT patients with information and details of follow-up prior to discharge to the community.

It is now generally encouraged to include patients with chronic disease in studies investigating the disease, as they are considered experts in their illness.[265] However the main question in this study is about identifying prognostic factors and methods of diagnosis used in practice and seeking clinician agreement on important ones. Patient knowledge on these was likely to be very low therefore the value of patients participating in this research was deemed to be also low. As a result they were not included in this study.

6.4.2.2 Selection of panel

Because of the highly defined attributes usually required in an expert, it is not often pragmatic to conduct a random sampling for panel selection of experts to be recruited in a Delphi study. In addition, experts have to be willing to participate in the study. Because of these reasons, experts were selected using purposive sampling, whereby the

researcher determines who is most likely to contribute relevant data to his/her study and is willing to participate.

Identifying expert sample via this method did not necessarily allow for all specialist groups involved in the management of PTS to be equally represented in the sample. Ideally, to increase the robustness of this study, a good mix of experts from the specialities mentioned above should be identified with the aim of achieving a balance of perspectives between expert groups. However, PTS is only beginning to gain recognition and it was expected that not all of these specialists would have a special interest in PTS, hence the purposive sampling method was used.

An international expert community would have been ideal for this e-Delphi study to aid generalisability of findings, as the study's findings would have been informed by experience of clinicians around the globe. However, experts in the international community were not sought for this e-Delphi study as it was pre-empted that it might be expensive to implement as it may require international travelling to meet with key informants (e.g. subcommittees of relevant international conferences such as the international society on thrombosis and haemostasis). Meeting face to face with key informants as was done in this e-Delphi was thought to be preferable to foster good relationship, get the best response from key informants and encourage interest and participation in the study. In addition, it was thought that limiting participants to UK experts would yield more manageable data which could potentially be explored in the wider international expert community at a later date.

The initial key informant for the sample of experts required for this study was sought from a network where specialists interested in PTS are likely to converge. The National

VTE Exemplar Centres Network is a nationally recognised network whose members are centres specialised in the prevention of VTE. These centres have multidisciplinary teams across the specialties relevant to this study who are involved in the prevention of VTE, management of VTE and prevention of VTE complications. The network was consequently identified as a good resource for identifying experts in PTS because of the overlap in the expertise of its members in prevention of VTE, management of VTE and and prevention of complications of VTE which includes PTS.

The Kings Thrombosis Centre was identified as the first Exemplar Network centre in the United Kingdom which is also internationally recognised for work on VTE, therefore, experts who acted as key informants were identified from the Kings Thrombosis Centre. The steps taken to select experts for this study were as follows;

1. Identification of members of the Kings Thrombosis Centre via their website (http://www.kingsthrombosiscentre.org.uk).

2. Members actively involved in PTS research in addition to diagnosing and managing PTS patients on a daily basis were noted. These members were approached in person to participate in this study. They acted as key informants and were requested to identify other experts in PTS across the United Kingdom.

3. Experts identified from step two were invited to participate in this study via e-mail. The aims and objectives of this study were explained to them in an invitation letter (See Appendix 6, Section 6.1). They also received a participant information sheet (See Appendix 6, Section 6.2) which explained the study and what it would entail to them. They were then requested to identify other specialists in PTS who were eligible to participate in this study.

6.4.3 Sample size

There is no hard and fast rule on the sample size of experts for a Delphi study (study that uses the Delphi method). Guidance from previous Delphi research and researchers who have used the Delphi method extensively have suggested that a minimum sample size of seven experts and a maximum of 15 experts would be sufficient to set up a panel of experts.[266,267] Some of these researchers suggest that seven to 15 experts was sufficient for a homogenous sample of experts while the sample size for heterogeneous experts would be expected to require a greater number.[267] They did not however state how many more experts were required in a heterogeneous sample of experts.

Taking in to consideration the heterogeneous nature of the experts to be recruited for this study, it was intended for at least 30 experts to be recruited in order to accommodate for attrition as well as encourage adequate representation of specialties throughout the study.

6.4.4 Anonymity

Anonymity is one of the bedrocks of the Delphi method[254] and one of the reasons for its success. It is important to the Delphi method because of the following reasons; it prevents loss of face if a suggestion by an expert was deemed unsuitable. It also minimises bias that may otherwise occur in some instances, for example experts could gravitate towards the suggestion of a well-known expert.[254,264] Therefore, for the purpose of this study, experts were anonymous to each other. However, they were aware of the roles of other members of the panel so that there was a sense of belonging to the project which was intended to encourage participation in all rounds of the study.

6.4.5 Ethics and confidentiality

Ethical approval for the e-Delphi study was sought from the University of Birmingham research ethics committee prior to commencement of the study.

Experts were informed of the aims and objectives of the study via the participant information sheet (see Appendix 6, Section 6.2) again prior to commencement of the first round. They were then asked to confirm their willingness to participate after reading a participant information sheet. They were also asked to confirm that should the identity of another expert involved in this study be revealed accidentally, it would be kept confidential.

6.4.6 Determination and description of rounds of the e-Delphi survey

A round of the Delphi method involves the administration of questions to experts and the subsequent collation of responses from experts. The maximum number of rounds involved in the Delphi method is not specified. However, the minimum number of rounds for a Delphi to achieve consensus is two, and three where the first round consists of open-ended questions.[264] To avoid prolonging the process which can lead to attrition, it is recommended to use as few rounds as possible while still fully addressing the objectives. Most Delphi studies in the literature have employed two to three rounds.[268]

Usually, the first round of the Delphi asks open-ended questions to gather intuitive knowledge that may not have been recorded yet.[254] Subsequent rounds build on this intuitive knowledge and/or previously recorded knowledge by requesting the judgement

of all experts. This is usually achieved with the aid of closed questions in subsequent rounds with an opportunity to note the reasons for their judgements.

For this e-Delphi study, three rounds were employed.

6.4.6.1 Pilot studies

A pilot round was undertaken before the implementation of each round to increase rigour and the validity of the process.[269] The pilot studies were undertaken to identify weakness in the questions, which may include ambiguous and or leading questions especially in the first round of the study. This process helped refine questions further in order to achieve valid and robust data collection.

Emails were sent out to general practitioner registrars of University of Birmingham's primary care department inviting them to participate in the pilot study. Five registrars responded and expressed their willingness to participate. The questions for each round of the main e-Delphi study were piloted among these five registrars and feedback on format and presentation of questions was requested to enable improvement of questions.

6.4.6.2 Round one

The aim of the first round was to gather the independent views of experts on what prognostic factors are associated with the development of PTS after DVT of the lower limb as well as to identify the methods of PTS diagnosis used by experts in their day to day activities.

Experts were requested to self-rate their level of expertise in the knowledge of PTS recognition and PTS management on a scale ranging from low to very high as in “very high”, “high”, “medium” and “low”.

They were then asked a set of open ended questions (See Appendix 6, Section 6.3) for more details) and asked to give reasons for their choices. The questions were open ended so as to prevent the facilitator from introducing bias by asking leading or closed questions at the beginning of the study. The questions focused on identifying any prognostic factor associated with the development of PTS as well as methods of diagnosis of PTS employed by experts in their daily practice.

In addition to the free text box provided after each question, a second free text box asking experts to make additional comments was provided at the end of the round. This was to encourage expression of views on preceding questions and or content and presentation of the round to increase robustness of conclusions and improve future rounds of this e-Delphi study as appropriate.

Reminder emails were sent if there was no response was received from an expert after one week; – if no response was received after the first reminder, a second reminder was sent two weeks later. The same process was repeated for round two and round three. The timing of the reminders was adjusted to take in to account holiday periods of experts.

6.4.6.3 Round one analysis

Potential prognostic factors and methods of PTS diagnosis listed by experts were extracted and compiled. They were then converted into statements for experts to give their judgements on in the next round.

6.4.6.4 Round two

The aim of round two was to ascertain levels of agreement of experts on potential prognostic factors associated with the risk of developing PTS after a DVT of the lower limb as well as on the reliability of methods of PTS diagnosis. This was done to aid the gradual reduction in numbers of factors and methods of PTS diagnosis round by round.

In this round, potential prognostic factors and methods of PTS diagnosis identified from round one were put forward for expert judgement .They were presented to experts in form of statements (see Appendix 6, Section 6.4). Experts were then asked to indicate their level of agreement with each statement using the Likert scale. There was a box for free text after each statement. Also presented in the same format in round two of the e-Delphi survey were other potential prognostic factors not listed by experts but identified from a previously conducted systematic review of systematic reviews and systematic review of primary studies regardless of the strength of evidence on them. This was done to allow for existing evidence from the reviews to be compared to views of experts to increase the robustness of the evidence. Methods for PTS diagnosis not listed by experts but identified from previously conducted reviews of the evidence were also presented to experts to gather their views on whether they were reliable PTS diagnostic methods or not. Where applicable (statements informed by data received from experts in round one

of the study), experts were informed of the proportion of experts that listed the factor associated with the development of PTS and method of PTS diagnosis.

In addition to the free text box provided after each statement, a free text box asking experts to make additional comments was provided at the end of the round. This was also done in round three.

6.4.6.5 Round two analysis

Presentation of findings for the e-Delphi study is done usually by using measures of central tendency (mean, mode and median) and measures of dispersion such as standard deviation.[270] The median is preferred for presentation of responses on the Likert scale. However, as the e-Delphi study encourages convergence, the mode has been used in several e-Delphi studies and is considered better than the median or mean particularly when there is clustering of responses around one point of the Likert scale.[267,271] Using the median or mean to present results where there is clustering around two or more points can be misleading.[201] A quick appraisal of responses from the round two of this e-Delphi demonstrated that responses were clustered around one point for the majority of the statement, therefore, the mode was used to summarise the results for round two. The levels of agreements among experts were determined for each statement as follows;

An ordinal figure was firstly assigned to each item on the Likert scale as presented below;

Strongly disagree – 1

Disagree – 2

Neither agree nor disagree – 3

Agree – 4

Strongly agree – 5

The option on the Likert scale that appeared most frequently (the mode) in response to each statement were identified and levels of agreement were categorised as:

High level of agreement – Statements with a mode of 4 and or 5 were grouped as statements with a high level of agreement.

Moderate level of agreement – Statements with a mode of 3, or with more than one mode that included 3 were grouped as statements with moderate level of agreement.

Low level of agreement – Statements with a mode of 1 and or 2 were grouped as statements with a low level of agreement.

No agreement – Statements with more than one mode located at opposite ends of the Likert scale and not including 3 were grouped as statements with no agreement. This indicated that experts could not reach an agreement on the statement.

6.4.6.6 Round three

The aim for round three of this e-Delphi study was to arrive at a consensus on what potential prognostic factors experts think are associated with the development of PTS after DVT of the lower limb and a consensus on what the reliable methods of PTS diagnosis are from the opinion of experts.

Statements with low levels of agreement from analysis of round two of the survey were not presented in round three. Only statements with high and moderate levels of agreement were presented (see Appendix 6, Section 6.5). Experts were informed of the findings of round two and were then asked to rate their level of agreement with each statement on the Likert scale while considering their responses in round two.

In addition to the free text box provided after each statement, a free text box asking experts to make additional comments was provided at the end of the round.

6.4.6.7 Round three analysis

There is no existing defined level of consensus that a Delphi study should aim to achieve.[267,268] However, a brief cross-examination of the literature demonstrates that the definition of consensus in the majority of Delphi studies was 75% without clear evidence as to why this level of consensus was favoured. This finding was further corroborated by a recently conducted systematic review which showed that Delphi studies used a median consensus level of 75%.[268] Therefore this e-Delphi study, consensus was said to be achieved on a statement when ≥ 75% of experts were in agreement or disagreement.

At the end of round three, the fraction of experts who selected each item on the Likert scale was converted to percentages. For example if five experts out of 20 chose agree, this was converted to 25%. Subsequently the degree of consensus for each statement on the Likert scale was determined. As per protocol, consensus on statements was therefore determined as below;

Agreement with the statement - This was said to occur when the percentage of experts that choose agree and strongly agree was ≥75%.

Disagreement with the statement - This was said to occur when the percentage of experts that choose disagree and strongly disagree was ≥75%.

No agreement – This was said to occur when there was neither an agreement with a statement or a disagreement with the statement as described above.

6.4.6.8 Free text comments

Free text comments from all three rounds were analysed together using thematic analysis. This was done manually. Each comment was assigned a code. Codes were then analysed for a pattern that was collated into themes. Emerging themes from the free text comments were then noted and described.

6.5 Results

6.5.1 Outcome of expert identification and selection

The identification of experts was carried out as described above. Expert identification and selection took place between March 2013 and May 2014.

Forty one experts were identified and were invited to participate in this e-Delphi study. Thirty experts responded to the invite, four of these apologised for not being able to participate in the study for the following reasons (two were retired and two were too busy to take part in the study). Thus, 26 experts had agreed to participate and although this was less than the intended sample size of 30, the study proceeded.

6.5.2 Demographics of experts

Twenty three out of 26 experts responded in round one of the e-Delphi study. Of these 23 experts, 11 were consultant haematologists, six were general practitioners, three were vascular surgeons, two were clinical nurse specialist and one was a tissue viability and wound specialist. The majority of the experts were consultant haematologists as PTS is a consequence of a pathological blood condition (DVT).

None of the experts rated themselves as having a low level of expertise in PTS recognition. Experts rated themselves as "very high" (six), "high" (eight) and "medium" (eight). It was not clear from one expert what the response was, as both high and medium were chosen, this expert's response was therefore discarded.

Only one expert rated him/her self as having a low level of expertise in the management of PTS, other experts rated themselves as "very high" (four), "high" (seven) and "medium" (11). It was not clear from one expert what the response was, as both high and medium were chosen, this expert's response was therefore discarded.

Half of the experts considered their level of expertise in the management of PTS as moderate. Asking experts to self-rate their level of expertise has been identified as a way of validating the sample of experts.[255] Therefore, taking into account the limitation in current PTS management strategies, the sample selection for this e-Delphi study was regarded as successful as 63% of experts rated their expertise in the knowledge of PTS recognition as high and above and 50% rated their knowledge in the management of PTS as high and above. Table 48 presents a summary of the characteristics of experts.

Table 48: Summary characteristics of experts that participated in the e-Delphi study

	Categories	**Percentage (n)**
Age	35 - 44	34.8 (8)
	45 - 54	17.4 (4)
	55- 64	47.8 (11)
Job role	Consultant haematologist	47.8 (11)
	General practitioner	26.1 (6)
	Vascular surgeon	13 (3)
	Clinical nurse specialist	8.7 (2)
	Tissue viability and wound specialist	4.4 (1)
Level of expertise in recognition of PTS (self-assessment)	Very high	26.1 (6)
	High	39.1 (9)*
	Medium	39.1 (9)*
	Low	0
Level of expertise in management of PTS (self-assessment)	Very high	17.4 (4)
	High	30.4 (7)
	Medium	47.8 (11)
	Low	4.4 (1)

Key: * - an expert self-assessed level of expertise in recognition of PTS as both high and medium

6.5.3 Findings from round one

Questions for round one were finalised after analysis of the results and feedback from the pilot preceding this round. All 26 recruited experts were sent the participant information sheet again as well as a link to the questions for round one. After two reminders, a total of 23 experts responded, giving a response rate of 88.5%.

6.5.3.1 Potential prognostic factors associated with the development of PTS after a DVT of the lower limb

Thirty four potential prognostic factors associated with the development of PTS after DVT of the lower limb were extracted from the free text comments made by experts.

Experts thought 30 of these potential prognostic factors were associated with an increased risk of PTS. They are listed in Table 49 in descending order of the percentage of experts that listed them.

Table 49: Potential prognostic factors associated with an increased risk of PTS listed by experts

	Potential prognostic factors associated with increased risk of PTS after DVT of the lower limb	Proportion of experts that listed factor
1.	Location and extent of DVT – a proximal DVT / an extensive clot	82%
2.	BMI >25	45.5%
3.	Sub-therapeutic anticoagulation during treatment of DVT	36%
4.	Reduced mobility	32%
5.	Older age	32%
6.	Ipsilateral recurrent DVT	27%
7.	Recurrent DVT	27%
8.	Residual vein thrombosis	27%
9.	Poor treatment compliance post DVT including anticoagulation and compression therapy	23%
10.	Previous ipsilateral varicose veins	18%
11.	Underlying thrombotic disease such as thrombophilia and antiphospholipid syndrome	14%
12.	A delay before presentation and treatment of DVT increases the risk of PTS	14%
13.	Female Gender	9%
14.	Venous valvular damage /venous reflux increases the risk of PTS	9%
15.	D-dimer levels; a high D-dimer levels post completion of anticoagulation and a high initial D-dimer level post DVT	9%
16.	Pregnancy	9%
17.	Previous ipsilateral dermatological conditions increases the risk of PTS	9%
18.	Arteriosclerosis and other arterial disease which will impair blood supply to the skin	9%
19.	Smoking	4.5%
20.	Intravenous drug users	4.5%
21.	Infection	4.5%
22.	Diabetes	4.5%
23.	Persistent DVT symptoms following initiation of treatment (when evaluated 2 to 4 weeks post initiation of DVT treatment)	4.5%
24.	Previous lymphoedema	4.5%
25.	Pre-existing PTS symptoms	4.5%
26.	Congenital vascular anomalies	4.5%
27.	Reduced calf muscle pump function	4.5%
28.	Occlusive thrombi	4.5%
29.	Use of hormones	4.5%
30.	Multiple asymptomatic DVT	4.5%

Experts thought four potential prognostic factors were associated with a decreased risk of PTS. These potential prognostic factors are listed in Table 50 in descending order of the percentage of experts that listed them.

Table 50: Potential prognostic factors associated with a decreased risk of PTS listed by experts

	Potential prognostic factors associated with decreased risk of PTS after DVT of the lower limb	Proportion of experts that listed factor
1.	Compression therapy	27%
2.	Good quality of initial anticoagulation after DVT	14%
3.	Longer duration of anticoagulation therapy	9%
4.	Systemic thrombolysis after acute DVT	4.5%

6.5.3.2 Methods of PTS diagnosis

Ten methods of PTS diagnosis used by experts in their practice were identified. These methods of PTS diagnosis are listed in Table 51 in descending order of the percentage of experts that listed them.

Table 51: Methods of PTS diagnosis used in daily practice by experts

	Methods employed for PTS diagnosis by experts	Proportion of experts that listed method
1.	Subjective clinical assessment – using signs and symptoms	100%
2.	Doppler ultrasound	41%
3.	Magnetic resonance venography	23%
4.	Objective clinical assessments – for example using tape measure to assess swelling of limbs and microlife twin cuff device to measure ankle brachial pressure index	14%
5.	Villalta score	14%
6.	Specialist advice	9%
7.	Clinical etiological anatomical and pathophysiological (CEAP) classification	4.5%
8.	Ankle brachial index with Doppler ultrasound	4.5%
9.	Venography (ascending venography or descending venography)	4.5%
10.	Abdominopelvic computed tomography	4.5%

6.5.4 Findings from round two

Questions for round two of the e-Delphi study were finalised after analysis of the results and feedback from the pilot preceding this round. All 26 recruited experts were sent a link to the questions for round two. After two reminders, a total of 19 experts responded, giving a response rate of 73%.

6.5.4.1 Potential prognostic factors associated with the development of PTS after a DVT of the lower limb

Out of 51 statements on potential prognostic factors put forward for round two, 19 of them had high a level of agreement (i.e. were accepted by experts), 30 statements had a moderate level of agreement (i.e. experts were undecided on them) and two statements had a low level of agreement (i.e. were rejected by experts). None of the statements fell in to the category of no agreement (i.e. experts could not agree on).

Statements on potential prognostic factors with high level of agreement (Mode 4 - 5)

The 19 statements on potential prognostic factors with a high level of agreement after round two of the e-Delphi study are presented in Table 52.

Table 52: Statements accepted by experts

	Statements with high level of agreement	Mode
1.	Location and extent of DVT – a proximal DVT / an extensive clot increases risk of PTS	5
2.	A BMI >25 increases the risk of PTS increases risk of PTS	4
3.	Reduced mobility increases risk of PTS	4
4.	Ipsilateral recurrent DVT increases risk of PTS	4
5.	Recurrent DVT increases risk of PTS	4
6.	Residual vein thrombosis increases risk of PTS	4
7.	Poor treatment compliance post DVT including anticoagulation and compression therapy increases risk of PTS	4
8.	Venous valvular damage /venous reflux increases risk of PTS	4
9.	Persistent DVT symptoms following initiation of treatment (when evaluated 2 to 4weeks post initiation of treatment) increases risk of PTS	4
10.	Previous lymphoedema increases risk of PTS	4
11.	Pre-existing PTS symptoms increases risk of PTS	4
12.	Systemic thrombolysis after DVT increases risk of PTS	4
13.	Occlusive thrombi increases risk of PTS	4
14.	Multiple asymptomatic DVT increases risk of PTS	4
15.	Calf swelling >3cm during index DVT increases risk of PTS	4
16.	Loco-regional thrombolysis for treatment of index DVT reduces risk of PTS	4
17.	Catheter directed thrombolysis as treatment of index DVT reduces risk of PTS	4
18.	Physical activity as part of treatment for index DVT reduces risk of PTS	4
19.	Cancer increases risk of PTS	4

Statements on potential prognostic factors with moderate level of agreement

(Mode 3 OR includes 3)

The 30 statements on potential prognostic factors that had a moderate level of agreement after round two of the e-Delphi study are presented in Table 53.

Table 53: Statements experts were undecided on

	Statements with moderate level of agreement	Mode
1.	A delay before presentation and treatment of DVT increases risk of PTS	3&4
2.	Sub-therapeutic anticoagulation during treatment of DVT increases risk of PTS	3
3.	Older age increases risk of PTS	3
4.	Compression therapy increases risk of PTS	3
5.	Previous ipsilateral varicose veins increases risk of PTS	3
6.	Underlying thrombotic disease such as thrombophilia and antiphospholipid syndrome increases risk of PTS	3
7.	Good quality of initial anticoagulation after DVT reduces risk of PTS	3
8.	Female gender increases risk of PTS	3
9.	Male gender increases risk of PTS	3
10.	Pregnancy increases risk of PTS	3
11.	Arteriosclerosis and other arterial disease which will impair blood supply to the skin increases risk of PTS	3
12.	Smoking increases risk of PTS	3
13.	Intravenous drug users increases risk of PTS	3
14.	Infection increases risk of PTS	3
15.	Diabetes increases risk of PTS	3
16.	Congenital vascular anomalies increases risk of PTS	3
17.	Reduced calf muscle pump function increases risk of PTS	3
18.	Use of hormones increases risk of PTS	3
19.	Unprovoked DVT increases risk of PTS	3
20.	Surgical thrombectomy as treatment of index DVT reduces risk of	3
21.	Use of inferior vena cava filters as treatment of index DVT increases risk of PTS	3
22.	High venous outflow resistance on strain-gauge plethysmography in the first 3 months post DVT increases risk of PTS	3
23.	High reflux velocity on Doppler ultrasound increases the risk of PTS	3
24.	High Villalta scores one month post DVT increases risk of PTS	3
25.	Absence of a pathway to assess for PTS risk after DVT increases risk of PTS	3
26.	High levels of C-reactive protein at presentation of index DVT increases risk of PTS	3
27.	High levels of interleukin 6 at presentation and 4 months post index DVT increases risk of PTS	3
28.	High levels of Intracellular adhesion molecule-1 4 months post DVT increases risk of PTS	3
29.	A high near infra-red spectrometry venous retension index 6 months post DVT	3
30.	D-dimer levels; high D-dimer levels post completion of anticoagulation and a high initial D-dimer level post DVT increases risk of PTS	2&3

Statements on potential prognostic factors with low levels of agreement (Mode 1 - 2)

The two statements that had low levels of agreement after round two of the e-Delphi study are listed in Table 54.

Table 54: Statement that experts rejected

	Statements with moderate levels of agreement	Mode
1.	Longer duration of anticoagulation therapy reduces the risk of PTS	2
2.	Previous ipsilateral dermatological conditions increases risk of PTS	2

6.5.4.2 Reliability of methods of PTS diagnosis

Experts were asked to indicate their agreement with how reliable PTS diagnostic methods (identified from previous reviews and from experts) were in diagnosing PTS.

Out of 17 statements on PTS diagnostic methods put forward to experts, one of them had a high level of agreement while the remaining 16 had a moderate level of agreement. There was no statement on PTS diagnostic methods that had a low level of agreement. The levels of agreements of experts on the reliability of these methods of PTS diagnosis are listed below.

Statements on PTS diagnostic methods with high level of agreement (Mode 4 and 5)

The only statement on PTS diagnostic method that had a high level of agreement was "subjective clinical assessment – using signs and symptoms is a reliable method for PTS diagnosis" – it had a Mode of 4.

Statements on PTS diagnostic methods with moderate level of agreement (Mode 3 or including 3)

The 16 statements on PTS diagnostic methods that had moderate levels of agreement after round two of the e-Delphi study are presented in Table 55.

Table 55: Statements experts were undecided on

	Statements on PTS diagnostic methods with moderate level of agreement	**Mode**
1.	Doppler ultrasound is a reliable method for PTS diagnosis	3
2.	Magnetic resonance venography is a reliable method for PTS diagnosis	3
3.	Objective clinical assessments – for example using tape measure to assess swelling of limbs and microlife twin cuff device to measure ankle brachial pressure index is a reliable method for PTS diagnosis	3
4.	Villalta score is a reliable method for PTS diagnosis	3
5.	Clinical aetiological anatomical and pathological classification is a reliable method for PTS diagnosis	3
6.	Venous clinical severity scoring is a reliable method for PTS diagnosis	3
7.	Ankle brachial index with Doppler ultrasound is a reliable method for PTS diagnosis	3
8.	Venography (ascending /descending) is a reliable method for PTS diagnosis	3
9.	Abdominopelvic computed tomography is a reliable method for PTS diagnosis	3
10.	Brandjes score is a reliable method for PTS diagnosis	3
11.	Widmer classification is a reliable method for PTS diagnosis	3
12.	Ginsberg score is a reliable method for PTS diagnosis	3
13.	Ambulatory venous pressure is a reliable method for PTS diagnosis	3
14.	Plethysmography is a reliable method for PTS diagnosis	3
15.	Patient reported outcome is a reliable method for PTS diagnosis	3
16.	Specialist advice is a reliable method for PTS diagnosis	2&3

6.5.5 Findings from round three

Questions for round three of the e-Delphi study were finalised after analysis of the results and feedback from the pilot preceding this round. All 23 recruited experts were sent a link to the questions for round three. After two reminders, a total of 19 experts responded, giving a response rate of 83%.

6.5.5.1 Potential prognostic factors associated with the development of PTS after a DVT of the lower limb

Out of 51 statements on potential prognostic factors presented in round two of the e-Delphi to experts, two statements had low level of agreements and these were not put forward for round three, leaving 49 statements that were presented in round three of the e-Delphi study. Out of these 49 statements, consensus was achieved on seven statements and not achieved on 42 statements.

Consensus achieved

Seven statements on potential prognostic factors associated with the development of PTS after DVT of the lower limb with an agreement level of ≥ 75% were identified. The seven statements which achieved the required consensus level are listed in Table 56 in descending order of degree of agreement.

Table 56: Statements that achieved consensus

	Statements on potential prognostic factors that achieved consensus	Degree of consensus
1.	Location and extent of DVT – a proximal DVT / an extensive clot increases the risk of PTS	100%
2.	Recurrent DVT increases the risk of PTS	94.74%
3.	Pre-existing PTS symptoms increases the risk of PTS	94.74%
4.	Poor treatment compliance post DVT including anticoagulation and compression therapy increases the risk of PTS	89.47%
5.	Venous valvular damage /venous reflux increases the risk of PTS	89.47%
6.	Ipsilateral recurrent DVT increases the risk of PTS	89.47%
7.	A BMI >25 increases the risk of PTS	84.21%

Consensus not achieved

Consensus was not achieved on 42 potential prognostic factors. The statements on which consensus (as defined by this study) could not be reached are detailed in Table 57 in descending order of degree of agreement.

Table 57: Statements on potential prognostic factors that did not achieve consensus

	Statements on potential prognostic factors that did not achieve consensus	Degree of agreement
1.	Reduced mobility increases risk of PTS	73.69%
2.	Persistent DVT symptoms following initiation of treatment (when evaluated 2 to 4weeks post initiation of treatment) increases risk of PTS	73.68%
3.	Residual vein thrombosis increases risk of PTS	68.42%
4.	Catheter directed thrombolysis as treatment of index DVT reduces risk of PTS	68.42%
5.	Good quality of initial anticoagulation after DVT reduces risk of PTS	63.16%
6.	Physical activity as part of treatment for index DVT reduces risk of PTS	63.15%
7.	High Villalta scores one month post DVT increases risk of PTS	63.15%
8.	Sub-therapeutic anticoagulation during treatment of DVT increases risk of PTS	57.9%
9.	A delay before presentation and treatment of DVT increases risk of PTS	57.9%
10.	Reduced calf muscle pump function increases risk of PTS	57.89%
11.	Older age increases risk of PTS	52.63%
12.	Previous lymphoedema increases risk of PTS	47.37%
13.	Intravenous drug users have increased risk of PTS	47.37%
14.	Calf swelling >3cm during index DVT increases risk of PTS	47.37%
15.	Loco-regional thrombolysis for treatment of index DVT reduces risk of PTS	47.37%
16.	Compression therapy increases risk of PTS	47.37%
17.	Occlusive thrombi increases risk of PTS	42.11%
18.	Multiple asymptomatic DVT increases risk of PTS	42.11%
19.	Arteriosclerosis and other arterial disease which will impair blood supply to the skin increases risk of PTS	36.84%
20.	Surgical thrombectomy as treatment of index DVT reduces risk of PTS	36.84%
21.	High venous outflow resistance on strain-gauge plethysmography in the first 3months post DVT increases risk of PTS	36.84%
22.	Previous ipsilateral varicose veins increases risk of PTS	31.58%
23.	D-dimer levels; high D-dimer levels post completion of anticoagulation and a high initial D-dimer level post DVT increases risk of PTS	31.58%
24.	Unprovoked DVT increases risk of PTS	31.58%
25.	Diabetes increases risk of PTS	26.32%
26.	Infection increases risk of PTS	26.32%
27.	High reflux velocity on Doppler ultrasound increases the risk of PTS	26.32%
28.	Pregnancy increases risk of PTS	26.31%
29.	Cancer increases risk of PTS	26.31%
30.	Smoking increases risk of PTS	21.06%
31.	Systemic thrombolysis after DVT increases risk of PTS	21.05%
32.	Female gender increases risk of PTS	21.05%
33.	Congenital vascular anomalies increases risk of PTS	21.05%
34.	Use of hormones increases risk of PTS	21.05%
35.	Use of inferior vena cava filters as treatment of index DVT increases risk of PTS	21.05%
36.	Underlying thrombotic disease such as thrombophilia and antiphospholipid syndrome increases risk of PTS	15.79%
37.	Male gender increases risk of PTS	15.79%
38.	Absence of a pathway to assess for PTS risk after DVT increases risk of PTS	15.79%
39.	High levels of Intracellular adhesion molecule-1 4months post DVT increases risk of PTS	15.79%
40.	High levels of interleukin 6 at presentation and 4months post index DVT increases risk of PTS	10.53%
41.	A high near infra-red spectrometry venous retension index 6months post DVT	5.26%
42.	High levels of C-reactive protein at presentation of index DVT increases risk of PTS	5.26%

6.5.5.2 Methods of PTS diagnosis

There was no statement on reliability of methods of PTS diagnosis that achieved a low agreement from round two of the e-Delphi study. Therefore all 17 statements from round two of the e-Delphi study were presented to experts in the round three of the e-Delphi study.

Consensus achieved

The statement "Subjective clinical assessment using signs and symptoms is a reliable method of PTS diagnosis" was the only statement on reliability of methods of PTS diagnosis that achieved an agreement level of ≥ 75%. The level of consensus on this statement was 84.21%.

Consensus not achieved

The statements on which consensus (as defined by this study) could not be reached are detailed in Table 58 in order of degree of agreement.

Table 58: Statements on PTS diagnostic methods that did not achieve consensus

	Statements on PTS diagnostic methods that did not achieve consensus	Degree of agreement
1.	Villalta score is a reliable method for PTS diagnosis	55.55%
2.	Specialist advice is a reliable method for PTS diagnosis	44.45%
3.	Objective clinical assessments – for example using tape measure to assess swelling of limbs and microlife twin cuff device to measure ankle brachial pressure index is a reliable method for PTS diagnosis	44.44%
4.	Patient reported outcome is a reliable method for PTS diagnosis	44.44%
5.	Venous clinical severity scoring is a reliable method for PTS diagnosis	33.34%
6.	Magnetic resonance venography is a reliable method for PTS diagnosis	33.33%
7.	Doppler ultrasound is a reliable method for PTS diagnosis	27.78%
8.	Venography (ascending /descending) is a reliable method for PTS diagnosis	27.78%
9.	Clinical etiological anatomical and pathological classification is a reliable method for PTS diagnosis	22.23%
10.	Ankle brachial index with Doppler ultrasound is a reliable method for PTS diagnosis	22.23%
11.	Ambulatory venous pressure is a reliable method for PTS diagnosis	11.11%
12.	Abdominopelvic computed tomography is a reliable method for PTS diagnosis	5.56%
13.	Brandjes score is a reliable method for PTS diagnosis	5.56%
14.	Widmer classification is a reliable method for PTS diagnosis	5.56%
15.	Ginsberg score is a reliable method for PTS diagnosis	5.56%
16.	Plethysmography is a reliable method for PTS diagnosis	5.56%

6.5.6 Free text comments analysis

Analysis of the free text comments using thematic analysis is described below.

6.5.6.1 Proportion of experts that made comments

All 23 experts who responded in round one of the e-Delphi study made comments as round one consisted of open ended questions. Only about a quarter of experts made free text comments in round two and round three of the e-Delphi study.

In round two of the e-Delphi study, six out of 19 experts (31.6%) made free text comments. All six experts commented on potential prognostic factors while 3 out of the 6 experts made comments on PTS diagnostic methods. In round three, five out of 19 respondents (26.3%) made free text comments, one of these experts commented on both potential prognostic factors and methods of PTS diagnosis, three of them made comments on only potential prognostic factors and two of these made comments on only PTS diagnostic methods.

Themes were generated from the free text comments made by these experts and are discussed below. Themes were categorised into those on potential prognostic factors and those on PTS diagnostic methods.

6.5.6.2 Themes generated from free text comments on potential prognostic factors

Poor data on PTS hinders conclusion of research on PTS

Five experts acknowledged that most evidence on prognostic factors associated with the development of PTS after a DVT of the lower limb was scanty, poorly understood and contradictory in some cases. One of these experts attributed this to the lack of understanding of the natural history of PTS:

"Data on PTS is scanty and contradictory and I'm not sure we understand the natural history at all" - Consultant haematologist 1

Another expert suggested that the factors that would be identified from this e-Delphi study were most likely going to be only slightly predictive of PTS risk:

"PTS is difficult to predict and the above are marginally predictive" – Vascular surgeon 1

Some potential prognostic factors are not encountered in daily practice

Four experts explained that there were some potential prognostic factors that they could not comment on because they were not commonly used in daily practice. Treatment strategies for DVT such as surgical thrombectomy, systemic thrombolysis, loco-regional thrombolysis, inferior vena cava filters and catheter directed thrombolysis fell

in to this category. For example, after indicating "agree" with the statement "loco-regional thrombolysis reduces the risk of PTS", an expert made the following comment:

"Often not feasible" – Consultant haematologist 2

The same problem was encountered with investigations such as measurements of level of inflammatory markers (C-reactive protein, interleukin 6 and intracellular adhesion molecule 1) and measurement of venous function (such as venous blood retension index). For example in response to the statement "high venous outflow resistance on strain-gauge plethysmography in the first three months post DVT increases the risk of PTS", an expert who neither disagreed nor agreed with the statement, made the following comment:

"No experience of this" – Consultant haematologist 2

Therefore for these potential prognostic factors, most experts could neither agree nor disagree on whether they were associated with an increased risk of PTS or not.

It is important to remember at this point that experts included in this study are practicing in the United Kingdom and therefore adhere to the NICE guideline which does not routinely advocate use of these treatments and investigation strategies in the management of DVT. The routine care of DVT in the UK is as described in the background to this thesis and only includes low molecular weight heparin, vitamin K antagonists and in a select group of patients with extensive cases of DVT, catheter directed thrombolysis may be used. While the routine investigations for DVT in the UK include D-dimers and Doppler ultrasound for DVT diagnosis.

Though for the above reason, most experts could not confirm the association between systemic thrombolysis and PTS, one expert affirmed that systemic thrombolysis was associated with an increased risk of bleeding. After agreeing with the statement, "systemic thrombolysis after acute DVT reduces the risk of PTS", the expert commented:

"As long as they don't die from bleeding....." – Consultant haematologist 2

Another expert thought catheter directed thrombolysis was associated with a reduced risk of PTS when used for ilio-femoral DVT. In response to "catheter-directed thrombolysis for treatment of index DVT reduces the risk of PTS", the expert made the following comment after agreeing with the statement:

"Only for iliofemoral events" – Consultant haematologist 3

Some other experts thought that light and not excessive physical activity in the treatment of DVT was associated with a reduced risk of PTS. For example; one expert's response to "physical activity reduces risk of PTS" was:

"As long as not excessive eg. leg weights" – Clinical nurse specialist 1

Mechanism of DVT was important in determining risk of developing PTS

Some experts suggested that the mechanism of DVT occurrence was important in determining the risk of PTS. Three experts proposed that recurrent DVT could lead to venous valve damage which could in turn cause venous congestion and hypertension, two anomalies identified in the pathogenesis of PTS:

"Recurrent DVT, damage to valves in veins, leading to venous congestion and hypertension" – General practitioner 1

Four experts thought proximal DVT increased the risk of PTS because of the wider bed of venous damage that is likely to be associated with it. An example comment was:

"Proximal DVT, affects wider vascular/venous bed, with more pronounced venous congestion" – General practitioner 1

The experts thought extensive clot was likely to increase the risk of PTS due to the same reasons.

Five experts thought that intravenous drug abusers tended to have an increased risk of PTS due to reasons such as:

"Intravenous drug users seem to have chance of ulceration than patients with spontaneous DVT." – Vascular surgeon 2

"Probably because their anticoagulation is suboptimal" – Consultant haematologist 2

Whether their anticoagulation was likely to be suboptimal due to drug-drug interaction or not was not made clear. However, another expert suggested they had poor compliance with anticoagulation which may indicate why they are likely to have poor compliance:

"Mostly because they are in poor general health / poor compliance with anticoagulation / still injecting pro-thrombotic substances"– Consultant haematologist2

Two experts thought a BMI greater than 25 was likely to increase the risk of PTS as it may lead to stasis due to greater immobility. For example one of the statements made

by one expert when asked to list factors associated with PTS after a DVT of the lower limb was:

"Obesity - likelihood of stasis greater" – Consultant haematologist 4

Two experts thought age increased immobility and hence the reason why older DVT patients are more likely to be at increased risk of developing PTS:

"Immobile elderly more" – General practitioner 2

Another expert thought the increased risk of PTS in older age groups was more likely due to loss of elasticity of the venous system in this age group:

"I assume this to be due the general loss of elasticity of the tissue" – General practitioner 3

Experts were aware of the risk of cofounders

Experts were also cautious about to what extent factors could be said to be independently associated with an increased risk of PTS. For example, out of all the experts who thought older age increased the risk of PTS after DVT, two experts did not think it was an independent factor. These two experts suggested that the association seen with PTS could be due to increased co-morbidities that could cause symptoms similar to those of PTS such as leg swelling:

"Not sure if age is an independent risk factor or just more likely to have co-morbidities" – Consultant haematologist 2

Another expert agreed that lymphoedema might be associated with increased risk of PTS but also commented that:

"But it's difficult to tell the difference..." – Consultant haematologist 2

Education may play a role in PTS prevention

One expert suggested that efforts to improve the understanding of patients and their carer with regards to PTS and how they can prevent it made a difference in reducing the risk of PTS:

"Engaging the patient and their partner / carer in understanding how they can help themselves in various ways to prevent PTS makes a difference" – Consultant haematologist 2

Judgements of experts was informed by daily clinical practice

Free text comments revealed that although some experts were aware and acknowledged the existing evidence on the questions asked, they also expressed views gathered from their practice even where it contradicted the evidence. For example, one expert reported awareness of studies that demonstrates that female gender increased the risk of PTS, however the expert disagreed with this as it was not an association that the expert noticed in daily practice. In response to the statement "female sex increases risk of PTS", the expert stated:

"I know this is theoretically true but I don't see this - maybe because the men often have worse clots"- Consultant haematologist 2

In addition, three experts acknowledged that there was conflicting evidence on the association between use of compression stockings after DVT and PTS. Two of these experts however thought that compression stockings may be associated with a reduced risk of PTS especially when it is properly assessed and fitted and when it is used for above knee DVT. An example comment was:

"Wearing appropriately fitting compression stockings may help reduce risk but evidence contradictory" – Consultant haematologist 1

The third expert could neither agree nor disagree with the statement on compression stockings because of the contradictory evidence.

Another expert stated that from clinical experience BMI was important in determining risk of PTS when it was greater than 30:

"Not my experience that BMI 25-30 is a problem, I don't think BMI relevant until >30 or even 40" – Consultant haematologist 2

6.5.6.3 Themes generated from free text comments on PTS diagnostic methods

PTS diagnosis is a clinical diagnosis

Two experts expressed that PTS diagnosis is a clinical diagnosis. They stated that therefore, imaging could not be used to make a diagnosis of PTS:

"Imaging is not a diagnostic tool, PTS is a clinical diagnosis" – Vascular surgeon 1

This judgement was shown further support when 100% of experts agreed that subjective clinical assessment was the most reliable method for PTS diagnosis.

One expert stated that only experience is required in diagnosing PTS using signs and symptoms of PTS:

"It does not have to be specialist advice – just someone used to looking out for PTS" – Consultant haematologist 2

Imaging can aid establishment of underlying pathology

Though experts unanimously agreed that subjective clinical diagnosis was most reliable in diagnosing PTS, two experts expressed that abdominopelvic CT (a form of imaging) had a role to play in the investigation of PTS, such as for identifying pathological changes and helping to decide whether a vascular intervention would be required or not. An expert made the following comment after disagreeing with the statement that abdomino-pelvic CT is a reliable method for diagnosing PTS:

"But maybe useful for establishing underlying pathology and whether a vascular intervention may be helpful" – Consultant haematologist 2

There is currently no scoring instrument that is reliable in making a diagnosis of PTS

One expert acknowledged the existence of multiple scoring instruments being used for PTS diagnosis. The expert thought although these had something to offer, they were not reliable and further work to develop a reliable PTS diagnostic tool was needed:

"None of the measurement tools have yet proved reliable. All offer something but work is needed" – Vascular surgeon 1

This judgement was supported by findings that only two scoring instrument were being used by experts in daily clinical practice, and only 14% of experts had used them.

Potential role of patient reported outcomes questionnaire for investigating PTS

Three experts thought patient reported outcome questionnaires may be helpful and have some role to play in PTS diagnosis:

"That's a good idea - I haven't done it though" – Consultant haematologist 2

One expert thought they might be useful for diagnosing mild disease and another expert thought they may be helpful in collecting data on how PTS impacts on a patient's life:

"Useful data about how impacts upon life" – Clinical nurse specialist 2

However a third expert expressed that:

"No questionnaire has been developed specifically for PTS. They are adapted and therefore not sensitive enough" – Vascular surgeon 1

6.6 Discussion

Previously conducted systematic reviews identified a wide range of potential prognostic factors associated with the development of PTS after a DVT of the lower limb. Some potential prognostic factors had inconclusive evidence supporting them. Therefore, the judgement of experts was sought on the association of these potential prognostic factors and the subsequent development of PTS after a DVT of the lower limb. Also sought was the judgement of experts on the reliability of methods used to diagnose PTS. Expert judgement on these issues was collated via an e-Delphi study.

In this section, a summary of the e-Delphi study is given and the final results compared to the findings of previously conducted reviews.

6.6.1 Summary of the e-Delphi study

Generally the response rate was good throughout the study. Although it declined slightly after round one of the study it remained the same thereafter.

Figure 11 illustrates the flow of experts through recruitment and the rounds of the e-Delphi. Figure 12 presents a summary of the findings of each round.

Figure 11: Summary of expert recruitment and flow through the e-Delphi study

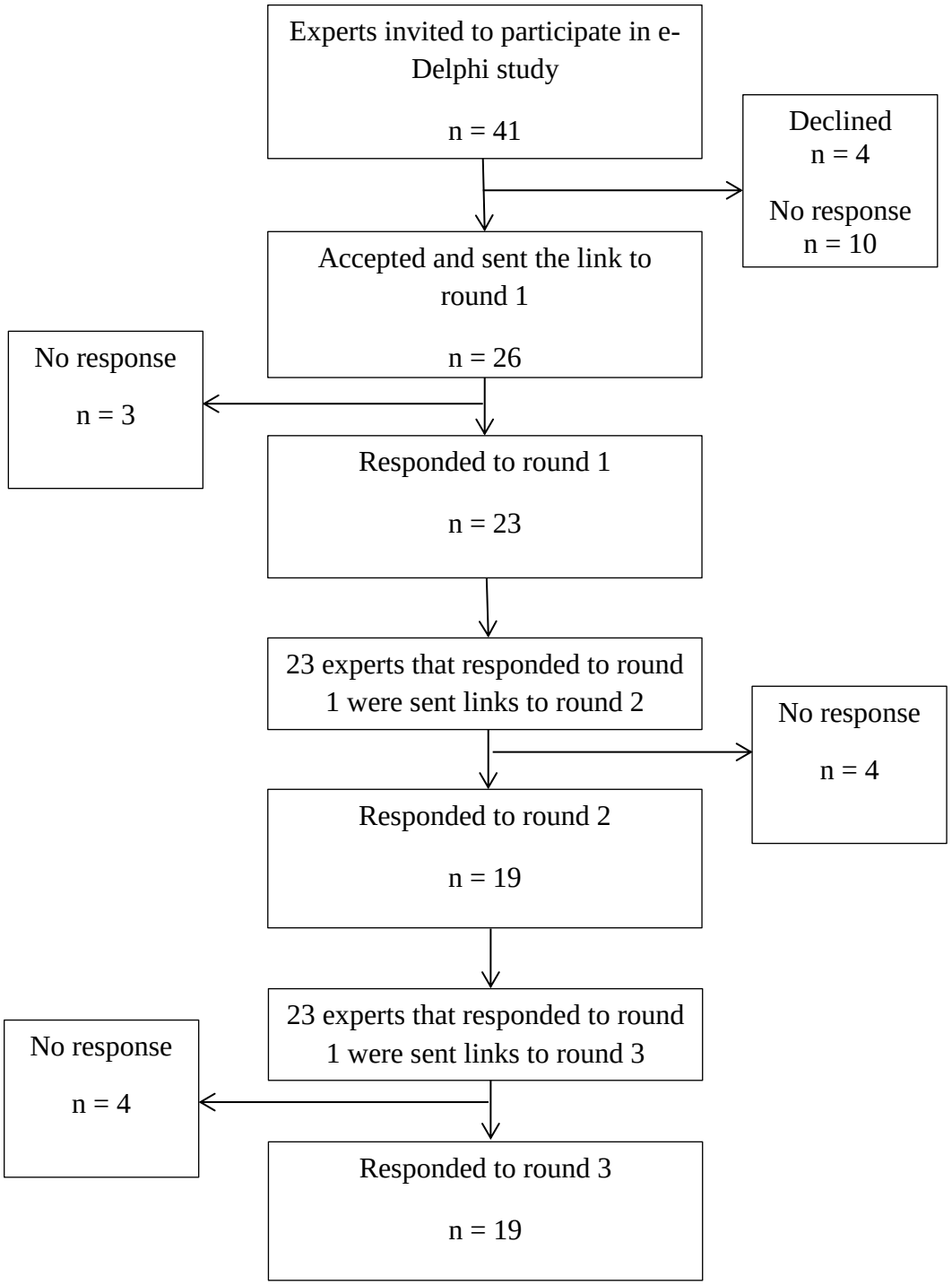
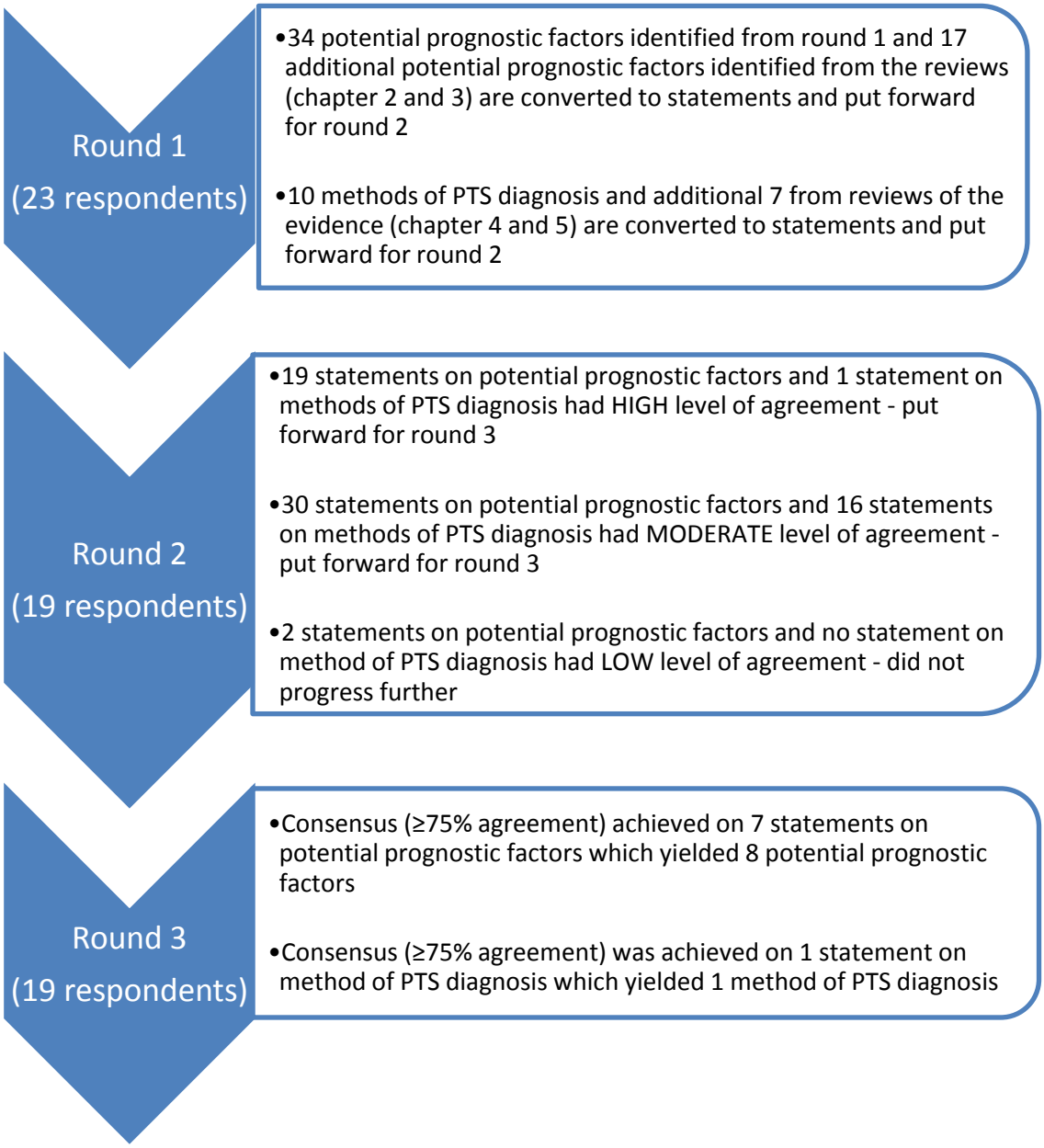


Figure 12: Summary of the e-Delphi study



6.6.2 Subgroup analysis

No subgroup analysis was done in this e-Delphi study as specialities were not represented in sufficient numbers for a subgroup analysis to be done.

6.6.3 Strengths of this e-Delphi study

One of the strengths of this e-Delphi was the rigorous method of identification of experts. This means that the output of this research is a valid summary of the opinions of experts on this topic and is therefore potentially relevant for consideration by future researchers.

Using email administration of the Delphi study allowed for the views of experts on PTS across the UK to be gathered. This gave more robustness to the findings of the study. It also ensured that there was anonymity and no peer pressure that could otherwise happen if all experts had been gathered together. It also ensured minimal cost.

An added strength of this study is that experts from all specialities involved in the management of PTS were represented in the sample of experts that participated in this study, so that views from all aspects of PTS management were gathered.

A pilot study was conducted before each round of the e-Delphi. This reduced the likelihood of presenting ambiguous and leading questions to experts.

Adequate time was given to experts to respond taking in to account holiday periods and breaks. As a result, a high response rate was achieved from each round of the e-Delphi study.

The free text comment box attached to each question allowed experts to expand on their views hence giving more perspective to why they hold a particular view.

6.6.4 Limitation of this e-Delphi study

Though a pilot study was conducted, it consisted of non-experts thereby limiting the potential for robust suggestions for improvement that could have been given. This could not be avoided as piloting with experts would have limited the already small pool of participants found eligible to participate in this study.

Too many factors were put forward to experts for their assessment, these most likely exhausted experts and prevented most of them from using the free text box option which was intended to gather more thoughts of experts on their choices.

To make the process less tiresome, some factors put forward to experts were grouped together to reduce the number of questions/statements put forward to experts. This led to some loss of information on individual factors or methods of diagnosis which could not be explored further.

Ideally all statements which experts neither agreed nor disagreed on should be further investigated to identify reasons for lack of consensus to increase the robustness of this evidence. As is the case with most e-Delphi studies, this e-Delphi study was not able to investigate this further because there was no avenue for experts to elaborate further. However, reasons for lack of consensus on some factors and methods of PTS diagnosis were deduced from free text comments of experts from which it was deduced that it was likely that experts could not provide judgements on these factors/methods of diagnosing PTS because they were not being encountered in daily clinical practice. While this indicates that findings from this study were informed by clinical practice and results would likely be transferable to clinical practice, it also poses a limitation to this e-

Delphi study because experts could not reliably judge these factors/methods of diagnosing PTS.

6.6.5 Potential prognostic factors associated with the development of PTS comparison between expert judgement and a review of the evidence

Seven statements on potential prognostic factors achieved the desired level of consensus of ≥75% among experts. These statements yielded eight potential prognostic factors. A comparison with existing evidence (from a systematic review of systematic reviews and a systematic review of primary studies) is made on these eight factors below.

1. **Location of DVT** – All of the experts unanimously agreed that the location of DVT was associated with an increased risk of PTS. The evidence from the systematic review of primary study demonstrates that the best quality of evidence that supports this were studies of fair quality. In these studies, a clot in the popliteal vein was significantly associated with an increased risk of PTS compared to a clot in the calf vein. The suggested odds of developing PTS were up to 13.3 times if the clot was located in the popliteal vein as opposed to a calf vein.
2. **Extent of DVT** – a proximal DVT / an extensive clot increases the risk of PTS – All of the experts unanimously agreed that the extent of DVT at DVT diagnosis was associated with an increased risk of PTS. The extent of DVT was also found to be significantly associated with an increased risk of PTS from the systematic review of primary studies. This finding was from studies of good quality. An

increased risk of PTS was seen in patients with a high thrombotic score or proximal DVT (both high thrombotic score and proximal clot essentially means a bigger clot). The evidence also demonstrated that a residual DVT as indicated by the thrombosis score months after DVT was associated with an increased risk of PTS. However, experts were not able to reach consensus on residual DVT by the end of the third round. This was likely due to tests for residual clot in daily practice not being readily accessible or routinely used.

3. **Recurrent DVT**– Recurrent DVT regardless of whether it was in the same limb or in a separate limb was included in this study as a result of experts' judgement. The majority of experts thought that it was significantly associated with PTS after a DVT of the lower limb. The evidence from the systematic review of primary study also suggests that a recurrent contra-lateral DVT may be associated with an increased risk of developing PTS in a significant relationship. This finding was not from the best evidence for prognostic factor studies.
4. **Ipsilateral recurrent DVT**– In line with recurrent DVT, experts agreed that recurrent DVT that occurred in the same limb (ipsilateral recurrent DVT) was associated with an increased risk of PTS. The evidence from studies of fair quality from the systematic review of primary studies supports this. It was suggested that patients with ipsilateral recurrent DVT may have an increased risk of PTS by up to eight times compared to if there was no ipsilateral recurrent DVT.
5. **Pre-existing PTS symptoms increases the risk of PTS** – Experts suggested that evidence of PTS symptoms prior to the index DVT was associated with an increased risk of PTS. It is probable that in most cases these symptoms are due

to chronic venous insufficiency and evidence from the systematic review of primary studies supports this expert judgement, as it suggested that there was a significant association between chronic venous insufficiency and an increased risk of PTS. This is probably because patients with features of chronic venous insufficiency prior to a DVT are likely to continue to have these features after the DVT and indeed their symptoms would most likely be worsened by the insult of DVT. It is worthwhile to consider that the "pre-existing PTS symptoms" might actually be due to a manifesting PTS as patients may have suffered an asymptomatic DVT in the past.

6. **Poor treatment compliance (including anticoagulation and compression therapy)** – Experts suggested that poor treatment compliance as a whole was associated with an increased risk of developing PTS after DVT. However, experts could not reach a consensus on individual therapies such as poor compliance with compression therapy and sub-therapeutic anticoagulation. This finding suggests that experts do not think individual DVT therapies were independently associated with the development of PTS and that overall compliance with treatment was more important in determining patients that will go on to develop PTS. The evidence has not explored the relationship between overall compliance with DVT treatment and the risk of developing PTS yet. However the two reviews on prognostic factors presented in this thesis demonstrated that sub-therapeutic anticoagulation and failure to use compression stockings are potentially independently associated with an increased risk of PTS. The evidence on sub-therapeutic anticoagulation was from good quality studies. The evidence on compression stockings was also

from good quality systematic reviews of five RCTs. However, one recent RCT of a relatively much larger sample size[248] has since contradicted the evidence on compression therapy demonstrating that compression stockings use was not associated with a reduced risk of PTS after DVT of the lower limb. Another study to investigate this disparity in the evidence is ongoing.[272]

7. **Venous reflux** – Experts agreed that venous reflux was associated with an increased risk of PTS after DVT of the lower limb. The prognostic value of venous reflux in determining the risk of PTS after a DVT of the lower limb has conflicting results from the previous review of the evidence. Two studies[156,161] suggest a significant association between venous reflux and subsequent development of PTS and two studies[33,169] show no association. These findings were from mostly good quality studies.
8. **BMI >25** – The systematic review of primary study demonstrated that a BMI greater than 25 was associated with an increased risk of PTS. This risk progressively increased as the BMI increased. This evidence was from good quality studies. This finding was also reflected in the views of experts. In addition, the finding from the previously conducted systematic review that the risk of PTS likely increased with increase in BMI was supported by comments from one expert who stated that in clinical practice, BMI was more likely to be associated with an increased risk of PTS when it was >30.

6.6.6 Methods of PTS diagnosis employed by experts in the UK

On requesting the information on what PTS diagnostic methods experts were using in daily practice (round one – 23 experts), it was demonstrated that; 100% of experts were using subjective clinical assessment (using signs and symptoms to make a diagnosis of PTS), 41% were using Doppler ultrasound, 23% were using magnetic resonance venography, 14% were using objective clinical assessments (for example using tape measure to assess swelling of limbs and micro life twin cuff device to measure ankle brachial pressure index), 14% were using the Villalta score while only 4% were using the CEAP tool, ankle brachial index with Doppler ultrasound, venography (ascending venography or descending venography) and abdominopelvic computed tomography.

6.6.6.1 Methods of diagnosing PTS (comparison between expert judgement and a review of the evidence)

In daily clinical practice subjective assessment for PTS diagnosis was being used much more than use of scoring instruments (100% versus 14%) while in research scoring systems were used for PTS diagnosis (see Chapter 4). It is clear that one of the contributing factors to this disparity in methods of PTS diagnosis between clinical practice and research is that experts in clinical practice did not think the scoring systems were as reliable as subjective clinical assessment in diagnosing PTS.

Out of all the identified scoring systems (see Chapter 4), only the CEAP classification and the Villalta scale had been used for PTS diagnosis by experts in daily practice unlike in research where other scoring instruments had been used. Whether factors such as ease of use and awareness of scoring instruments by experts in clinical practice, or absence of a guideline played a role in the disparity between methods of PTS diagnosis used in research and clinical practice is not yet clear. It was however, an unexpected finding that scales used for clinical assessments were considered less reliable than subjective clinical assessments without scales.

6.7 Conclusions

In this chapter the views of experts on potential prognostic factors associated with the development of PTS after DVT of the lower limb and reliability of PTS diagnostic methods was explored via an e-Delphi study. The study allowed an integration of preliminary findings from the systematic review of systematic reviews and systematic review of primary studies of this project with expert assessments on what prognostic factors for developing PTS after DVT of the lower limb are and what the reliable methods of PTS diagnosis are.

It was evident from free text comments that experts did not rely solely on evidence from previous research to make their judgements. Rather they made judgements based on their experience in daily clinical practice as well as the evidence. This demonstrates that the intended aims of conducting the e-Delphi was achieved which was to use expert opinion from their experience of PTS in daily clinical practice to identify most relevant potential prognostic factors and most reliable methods for PTS diagnosis

A consensus level was reached on eight potential prognostic factors. The majority of experts agreed that location of DVT, extent of DVT, recurrent DVT, pre-existing PTS symptoms, poor treatment compliance post DVT (including anticoagulation and compression therapy), venous reflux, ipsilateral recurrent DVT and BMI greater than 25 were all associated with an increased risk of PTS. The evidence from the earlier review of the evidence supports six out of these potential prognostic factors - location of DVT, extent of DVT, pre-existing PTS symptoms, poor treatment compliance post DVT (including anticoagulation and compression therapy), ipsilateral recurrent DVT and BMI greater than 25. The evidence from the reviews on two of the factors was

inconclusive (venous reflux, compression therapy part of poor treatment compliance) and from poor quality evidence on one of the factors (recurrent DVT).

This study also demonstrated that some experts were not employing the treatment strategies in the evidence from chapters 2 and 3 (such as systemic thrombolysis, surgical thrombectomy and inferior vena cava filters) in their daily management of PTS involved in the treatment of DVT and so were not able to comment on their association with the risk of PTS. This was likely because these treatment options are not readily encountered in daily clinical practice.

Subjective clinical assessment was considered the most reliable PTS diagnostic method from the judgements of 100% of experts. It demonstrates that scoring instruments were not routinely used in clinical practice. The judgements of experts suggest this was likely due to experts' lack of confidence in their clinical reliability. However, it is not clear if lack of awareness of these scoring systems and ease of use were contributing factors.

This study was able to identify what potential prognostic factors experts think are important in determining the future risk of developing PTS from the wide range of potential prognostic factors that have been identified from the evidence so far. These factors may be potentially considered for PTS prognostic model development in the future. This is particularly feasible because the potential prognostic factors identified from this study are factors that are easily measured in clinical practice and so lend themselves to potentially low cost use.

In view of the above, though the conclusions of the e-Delphi study should not be regarded as the final judgement, this e-Delphi study has been able to identify what experts considered as important prognostic factors associated with the development of

PTS after a DVT of the lower limb and most reliable method of PTS diagnosis and so findings are reliable in this sense.

Chapter 7: Overall discussion

Different methods were used to achieve the aims of this thesis. These included a systematic review of systematic reviews, two systematic reviews of primary studies and an e-Delphi study. Therefore it was considered appropriate that the strengths and limitations of each research method and subsequent findings be discussed under each main body of work (presented in chapters 2 to 6) for ease of reference and understanding. This section concentrates on summarising the overall findings of this thesis, comparing this thesis to other published works and giving a broader view to the implications of the findings for research. It concludes with suggesting potential areas that may benefit from future research.

7.1 Statement on main findings

7.1.1 Identification of prognostic factors associated with the development of PTS after a DVT of the lower limb

Fifty one potential prognostic factors were identified from the best evidence on prognostic factors (see Chapter 2 and 3) and expert's views (see Chapter 6). These were presented to experts for their judgements. Consensus on factors associated with developing PTS after a DVT of the lower limb was reached on only eight potential prognostic factors (location of DVT, extent of DVT, recurrent DVT, pre-existing PTS symptoms, poor treatment compliance post DVT, venous reflux, ipsilateral recurrent

DVT and a BMI > 25). These factors were all deemed to be unfavourable prognostic factors.

7.1.2 Identification of the most reliable methods of PTS diagnosis

The evidence on current methods used to diagnosis PTS from reviews of the evidence (see Chapters 4 and 5) and an initial exploration of expert's views (see Chapter 6) were presented to experts for their judgements. Consensus on reliability of PTS diagnostic methods was reached on only one method. This method was "subjective clinical assessment of PTS".

7.2 Comparisons to similar published works

Considering the broad scope of this thesis and the three research methodologies used to achieve the aims of this thesis, it was expected that it would be difficult to find exactly similar work that had been published. However, four published studies that attempted to address some aspects covered by this thesis were identified.[214,273-275] These four studies were systematic reviews and had not been published at the time the systematic review of systematic reviews in this thesis was conducted.

The first two studies discussed are, the systematic review conducted by Rabinovich and colleagues[273] and the systematic review conducted by Bouman et al.[214] Both aimed to investigate the association between thrombophilia and development of PTS after a DVT of the lower limb using a review of the evidence.

The study designs included in these reviews were similar to those included in the systematic review of primary studies conducted in this thesis. Their search strategy was less broad than those used in this thesis because of the relatively smaller aspect they investigated (i.e. they focused on thrombophilia as opposed to this thesis that aimed to investigate all factors associated with developing PTS after DVT). They also searched multiple databases and areas of grey literature. The systematic reviews by Rabinovich et al and Bouman et al included studies that had no pre-specified definition of PTS as an outcome (studies were included once they looked at any of the symptoms or signs of PTS) in contrast to the systematic review conducted in this thesis which included only studies that had a pre-specified definition for PTS. This difference accounted for most of the differences in number of included studies between these systematic reviews and that conducted in this thesis. Rabinovich et al included 16 relevant primary studies while Bouman et al included 24 relevant primary studies in their review. Meanwhile out of 73 primary studies included in the review of primary studies in this thesis, 16 of them assessed the association between thrombophilia (including factor V, factor VIII, protein C and S, fibrinogen and anti-thrombin III deficiency) and PTS (See Appendix 3, Section 3.9). Similar to the review conducted in this thesis, both reviews by Rabinovich et al and Bouman et al reported that quality assessment was carried out on included primary studies.

The analysis employed by the two systematic reviews differed. For analysis, Rabinovich and colleagues extracted data on exposure and outcomes in all included studies to calculate odds ratios and 95% confidence intervals which were combined in a meta-analysis. Bouman et al on the other hand extracted effect sizes reported from studies and pooled them together in a meta-analysis. In this thesis, analysis was stratified according

to best evidence on prognostic factors. Extraction of data to calculate effect sizes in order to pool data was not done in the systematic review conducted in this thesis because only one study out of 16 included studies (assessing the relationship between thrombophilia and PTS) met the criteria for best evidence on prognostic factors. As earlier discussed, the prognostic ability of a factor can only be reliably assessed if the factor retained a significant association identified in univariate analysis when it had been adjusted for potential confounders. So that in the systematic review of primary studies conducted in this thesis, only factors that had been investigated for an association with PTS in a multivariate analysis of a prospective cohort studies were analysed in greater detail (prospective cohort studies were used because it was the best level of evidence for prognostic factors). The limitations of this method of analysis include heterogeneity in factors adjusted for and heterogeneity in effect sizes reported across studies. Therefore a meta-analysis was not conducted in this thesis. In addition, there were differences in follow up duration of participants, and PTS diagnostic measures such that it would not have been appropriate to pool data in to one statistical summary.

The findings of this thesis demonstrate that factor V Leiden and prothrombin mutations were weakly associated with a reduced risk of developing PTS after DVT of the lower limb and this finding was from one fair quality prospective cohort study with multivariate analysis. Other thrombophilias such as anti-thrombin III deficiency, protein S deficiency and protein C deficiency were not found to be associated with development of PTS from univariate analysis in this thesis. These findings were similar to those of the systematic review by Rabinovich and colleagues. In contrast, Bouman et al found no association between factor V Leiden and PTS. The evidence from the systematic review

conducted in this thesis is likely more reliable and robust than the evidence from these other two reviews because the review conducted in this thesis used level of evidence and quality of primary studies to categorise and analyse evidence. Subsequent exploration of expert judgement by this thesis however, found that thrombophilia was not considered an important potential prognostic factor in the opinion of experts.

The third systematic review was conducted by Rabinovich and colleagues.[274] They conducted a systematic review with an aim to identify the predictive value of markers of fibrinolysis and endothelial function in PTS. The same methodology and analysis similar to their systematic review on thrombophilia was used. Eleven primary studies were included in their systematic review. In the review conducted in this thesis, 11 primary studies were also included. They could not make conclusive findings on the association between D-dimers and PTS. This is in contrast to the systematic reviews conducted in this thesis that found that elevated levels of D-dimers three to four months after DVT was associated with an increased risk of PTS from multivariate analysis of prospective cohort studies with fair to good quality. This difference in findings was likely because they had considered results from all primary studies together regardless of the quality or hierarchy of evidence unlike in the systematic review conducted in this thesis that considered both in making conclusions. The findings from this thesis were supported by the findings of Bouman et al where it was also demonstrated that D-dimers were associated with an increased risk of PTS. Similar to the systematic review conducted in this thesis, both reviews could not find conclusive evidence on other markers of fibrinolysis and endothelial function such as fibrinogen, von williebrand factor, ADAMTS 13 antigen and plasminogen activator inhibitor gene. An additional marker was identified by their review – FXIII, the evidence found on this was also

inconclusive. The exploration of expert judgement on the association of D-dimers levels and subsequent development of PTS revealed that it was not considered to be an important potential prognostic factor.

The fourth systematic review also conducted by Rabinovich and colleagues[275] aimed to identify the predictive value of markers of inflammation and in PTS. The same methodology and analysis similar to their two systematic reviews discussed earlier was used. Ten primary studies were included in their systematic review, while eight primary studies assessing the same were identified by the systematic review conducted in this thesis. The review reported inconclusive findings on the association between markers of inflammation studies and PTS. In contrast, this review was able to identify from the best evidence on prognostic information, that elevated levels of intracellular adhesion molecule 1 and C-reactive protein at greater than one month after DVT were associated with an increased incidence of PTS. This association got stronger with increased interval between DVT and measurement of the inflammatory markers. However, exploration of expert judgement in the e-Delphi study showed that experts did not think there was an association between PTS and C-reactive protein and intracellular adhesion molecule 1.

A recently published work – the SOX trial,[248] published findings that shed doubt on some of the findings from the systematic review of systematic reviews conducted in this thesis. It was reported in the trial that compression stockings was not associated with a reduced risk of developing PTS after a DVT of the lower limb. While, the systematic review of systematic reviews in this thesis had identified that compression stockings was associated with a reduced risk of developing PTS after DVT of the lower limb from a systematic review of five RCTs which were of good quality. The main differences

between the RCTs included in the systematic review and the SOX trial were; multicentre (SOX trial) versus single centre (RCTs included in systematic reviews) a larger sample size (806 patients in SOX trial versus 194 patients in the RCT that included the maximum number of patients from the review); blinding in the SOX trial (all patients wore stockings although 410 patients were randomised to active stockings and the remaining patients to placebo stockings) unlike in the other RCTs where the control groups wore no stockings and hence blinding was not possible. The differences in results may be due to these differences. But this raises another question, on whether placebo stocking are really ineffective or not. Studies may be needed to assess this before the previous evidence on compression stockings is changed. Findings from further studies to confirm or refute the SOX trial findings are also needed. Currently, there is an ongoing study that is also investigating the relationship between compression stockings and PTS.[272] Perhaps findings from this ongoing study will aid conclusions on the association between compression stockings and PTS after DVT of the lower limb.

7.3 Implications of findings

7.3.1 Implications of findings – Potential prognostic factors

Evidence from the review of reviews highlights that treatment adopted for managing DVT may be important in modulating the risk of a patient for developing PTS after DVT. This finding was supported by the e-Delphi findings which showed that experts thought poor treatment compliance including oral anticoagulation and compression therapy increased the risk of PTS after DVT. Therefore clinicians should ensure optimal

anticoagulation (with renewed efforts at achieving target international normalised ratio in DVT patients) and compliance with compression stockings in DVT patients.

The findings from the review of primary studies that persistent abnormality in the vein after DVT was associated with an increased risk of PTS supports findings from the review of reviews, that rigorous DVT treatment to conserve venous function is important in reducing PTS risk. Therefore, a finding suggesting that longer duration of oral anticoagulation for DVT treatment could increase risk of PTS is interesting. No theory for this potential association was found and it may be due to a spurious finding. But future research should investigate this relationship further, as it may mean revising the length of oral anticoagulation.

The findings that elevated levels of some biomarkers such as D-dimers, C-reactive protein and intracellular adhesion molecule 1 after the acute phase of DVT may increase risk of PTS is interesting as this could mean testing blood levels after the acute phase of DVT can identify patients at risk of subsequent development of PTS.

The suggested risk of developing PTS in obese patients as identified by this thesis adds to the many reasons why clinicians should encourage weight loss in high risk DVT patients, particularly after a patient has suffered DVT. This may however be difficult to achieve in patient with immobilisation as a risk factor for DVT.

Ideally, the development of a prognostic model should utilise easily measured factors that are regularly encountered in daily practice. The final factors collated by this thesis fit these criteria. What this means is that a potential prognostic model developed from these factors is more likely to be feasible and readily used in daily practice. This further justifies the exploration of clinical expert views. Other factors found to be strongly

associated with the development of PTS from good quality studies may also be considered for development of a prognostic model depending on ease of use in clinical practice.

7.3.2 Implications of findings – PTS diagnosis

This thesis discussed in the background that there were no national guidelines for the diagnosis of PTS in the UK. In addition, it was demonstrated in this thesis (see Chapter 4 and Chapter 6) that there was a wide variety of methods being used to diagnose PTS and that there is a huge difference in methods of PTS diagnosis employed by researchers (identified from a review of the evidence – Chapter 4) and methods of PTS diagnosis employed by clinicians (identified from an e-Delphi survey – Chapter 6). What this implies is that findings resulting from research may not easily be transferable to clinical practice. This further stresses the importance of developing a reference standard and guidelines in PTS diagnosis. This will encourage conduct of research in PTS and homogeneity for comparison of results, and easy transfer of research findings to clinical practice.

In Chapter 4 of this thesis, it was demonstrated that there is limited evidence on comparison of the accuracy of PTS diagnostic methods. In addition, available studies were not of the best quality. Further primary studies of good quality are required to compare current PTS diagnostic methods with an aim to identify the most reliable method for PTS diagnosis. In the same chapter it was also demonstrated that pooling of results across studies on PTS that have used different PTS diagnostic methods is potentially not valid as the numbers of patients in the same population diagnosed as having PTS tend to vary significantly depending on the PTS diagnostic method used.

The evidence gathered from this thesis demonstrates that experts believe subjective clinical assessment is the most reliable for PTS diagnosis. This suggestion is supported by other researchers who have also advocated that PTS diagnosis should be made primarily on clinical grounds.[21,276] However, one expert included in the e-Delphi study pointed out that clinical experience was needed for this purpose. Overall, expert opinion that subjective clinical assessment is the most reliable PTS diagnostic method implies that experts may think the way forward for PTS diagnosis may be similar to those of early stage dementia and attention deficit hyperactivity disorder – where expert clinical assessment and patient/carer self-report are the reference standards for assessment.[277,278] In addition to the lack of an objective method of diagnosis which discourages reproducibility of results, another drawback to this is that clinicians will need to have the clinical acumen or required expertise that is necessary to make a diagnosis in the absence of objective methods of diagnosis. Therefore, additional training to equip clinicians to make a diagnosis of PTS will be needed. However, it may be more useful to regard subjective clinical assessment in PTS diagnosis as the foundation of PTS diagnosis which should be supported by the addition of other components such as establishing a history of DVT and measuring patient's symptoms over a period of time.

Differentiating between PTS and chronic venous insufficiency is an important step to establishing a reference standard in PTS diagnosis. It is unlikely that any PTS diagnostic method will be able to differentiate between chronic venous insufficiency and PTS without taking a history to detect a previous episode of DVT. A history of pulmonary embolism is usually overlooked. However a history of pulmonary embolism usually means that the patient is more likely to have had an asymptomatic DVT. Therefore, an additional component to subjective clinical assessments enquiring about a

history of DVT or pulmonary embolism may be beneficial to differentiate between a PTS and chronic venous insufficiency.

Findings from the e-Delphi study suggest that patient reported outcomes questionnaires may have a role to play in diagnosis of PTS. This is not surprising as measuring patient's symptoms are a prominent feature in the definition of PTS. Therefore, patient reported outcome questionnaires may be useful especially where they record symptoms over a period of time (the patient may be given a diary to take home for this purpose) as this will account for the variable course of PTS.

Putting all the above into perspective, the suggestion from this thesis for PTS diagnosis would be a tool that comprised of subjective clinical assessment by clinicians plus a patient reported outcomes questionnaire which includes components to detect a previous history of DVT and symptoms of PTS over a specified time period. This could potentially lead to a tool that will account for confirmation of a history of DVT, signs and symptoms of PTS, the variable course of PTS and detect changes in severity of PTS.

It has also been recommended that a diagnosis of PTS can be made when there is confirmation of venous valvular incompetence on radiological investigations in a symptomatic patient,[7,279] thereby, confirming the pathophysiology of PTS in a patient with symptoms. It is therefore an attractive option to add a radiological component to subjective clinical assessments for PTS diagnosis. However this may identify only severe disease leaving out the possibility of rigorous management that could have been implemented to prevent progression of disease/ improve quality of life for patients presenting with mild symptoms.

In summary, further research to identify the most accurate PTS diagnostic method is required. Identification of the most accurate PTS diagnosis means research and clinical practice could begin to use uniform methods for PTS diagnosis not just for the sake of being able to directly compare study findings (for which the International Society of Thrombosis and Haemostasis recommends the Villalta scale[237] even though it is known to have some limitations). Instead it would mean that valid conclusions could potentially be made from studies when they are combined.

7.3.3 Potential areas for more exploration in future research

This thesis was able to identify important potential prognostic factors associated with the development of PTS after a DVT from a review of the evidence and exploration of the opinion of expert's in the UK via an e-Delphi study. While the reviews were general in focus, the e-Delphi study was restricted to UK experts. The extension of the e-Delphi study to experts internationally would add further validity and generalisability.

No good quality prognostic model that had been internally and externally validated was identified by this thesis. Therefore, one of the areas for research stemming directly from this thesis is the development of a prognostic model using the set of potential prognostic factors deemed to be important from expert judgement. The prognostic model should ideally be developed from data collected through a prospective cohort study.

However, a prospective cohort study is not always possible because of the increased expenses associated with it compared to other study designs such as a retrospective study. An alternative less expensive method that could be used to develop a prognostic

model is by gathering necessary information on the prognostic factors identified from existing databases such as "The health improvement network" (THIN) database. However, with the poor definition and diagnosis of PTS, it is expected that PTS might not be coded at all and where it is, that it might not be coded properly in these databases. Therefore a quick survey to determine if this assumption is right or wrong would be beneficial prior to conducting such a study. Where it is discovered that PTS is not being coded or being coded incorrectly, an intervention aimed at health care professionals via update programmes to encourage proper coding of PTS would be beneficial. Coding PTS appropriately could also give more information on the prevalence of PTS and aid the true estimation of the cost of PTS.

A finding from this study was that low molecular weight heparin was associated with a reduced incidence of PTS compared to standard anticoagulation (see Chapter 2, Section 2.5.3.1.1). This finding implies that changing guidelines for DVT treatment to a longer duration of low molecular weight heparin only from standard DVT treatment (currently includes low molecular weight heparin for five days switched later to vitamin K antagonists) could lead to a reduction in the incidence of PTS. Further randomised controlled trials assessing this relationship and comparing the cost effectiveness of these DVT treatments in relation to preventions of PTS would be beneficial.

Usually the aim of an objective method for PTS diagnosis is to improve reliability of diagnosis. This is clearly not being met by current PTS diagnostic methods. Hence the suggestion by experts that subjective clinical assessment be used for PTS diagnosis, as experts believe it to be more reliable than other methods of PTS diagnosis. This thesis identified that the most widely used clinical assessment method that has been used for objective diagnosis of PTS in research is the Villalta scale but that this scale was rarely

being used in clinical practice, most likely due to cumbersome of use in daily practice or lack of a guideline recommending its use. Hence research to investigate ease of use of the Villalta scale in clinical practice may be needed as this may have an impact on why experts did not rate the Villalta scale as reliable.

The background review to this thesis identified that the corner stone of PTS management currently is symptomatic management. More research investigating active managements of PTS including uses of exercise which evidence has suggested may be useful in PTS treatments are required.

Another important area of PTS that will benefit from future research is the estimation of the actual cost of PTS. An economic analysis of the cost of PTS to the UK in particular is required because of the lack of information in this area.

7.4 Final conclusion

In conclusion, this thesis identified a wide array of prognostic factors. However there were limitations to the conclusions that could be made on the evidence backing most of them. Eight of the identified factors were considered important (location of DVT, extent of DVT, recurrent DVT, pre-existing PTS symptoms, poor treatment compliance post DVT (including anticoagulation and compression therapy), venous reflux, ipsilateral recurrent DVT and BMI greater than 25). This thesis recommends that these factors should be used in future research as potential prognostic factors.

A wide variation in methods used to diagnose PTS was identified in this thesis. However, experts unanimously agreed that subjective clinical assessment the most reliable. Objective diagnostic methods are easier to use accurately and reliably especially by less experienced clinicians. Therefore research should continue efforts in finding a reliable PTS diagnostic tool in addition to investigating other deficient areas of PTS.

Appendix 1: Diagnosis of PTS

1.1 Rating scales used for PTS diagnosis

Described below in order of year of development are the rating scales that have been used for PTS diagnosis.

1.1.1 Widmer classification

This tool was developed in 1981 by Swiss researchers Widmer and colleagues.[12] It was developed for the general classification of chronic venous insufficiency. It is based on only clinical signs recorded in one assessment of the patient. It groups patients into stages one to three based on the following symptoms; signs of ankle flare and or subclinical oedema (stage one); oedema, pigmentation, lipodermatosclerosis and or white atrophy (stage two); presence of leg ulcer or history of leg ulcer (stage three).

An important component lacking in this diagnostic tool is the assessment of patient's symptoms thereby potentially decreasing the accuracy of the scale as this means that the scale may not be able to reflect health outcomes of the patient on quality of life instruments. It is non-invasive and simple to apply. It can be readily implemented at clinic visits without need for radiological referral therefore requiring less man power. But, this scale does not lend itself to detecting a change in PTS severity as it has static and unquantifiable components. For example, once it diagnoses a patient as stage three (present or past leg ulcer), a patient cannot move into the earlier stages of the scale. Another drawback of this scale is that there is no function to detect the level of lesion in

the venous system. This is particularly important in cases where an intervention may be required. The scale is applied at one time point to make a diagnosis of PTS and so cannot account for the variable course of PTS.

Widmer classification

Classification	**Symptom**
Class I	Ankle flare
	Subclinical oedema
Class II	Oedema
	Pigmentation
	Lipodermatosclerosis
	White (skin) atrophy
Class III	Leg ulcer
	Leg ulcer in the past

1.1.2 Villalta scale

In 1994, a rating scale specific for PTS was developed by Villalta and colleagues. It was initially called the Villalta-Prandoni scale but is now more commonly known as the Villalta scale.[10] The scale makes use of five clinical symptoms (pain, cramps, heaviness, pruritus and paraesthesia) and six clinical signs (oedema, skin induration, hyperpigmentation, venous ectasia, redness, pain on calf compression). Each component of the scale is rated as zero (absent), one (mild), two (moderate), or three (severe). The scores from each component of the Villalta scale are then summed up and this places the patient in one of the following four categories; Villalta score zero to four for no

PTS, five to nine for mild PTS, 10 to 14 for moderate PTS and score ≥15 or presence of leg ulcer for severe PTS. The scale has a minimum score of zero and a maximum score of 33. The Villalta scale was developed for making a diagnosis of PTS after one assessment, however some studies have attempted to account for the variable course of PTS by only making a diagnosis of PTS after a patient have crossed the threshold for PTS diagnosis on two consecutive occasions.[165,200 156,159,164 34,150]

Similar to the Widmer scale, a drawback of this scale is that there is no radiology component to identify where the lesion is. In addition, the clinical sign assessment components such as redness and hyperpigmentation may be a drawback to the use of the Villalta scale in dark skinned people.

Villalta scale

	None (0)	Mild (1)	Moderate (2)	Severe (3)
Symptoms				
Pain				
cramps				
Heaviness				
Pruritus				
Paraesthesia				
Signs (Including a description guide)				
Oedema	No loss of bony landmarks, No pitting with pressure over ankle or shin	Minimal loss of bony landmarks; Shallow pitting with pressure over ankle or shin	Noticeable swelling and loss of bony landmark; moderate pitting with pressure over ankle or shin	Severe swelling and loss of bony landmarks; deep pitting with pressure over ankle, shin or knee
Skin induration	Skin of shin and ankle not thickened and freely mobile over underlying bone or tissue	Skin of shin and ankle slightly thickened or slightly adherent to underlying tissue or bone	Skin of shin and ankle moderately thickened or moderately adherent to underlying tissue or bone	Skin of shin and ankle very thickened or tightly adherent to underlying tissue or bone
Hyperpigmentation	None	Faint speckled brownish discolouration around ankle	Obvious brownish discolouration around ankle and lower shin	Patches of dark confluent brownish discolouration around ankle and shin
Venous ectasia	No venules or varicose veins	A few faint reddish or purplish venules around the ankle or foot area	Prominent purplish venules around the ankle and foot area	Numerous confluent and prominent and purplish venules or varicose veins around the ankle, shin or elsewhere on the leg
Redness	Normal colour of leg	Faint redness of foot or lower limb	Moderate redness of foot or lower leg	Pronounced redness or purplish colour of foot and lower leg
Pain during calf compression	None	Patient says pain is mild in intensity	Patient says pain is moderate in intensity	Patient says pain is severe in intensity
Leg ulcer	Absent			Present
0 – 4	No PTS			
5 – 14	Mild or moderate PTS			
≥15 OR presence of ulcer	Severe PTS			

1.1.3 CEAP classification

In the same year that the Villalta scale was developed another classification system for chronic venous insufficiency was developed by the North American Society of Phlebology. This classification was called the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification.[36] The classification as the name implies used clinical, aetiological, anatomical and pathophysiological criteria to make a diagnosis of chronic venous insufficiency. The scale makes use of patient symptoms, clinical signs and radiological findings (venous obstruction, venous reflux or both) on one assessment to classify chronic venous insufficiency. Clinical signs and symptoms are grouped into seven classes (class zero to class six). Each class are then grouped according to aetiology (congenital, primary, secondary), anatomy (superficial, deep, perforator veins) and pathophysiology (reflux, obstruction, both). Though there is yet to be a standardisation for the cut off point for PTS diagnosis with use of the CEAP classification,[280] most studies use a cut-off point of ≥ class three as the cut off for a diagnosis of PTS.

It is regarded as the most comprehensive and complete rating scale available for chronic venous insufficiency.[281] In daily practice however, it is cumbersome to use because of the numerous components it includes. It also does not rate severity of PTS because components are not quantifiable and are sometimes static so that the CEAP classification cannot accurately reflect the movement of patients across PTS stages. For example, a patient with an active ulcer is classified as class six. If this ulcer healed the patient would be classified as class five. However, no matter how much improvement there is in the other symptoms, the patient will not leave class five. This limitation of

the CEAP classification was also noted by Rutherford and colleagues[282] and this led to the refinement of the CEAP classification to reflect more accurately, severity of disease and changes in venous disease progression over time. The following scales were developed by the American Venous Forum Ad Hoc committee[282] as a result; the venous clinical severity score – based on only the anatomic and physiologic components of the classification and reflected components of the CEAP that could change over time; venous segmental score – based on venous segments involved in the disease process and the venous disability score – based on ability of an individual suffering from PTS to work with or without a support device[282] and reflects only the patient's view. The VCSS is the only scale out of all three that is used in PTS diagnosis. It is therefore discussed later in this chapter. The other two tools have been used only in the evaluation of impact of PTS in patients.[241]

CEAP classification

Clinical aetiological anatomical and pathophysiological classification (CEAP) Classification	**Signs and symptoms**
Class 0	Symptoms* only, no visible or palpable signs
Class 1	Telangiectasia, reticular veins
Class 2	Varicose veins
Class 3	Oedema, no skin changes
Class 4	Skin changes (cutaneous atrophy, subcutaneous nodules), pigmentation, lipodermatosclerosis
Class 5	Skin changes with healed ulcer
Class 6	Skin changes with active ulcer
*Pain, swelling, heaviness, cramps, paraesthesia, and itching Each of the classes above (class 0 to class 6) are then classified based on their; • Aetiology (Congenital, primary, secondary) • Anatomy (superficial, deep, perforator veins) • Pathophysiology (reflux, obstruction, both)	

1.1.4 Brandjes score

In 1997, the Brandjes score[11] was developed specifically for PTS diagnosis. Eight clinical symptoms and seven clinical signs were included in this diagnostic tool. Each component of the Brandjes score besides the presence of a venous ulcer was given a score of one. A score of four was given for the presence of a venous ulcer. The Brandjes score classifies PTS as mild to moderate if a patient scored ≥ 3 which should include at least one clinical sign and classifies PTS as severe when patients scored ≥ 4 For PTS to be diagnosed, the threshold for PTS diagnosis had to have been crossed on two consecutive follow up visits that were three months apart.

This was the first scale that took in to account the variability of the course of PTS at inception. The scale cannot identify where the lesion is in the venous system but it is easy to use and administer on patients. It may be sensitive to changes in PTS severity as it has no static component however there have been no studies to investigate this.

Brandjes score

	Symptoms	**Score**	**Signs**	**Score**
Mild to moderate PTS (score ≥ 3)*	Spontaneous pain in calf	1	Calf circumference increased by 1cm	1
	Spontaneous pain in thigh	1	Ankle circumference increased by 1cm	1
	Pain in calf on standing/walking	1	Pigmentation	1
	Pain in thigh on standing/walking	1	Venectasia	1
	Oedema of foot/calf	1	Newly formed varicose	1
	Heaviness of leg	1	Phlebitis	1
Severe PTS (score ≥ 4)	Spontaneous pain and pain on standing/walking	1	Calf circumference increased by 1cm	1
	Oedema of calf	1	Pigmentation, discolouration, and venectasia	1
	Impairment of daily activities	1	Venous ulcer	4

1.1.5 Ginsberg measure

In 2000, the Ginsberg measure[35] was developed by Ginsberg and colleagues specifically for PTS measurement. It made use of clinical symptoms and radiological evidence of venous valvular incompetence (on Doppler ultrasound, air plethysmography and photo plethysmography). It diagnosed a patient with PTS if ≥ six months after an acute DVT, the patient develops pain and swelling of limb > one month duration of a typical character (worse at end of day or with prolonged sitting/standing, better after

night's rest and leg elevation) as well as an objective evidence of valvular incompetence (diagnosed via plethysmography or venous Doppler). A global rating questionnaire is given to the patient to rate overall improvement or worsening of PTS over time.

It may require referral to radiologist as it has a component that assesses for venous reflux, this reduces acceptability as evidenced by it being left out of one study[40] that underwent comparisons of existing PTS diagnostic tools because it required extra resources to implement. However, it is more likely to flag the point of lesion in the venous system and this may be useful for interventional purposes. It cannot be used to monitor treatment effect as it has only static components and is also not useful for classifying PTS according to severity. However, because it identifies more severe PTS, it probably has increased specificity compared to other rating scales.

1.1.6 Venous clinical severity score (VCSS)

As explained under CEAP classification above, the VCSS score was designed to complement the CEAP classification. It takes into account the progressive nature of the signs and symptoms that chronic venous insufficiency may present with, and is graded as such in an increasing order of severity.[281] The VCSS score comprises of 10 attributes which is a mixture of patient symptoms, clinical signs and a treatment component (pain, varicose veins, venous oedema, skin pigmentation, inflammation, induration, number of active ulcer, active ulcer duration, size of active ulcer and compliance with compression stockings). Each attribute is assigned a score between zero and three (zero – absent, one – mild, two – moderate and three – severe). After one assessment, PTS was said to be absent if the total score was ≤ three, mild if total score was four to seven and severe if

total score was ≥ eight. It has been used to detect PTS[40,245,251] and rate severity of PTS.[283]

It is more sensitive to change in disease severity because it has no static component unlike the CEAP classification. It however cannot identify the level of lesion for intervention planning. It is easily administered and so is likely to be acceptable to patients and clinicians alike.

Venous clinical severity score (VCSS)

Attribute	**Absent = 0**	**Mild = 1**	**Moderate = 2**	**Severe = 3**
Pain	None	Occasional not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe, limiting activities or requiring regular analgesic use
Varicose veins	None	Few, scattered: branch VVs	Multiple: GS varicose veins confined to calf or thigh calf or thigh	Extensive: thigh and calf, or GS and LS distribution
Venous oedema	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
Skin pigmentation	None or focal low intensity (tan)	Diffuse but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower third) or recent pigmentation (purple)	Wider distribution (above lower third) and recent pigmentation
Inflammation	None	Mild cellulites, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower third)	Severe cellulitis (lower third and above) or significant venous eczema
Induration	None	Focal, circum-malleolar (<5 cm)	Medial or lateral, less than lower third of leg	Entire lower third of leg or more
No. of active ulcers	0	1	2	>2
Active ulceration, duration	None	<3 months	>3 months, <1 year	Not healed >1 year
Active ulcer, size	None	<2 cm diameter	diameter 2–6 cm	diameter >6 cm
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance (stockings and elevation)

1.2 Radiological tools that have been used to diagnose PTS

1.2.1 Doppler ultrasound

This is a non-invasive test which employs a combination of ultrasonography and Doppler scanning for the anatomic and pathophysiologic evaluation of the venous system. The patient is initially placed in a supine position in a reverse trendenlenburg position. Using Doppler flow patterns and B-mode ultrasound imaging, the Doppler ultrasound examines the perforating veins for patency and the deep venous system for patency and valvular competency.[281,284] Researchers that have used Doppler ultrasound for PTS diagnosis usually make a diagnosis of PTS on detection of any of the following on Doppler ultrasound - venous reflux, venous occlusion and or thickened venous wall.[196,285,49]

The Doppler ultrasound is non-invasive, easily applied in the clinic by trained personnel, can readily be repeated and is not as expensive as other tools.

1.2.2 Venous plethysmography

Plethysmography is defined as determinations of changes in volume.[284] It is divided into air plethysmography and photo plethysmography/light reflection rheography depending on the instruments used during the procedure (an air filled chamber for air plethysmography and a light emitting diode for photo plethysmography). It measures

the efficacy of the pumping action of the muscles. It also detects venous reflux and or venous outflow obstruction. Studies used the presence of either or both of these criteria for diagnosis of PTS.[285,49]

It is non-invasive and easier to apply than venography.

1.2.3 Venography

Venography in simple terms involves the examination of veins using imaging techniques and contrast materials. It is an invasive method which used to be the gold standard for diagnosis of DVT and chronic venous insufficiency.[281] This is no longer the case because of the limitations associated with it. Venography is divided in to ascending and descending venography. Both ascending and descending venography are carried out in the reverse tredenlenburg position.[281] Essentially, the patency of the vein (by ascending venography) and venous reflux (assessed by descending venography) are measured. Venography can define the anatomy of the valves or identify problematic perforating veins. PTS diagnosis is made on Venography if the following are present, venous occlusion and or valvular reflux.

The limitations of venography have caused its attribute as the gold standard diagnosis for chronic venous insufficiency to be reviewed. These limitations of venography for diagnosis of chronic venous insufficiency also apply to PTS diagnosis. They include – it is invasive, it is expensive and it requires much more specialized skills than that required for non-invasive tests.[286] Venography involves gaining access to the veins; therefore there are associated higher rates of complications like phlebitis (inflammation of the vein) unlike with non-invasive tests, extravasations of contrast material into the tissue which may result in cellulitis.

Appendix 2: Identification of potential prognostic factors associated with the development of PTS after a DVT of the lower limb (systematic review of systematic reviews)

2.1 Search strategy (EMBASE, MEDLINE, and MEDLINE in-process databases)

	Search terms applied to; **MEDLINE (1946 – September 2012)** **EMBASE (1947 – September 2012)**
1	exp deep vein thrombosis/ or deep vein thrombo$.mp.
2	Venous thromboembolism.mp. or Venous Thromboembolism/
3	DVT.mp
4	Venous thrombos$.mp.
5	VTE.mp
6	PTS.mp
7	Postthrombotic syndrome.mp. or Postphlebitic Syndrome/ or Postthrombotic Syndrome/
8	Venous stasis syndrome.mp.
9	Chronic venous insufficiency.mp. or chronic vein insufficiency/
10	Venous ulcer.mp.
11	or /1-5
12	or/6-10
13	11 or 12
14	limit 13 to review articles

2.2 Search strategy (Cochrane library)

	Search terms (Cochrane library 1959 – September 2012)
1	MeSH descriptor [venous thrombosis] explode all trees
2	"venous thromboembolism":ti,ab,kw
3	"deep vein thrombosis":ti,ab,kw
4	"deep vein thromboses": ti,ab,kw
5	"DVT or VTE":ti,ab,kw
6	MeSH descriptor [Post thrombotic syndrome] explode all trees
7	"Post phlebitic syndrome" or "postthrombotic syndrome" or "PTS":ti,ab,kw
8	"Venous stasis syndrome" ti,ab,kw
9	"Chronic venous insufficiency" or "chronic vein insufficiency": ti,ab,kw
10	"Venous ulcer" ti,ab,kw
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

2.3 Excluded studies and reasons for exclusion

	Excluded reviews	Reason(s) for exclusion
1.	Akl EA, Rohilla S, Barba M, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer: a systematic review. *Cancer.* 2008;113(7):1685-1694.	B
2.	Bond RT, Cohen JM, Kahn SR. Systematic review of the surgical treatment of moderate to severe post-thrombotic syndrome. *Blood. Conference: 52nd Annual Meeting of the American Society of Hematology, ASH.* 2010;116(21)	C
3.	Broholm R, Panduro Jensen L, Baekgaard N. Catheter-directed thrombolysis in the treatment of iliofemoral venous thrombosis. A review. *Int Angiol.* 2010;29(4):292-302	B
4.	Cohen JM, Akl EA, Kahn SR. Pharmacologic and compression therapies for postthrombotic syndrome: a systematic review of randomized controlled trials. *Chest.* 2012;141(2):308-320.	C
5.	Forster AJ, Wells PS. The rationale and evidence for the treatment of lower-extremity deep venous thrombosis with thrombolytic agents. *Current Opinion in Hematology.* 2002;9 (5):437-442.	A
6.	Gutt CN, Oniu T, Wolkener F, Mehrabi A, Mistry S, Buchler MW. Prophylaxis and treatment of deep vein thrombosis in general surgery. *American Journal of Surgery.* 2005;189(1):14-22.	B
7.	Kanaan AO, Lepage JE, Djazayeri S, Donovan JL. Evaluating the Role of Compression Stockings in Preventing Post thrombotic Syndrome: A Review of the Literature. *Thrombosis.* 2012;694851.	A
8.	Kolbach DN, Sandbrink MWC, Prins M H, Neumann Martino HAM. Compression therapy for treating stage I and II (Widmer) post-thrombotic syndrome. *Cochrane Database of Systematic Reviews.* 2003(4).	C
9.	Malgor RD, Gasparis AP. Pharmaco-mechanical thrombectomy for early thrombus removal. *Phlebology.* 2012;27 Suppl 1:155-162.	B
10.	Masuda, E. M., et al. (2012). "The controversy of managing calf vein thrombosis." Journal of Vascular Surgery 55(2): 550-561.	B
11.	Meissner MH, Gloviczki P, Comerota AJ, et al. Early thrombus removal strategies for acute deep venous thrombosis: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2012;55(5):1449-1462. Epub 2012 Apr 1441.	A
12.	Rodriguez AL, Wojcik BM, Wrobleski SK, Myers DD, Jr., Wakefield TW, Diaz JA. Statins, inflammation and deep vein thrombosis: a systematic review. *Journal of Thrombosis & Thrombolysis.* 2012;33(4):371-382.	B

Key: A-Not a systematic review, B-Outcomes not relevant, C-Relevant target population not included

2.4 AMSTAR checklist

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes / No/ Can't answer/ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	Yes/ No/ Can't answer/ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	Yes/ No/ Can't answer/ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes/ No/ Can't answer/ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	Yes/ No/ Can't answer/ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, gender, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes/ No/ Can't answer/ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes/ No/ Can't answer/ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	Yes/ No/ Can't answer/ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	Yes/ No/ Can't answer/ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	Yes/ No/ Can't answer/ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	Yes/ No/ Can't answer/ Not applicable

Reference: Shea, B., et al. (2007). "Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews." BMC Medical Research Methodology 7(1): 10

2.5 Application of the AMSTAR checklist

AMSTAR question[93]	Alesh et al 2007[109]	Casey et al 2012[38]	Fox & Kahn 2008[112]	Giannoukas et al 2006[111]	Hull et al 2011[39]	Kahn et al 2008[78]	Kakkos et al 2006[116]	Kolbach et al 2003[117]	Luo et al 2006[113]	Musani et al 2010[118]	Ng et al 1998[114]	Segal et al 2007[110]	Watson et al 2004[59]	Wells and Forster et al 2001[115]
Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	Can't answer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't answer	Yes	Yes	Can't answer
Was comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes
Was a list of studies (included and excluded) provided?	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No

AMSTAR question[93]	Alesh et al 2007[109]	Casey et al 2012[38]	Fox & Kahn 2008[112]	Giannoukas et al 2006[111]	Hull et al 2011[39]	Kahn et al 2008[78]	Kakkos et al 2006[116]	Kolbach et al 2003[117]	Luo et al 2006[113]	Musani et al 2010[118]	Ng et al 1998[114]	Segal et al 2007[110]	Watson et al 2004[59]	Wells and Forster et al 2001[115]
Were the characteristics of the included studies provided?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Can't answer	Yes	Can't answer	Can't answer	Yes	Yes	Can't answer	Yes	Yes	Yes	Can't answer	Yes	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Not applicable	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes

AMSTAR question[93]	Alesh et al 2007[109]	Casey et al 2012[38]	Fox & Kahn 2008[112]	Giannoukas et al 2006[111]	Hull et al 2011[39]	Kahn et al 2008[78]	Kakkos et al 2006[116]	Kolbach et al 2003[117]	Luo et al 2006[113]	Musani et al 2010[118]	Ng et al 1998[114]	Segal et al 2007[110]	Watson et al 2004[59]	Wells and Forster et al 2001[115]
Was the likelihood of publication bias assessed? (all studies included <10 studies)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Was the conflict of interest stated?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Proportion of criteria met	6/11	9/11	7/11	5/11	9/11	8/11	6/11	10/11	7/11	8/11	4/11	8/11	10/11	8/ 11

2.6 Assessing the need for updating the evidence on prognostic factors identified from systematic review of systematic reviews

Quality of the systematic review – The rationale here was that if a previous systematic review was of poor quality, then it would definitely need an update regardless of whether other criteria were fulfilled. To assess the quality of systematic reviews, the AMSTAR tool was used as described in the main thesis. The quality of the systematic review was rated as good, fair or poor.

Age of the evidence – It is recommended that the availability of new relevant studies should be considered when a systematic review is greater than two years old.[95,94] A two year cycle updating policy was advocated by Lutje and Moher so that a review of less than two years did not require an update while a review of two years or more may require an update.[94] Therefore, if the date of the search strategies across systematic reviews that have assessed a prognostic factor was less than two years from conclusion of the systematic review of systematic reviews, the factor was categorised as does not require an update of the evidence. Otherwise, the level of evidence was considered.

The level of evidence – The rationale for considering the level of evidence was to allow for an update with the best additional evidence possible while conserving time and resources. If existing evidence was the best on the reference scale, the next step was to conduct a scoping search to identify primary studies with similar study designs that

would best complement this evidence. If primary studies with similar study designs were not available, then existing evidence could be relied on as the best evidence possible. So there would be no need to conduct an extensive search to identify primary studies with other study designs that are less likely to change the current evidence, thereby saving time and resources. However, if primary studies with similar study designs were identified, then the evidence on the prognostic factor would be categorised as requires an update.

Determination of availability of new relevant studies – After determining the level of evidence as determined by the Oxford centre for evidence-based medicine level of evidence reference scale,[96] a scoping search to identify if there were existing relevant studies that would best complement the evidence was carried out. Where new studies were identified, the evidence on the corresponding factor was categorised as requires updating, otherwise the evidence was categorised as does not require updating.

2.6.1 Oxford Centre for Evidence-based medicine - Levels of Evidence

Level	Therapy / Prevention, Aetiology / Harm	Prognosis
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations
1b	Individual RCT (with narrow Confidence Interval")	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population
1c	All or none	All or none case-series
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample only
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research
3a	SR (with homogeneity*) of case-control studies	
3b	Individual Case-Control Study	
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Key: * – By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted below, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level

CDR – Clinical decision rule (same as prognostic model) RCT – Randomised controlled trials

Note:

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

EITHER a single result with a wide Confidence Interval

OR a Systematic Review with troublesome heterogeneity.

(Such evidence is inconclusive, and therefore can only generate Grade D recommendations).

Reference: Howick, J., et al. (2011). Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). http://www.cebm.net/index.aspx?o=5653, Oxford Centre for Evidence-Based Medicine

Appendix 3: Identification of potential prognostic factors associated with the development of PTS after a DVT of the lower limb (systematic review of primary studies)

3.1 Search strategy (EMBASE and MEDLINE)

	Search terms applied to; **MEDLINE (1946 – 9 April 2015)** **EMBASE (1947 – 9 April 2015)**
1	exp deep vein thrombosis/ or deep vein thrombo$.mp.
2	Venous thromboembolism.mp. or Venous Thromboembolism/
3	DVT.mp
4	Venous thrombos$.mp.
5	VTE.mp
6	PTS.mp
7	Postthrombotic syndrome.mp. or Postphlebitic Syndrome/ or Postthrombotic Syndrome/
8	Venous stasis syndrome.mp.
9	Chronic venous insufficiency.mp. or chronic vein insufficiency/
10	Venous ulcer.mp.
11	or /1-5
12	or/6-10
13	11 and 12

3.2 Search strategy (Cochrane library)

	Search terms (Cochrane library 1959 – April 2015)
1	MeSH descriptor [venous thrombosis] explode all trees
2	″venous thromboembolism" or "deep vein thrombosis" or "deep vein thromboses" or “DVT” or “VTE”
3	MeSH descriptor [Postthrombotic syndrome] explode all trees
4	"PTS" or “post phlebitic syndrome” or “venous stasis syndrome” or “venous ulcer” or “chronic venous insufficiency”: ti,ab,kw
5	1 or 2 AND 3 or 4

3.3 Journals and conferences searched in Zetoc Database

Journals and Conferences searched (up to April 2015)
American Society of Hematology
British Society for Haematology
European Hematology Association
European Venous Forum
International Society on Thrombosis and Haemostasis

3.4 Search strategy (ongoing trials)

Databases (dates covered)	Search terms used / Section searched in database
WHO International Clinical Trials Registry Platform (2011 to April 2015)	″venous thrombosis" OR "venous thromboembolism" OR "deep vein thrombosis" OR "deep vein thromboses" OR “DVT” OR “VTE” OR "PTS" OR “Postthrombotic syndrome” OR “post phlebitic syndrome” OR “venous stasis syndrome” OR “venous ulcer” OR “chronic venous insufficiency” in Title (Advanced search)
UK Clinical Research Network study portfolio (searched on 9 April 2015)	Specialty searched - “haematology” Specialty group searched -“ non-malignant haematology” Disease/Diagnosis searched - “non-malignant haematology”
metaRegister of Controlled Trials (searched on 9 April 2015)	“Post-thrombotic syndrome” searched in “conditions studied” “Deep vein thrombosis” searched in “conditions studied” “Venous thromboembolism” searched in “conditions studied”

3.5 Rationale for study design inclusion and analysis

Multiple sources have acknowledged that prospective cohort studies and prognostic model studies are the best study designs for gathering prognostic information.[96,139,142,143] Prospective cohort studies are better than the retrospective study in this respect because it has more comprehensive data collection with regards to the subject of interest than retrospective studies (as retrospective cohort studies often makes use of data collected for other purposes). In addition it has less likelihood for introducing bias such as recall bias.[142,143] Prospective cohort studies are also better than case-control studies for collation of prognostic information as the latter like retrospective cohort studies is prone to recall bias amongst other biases such as sampling bias and observational bias.[142] In addition, it is easy to influence the absolute risk in case-control studies, hence case control studies are not useful for calculating relative risk.[142,215] For rare conditions however, the case-control study has been found useful,[142] but as discussed in the background to the thesis, PTS is not a rare condition. Clinical trials are not the gold standard for gathering prognostic information but they have been used for this purpose particularly were a treatment effect has been identified.[143] Clinical trials are particularly important to this study as the first phase of this project was able to demonstrate that the type of treatments employed in managing DVT may determine if a patient develops PTS or not.

To improve quality of prognostic information, prognostic models should ideally have been internally and externally validated.[96] While prospective cohort studies that have

not developed a prognostic model should at the minimum have accounted for confounding variables by conducting a multivariate analysis.[143,287]

For these reasons (cited above), prognostic model studies and prospective cohort studies with multivariate analysis was considered the ideal study design for inclusion in this review. However, because it was anticipated that there will be few of the desired study designs available that have investigated the association between various factors and later development of PTS after DVT, the other study designs were also included in this review.

Therefore, the study designs that were considered for inclusion in this systematic review were; prospective cohort studies, retrospective cohort studies, clinical trials and case-control studies. However, only identified prognostic models and potential prognostic factors assessed in multivariate analysis of prospective cohort studies were analysed in detail. While potential prognostic factors from the remaining evidence not already assessed were noted.

3.6 Excluded studies and reasons for exclusion

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
1.	Akesson, H., et al. (1990)	"Venous function assessed during a 5 year period after acute ilio-femoral venous thrombosis treated with anticoagulation."	A
2.	Albrechtsson, U., et al. (1981).	"Streptokinase treatment of deep venous thrombosis and the postthrombotic syndrome. Follow-up evaluation of venous function." Archives of Surgery **116**(1): 33-37.	A
3.	Alhadad, A., et al. (2011).	"Iliocaval vein stenting: Long term survey of postthrombotic symptoms and working capacity." Journal of Thrombosis & Thrombolysis **31**(2): 211-216.	B
4.	Andersen, M. and P. Wille-Jorgensen (1991)	"Late complications of asymptomatic deep venous thrombosis." European Journal of Surgery **157**(9): 527-530.	C
5.	Arnesen, H., et al. (1978).	"A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis." Acta Med Scand **203**(6): 457-463.	A
6.	Arnesen, H., et al. (1982)	"Streptokinase or heparin in the treatment of deep vein thrombosis. Follow-up results of a prospective study." Acta Medica Scandinavica **211**(1-2): 65-68.	A
7.	Aschwanden, M., et al. (2008)	Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. Journal of Vascular Surgery **47**, 1015-102	A
8.	Ashrani, A. A., et al. (2009).	"Risk factors and underlying mechanisms for venous stasis syndrome: a population-based case-control study.[Erratum appears in Vasc Med. 2010 Feb;15(1):79]." Vascular Medicine **14**(4): 339-349.	C
9.	Barras, J. P., M. T. Widmer, et al. (1991)	"Sequelae of venous thrombosis. Incidence in of the post-thrombosis syndrome after 5 years." " Journal des Maladies Vasculaires **16**(2): 115-118. [French]	C

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
10.	Bieger, R., et al. (1976)	"Is streptokinase useful in the treatment of deep vein thrombosis?" Acta Medica Scandinavica **199**(1-2): 81-88.	A
11.	Bittar, L. F., et al. (2011).	"Prospective evaluation of plasma levels of FVIII in patients with venous thromboembolism." Blood **118 (21)**.	D
12.	Brandjes, D. P., et al. (1997)	"Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis." Lancet **349**(9054): 759-762.	A
13.	Broholm, R., et al. (2011).	"Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis." Journal of Vascular Surgery **54**(6 Suppl): 18S-25S.	A
14.	Caprini, J. A., et al. (1999).	Caprini, J. A., et al. (1999). "Deep vein thrombosis outcome and the level of oral anticoagulation therapy." Journal of Vascular Surgery **30**(5): 805-811.	B
15.	Carpentier, P. H., et al. (2012)	"A therapeutic education program for the prevention of the postthrombotic syndrome." Journal of Vascular Surgery **55 (1)**: 306.	B
16.	Chang, R., C. C. Chen, et al. (2008).	"Deep vein thrombosis of lower extremity: direct intraclot injection of alteplase once daily with systemic anticoagulation--results of pilot study." Radiology **246**(2): 619-629.	B
17.	Comerota, A. J. (2002).	"Quality-of-life improvement using thrombolytic therapy for iliofemoral deep venous thrombosis." Reviews in Cardiovascular Medicine **3 Suppl 2**: S61-67.	B
18.	Comerota, A. J. (2012).	"Catheter-directed thrombolysis prevents post-thrombotic syndrome in patients with acute deep vein thrombosis in the upper half of the thigh." Evidence-Based Medicine **17**(6): 182-183.	F
19.	Comerota, A. J., et al. (2012).	"Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis.[Erratum appears in J Vasc Surg. 2012 May;55(5):1547]." Journal of Vascular Surgery **55**(3): 768-773.	C
20.	Common, H. H., et al. (1976).	"Deep vein thrombosis treated with streptokinase or heparin. Follow-up of a randomized study." Angiology **27**(11): 645-654.	A
21.	de Araujo Bessa, J. C. (1986)	"Femoral and iliofemoral thrombectomy to prevent chronic venous insufficiency. Follow-up of 18 patients." Journal of Cardiovascular Surgery **27**(4): 443-446.	A

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
22.	Decousus, H. (2005).	"Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study." Circulation **112**(3): 416-422.	A
23.	Deehan, D. J., et al. (2001)	"Postphlebitic syndrome after total knee arthroplasty: 405 patients examined 2-10 years after surgery." Acta Orthopaedica Scandinavica **72**(1): 42-45.	D
24.	Denck, H. (1986).	"Indications for surgery in acute thrombosis of the leg and pelvic veins. Langenbecks Archiv fur Chirurgie **369**: 599-602. [German]	A B
25.	Dietzek, A. M. (2010)	"Isolated pharmacomechanical thrombolysis of deep venous thrombosis utilizing a peripheral infusion system: Manuf." International Angiology **29**(4): 308-316.	B
26.	Elliot, M. S., et al. (1979)	"A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: An interim report of a prospective trial." British Journal of Surgery **66**(12): 838-843.	A
27.	Enden, T. R., et al. (2009)	"Additional catheter-directed venous thrombolysis in iliofemoral deep vein thrombosis; short-term results from the cavent study, a multicenter, randomized controlled trial." Journal of Thrombosis and Haemostasis **7 (S2)**: 6.	B
28.	Enden, T. R., et al (2012)	Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial	A
29.	Eriksen, L., et al. (1997)	"Venous thrombectomy in pregnancy: A follow-up study." Phlebology **12**(4): 146-150.	A
30.	Fanikos, J., et al. (2009).	"Long-term complications of medical patients with hospital-acquired venous thromboembolism." Thrombosis & Haemostasis **102**(4): 688-693.	D
31.	Fasolini, F. G. and H. K. Streuli (1985)	"Thrombectomy versus conservative therapy of deep venous thromboses in the leg. Late results after 10 years. Thrombektomie Versus Konservative Therapie Tiefer Becken-Bein- Venenthrombosen. Spatergebnisse 10 Jahre Danach." Helvetica Chirurgica Acta **52**(5): 735-738. [German]	A B
32.	Fitzgerald, S. J., C. M. McAndrew, et al. (2011).	"Incidence of postthrombotic syndrome in patients undergoing primary total hip arthroplasty for osteoarthritis." Clinical Orthopaedics & Related Research **469**(2): 530-534.	A
33.	Francis, C. W., J. J. Ricotta, et al. (1988)	"Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty." Clin Orthop Relat Res(232): 271-278.	B

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
34.	Gaber, Y., et al. (2001).	"Resistance to activated protein C due to factor V Leiden mutation: High prevalence in patients with post-thrombotic leg ulcers." British Journal of Dermatology **144**(3): 546-548.	D
35.	Galanaud, J. P., C. A. Holcroft, et al. (2012).	"Comparison of the Villalta post-thrombotic syndrome score in the ipsilateral vs. contralateral leg after a first unprovoked deep vein thrombosis." Journal of Thrombosis & Haemostasis **10**(6): 1036-1042.	A
36.	Ganger, K. H., et al. (1989)	"Surgical thrombectomy versus conservative treatment for deep venous thrombosis; functional comparison of long-term results." European Journal of Vascular Surgery **3**(6): 529-538.	A
37.	Gao, B., et al. (2011).	"Catheter-directed thrombolysis with a continuous infusion of low-dose urokinase for non-acute deep venous thrombosis of the lower extremity." Korean Journal of Radiology **12**(1): 97-106.	F
38.	Gasparis, A. P., et al. (2009).	"Midterm follow-up after pharmacomechanical thrombolysis for lower extremity deep venous thrombosis." Vascular & Endovascular Surgery **43**(1): 61-68.	F
39.	Geier, B., C. Lindow, et al. (2009).	"Long-term results after venous thrombectomy in iliofemoral thrombosis. Langzeitergebnisse nach venoser thrombektomie bei iliofemoraler thrombose." Vasomed **21**(3): 101-104. [German]	A
40.	Ghanima, W., et al. (2011).	"Health related quality of life (HRQOL) after catheter-directed thrombolysis in deep venous thrombosis (DVT) -a case-control study." Journal of Thrombosis and Haemostasis **9**: 613.	A
41.	Ghanima, W., et al. (2011).	"Recurrent venous thrombosis, post-thrombotic syndrome and quality of life after catheter-directed thrombolysis in severe proximal deep vein thrombosis." Journal of Thrombosis & Haemostasis **9**(6): 1261-1263.	A
42.	Ginsberg, J. S., F. Turkstra, et al. (2000).	"Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study." Archives of Internal Medicine **160**(5): 669-672.	F
43.	González-Fajardo, J. A., et al. (2008)	"Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin" Journal of Vascular Surgery **48**, 953-959	A

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
44.	Gonzalez-Fajardo, J. A., M. Martin-Pedrosa, et al. (2010)	"Quality of life after deep venous thrombosis". Evaluacion de la calidad de vida en pacientes con sindrome postrombotico." Angiologia **62**(4): 140-145. [Spanish]	A
45.	Grewal, N. K., J. Trabal Martinez, et al. (2010).	"Objective outcome measures of patients with iliofemoral deep venous thrombosis treated with catheter-directed thrombolysis." Journal of Vascular Surgery **51 (3)**: 787.	F
46.	Grewal, N. K., J. T. Martinez, et al. (2010).	"Quantity of clot lysed after catheter-directed thrombolysis for iliofemoral deep venous thrombosis correlates with postthrombotic morbidity." Journal of Vascular Surgery 51(5):1209-14.	F
47.	Decousus et al (2005).	"Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study." Circulation **112**(3): 416-422.	A
48.	Haig, Y., T. Enden, et al. (2013).	"Determinants of early and long-term efficacy of catheter-directed thrombolysis in proximal deep vein thrombosis." Journal of Vascular & Interventional Radiology **24**(1): 17-24; quiz 26.	A B
49.	Hartung, O., et al. (2008)	"Late results of surgical venous thrombectomy with iliocaval stenting." J Vasc Surg **47**(2): 381-387.	A
50.	Hold, M., et al. (1992)	"Deep venous thrombosis: results of thrombectomy versus medical therapy. Presented at the 5th European-American Symposium on Venous Diseases, Vienna, Austria, Nov. 7-11, 1990." Vasa **21**(2): 181-187.	A
51.	Holmstrom et al. (1999)	"Long term clinical follow-up in 265 patients with deep venous thrombosis initially treated with either unfractionated heparin or dalteparin: A retrospective analysis." Thrombosis and Haemostasis **82**(4): 1222-1226.	A
52.	Holper, P., et al. (2010)	"Long term results after surgical thrombectomy and simultaneous stenting for symptomatic iliofemoral venous thrombosis." Eur J Vasc Endovasc Surg. **39**(3): 349-355. doi: 310.1016/j.ejvs.2009.1009.1028. Epub 2010 Jan 1018.	A
53.	Hosoi, Y., H. Yasuhara, et al. (1999).	"Influence of popliteal vein thrombosis on subsequent ambulatory venous function measured by near-infrared spectroscopy." American Journal of Surgery **177**(2): 111-116.	D

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
54.	Houweling, A. H., et al. (2012)	"Monitoring blood sample collection and shipment in a publicly funded Post Thrombotic Syndrome (PTS) Randomized Controlled Trial (RCT)." Clinical Trials **9 (4)**: 548.	A B
55.	Hull, R. D., et al. (2009)	"Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome." American Journal of Medicine **122**(8): 762-769.e763.	A
56.	James, K. V., et al. (1996)	"Venous thrombotic complications of pregnancy." Cardiovascular Surgery **4**(6): 777-782.	C
57.	Janjua, M., et al. (2009)	"Outcome with retrievable inferior vena cava filters." Chest **136 (4)**.	F
58.	Jayaraj, A., et al. (2011)	"Impact of graduated compressive stockings on the prevention of P-thrombotic syndrome: Results of a randomized trial." Journal of Vascular Surgery **1)**: 103S-104S.	A
59.	Jeon, Y. S., Y. H. Yoon, et al. (2010).	"Catheter-directed thrombolysis with conventional aspiration thrombectomy for lower extremity deep vein thrombosis." Yonsei Medical Journal **51**(2): 197-201.	F
60.	Johansson, L., et al. (1979)	"Comparison of streptokinase with heparin: late results in the treatment of deep venous thrombosis." Acta Med Scand **206**(1-2): 93-98.	A
61.	Juhan, C. M., et al. (1997)	Juhan, C. M., et al. (1997). "Late results of iliofemoral venous thrombectomy." Journal of Vascular Surgery **25**(3): 417-422.	A
62.	Kahn, S. R., et al. (2012)	Kahn, S. R., et al. (2012). "A multicenter randomized placebo controlled trial of compression stockings to prevent the post-thrombotic syndrome after proximal deep venous thrombosis: The S.O.X. trial." Blood **120 (21)**.	A
63.	Kalkowski, H., et al. (1984).	"Treatment of thrombotic occlusion of the pelvic and extremity veins. Comparison of three different types of treatment." Zentralblatt fur Chirurgie **109**(2): 97-103. [German]	A E
64.	Kamphausen, M., et al. (2005)	"Clinical and functional results after transfemoral thrombectomy for iliofemoral deep venous thrombosis: a 5-year-follow-up."Zentralblatt fur Chirurgie **130**(5): 454-461; discussion 461-452. [German]	A
65.	Khuangsirikul, S., et al. (2009).	"Lower extremities' postthrombotic syndrome after total knee arthroplasty." Journal of the Medical Association of Thailand **92 Suppl 6**: S39-44.	A

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
66.	Killewich, L. A., et al. (1985).	"An objective assessment of the physiologic changes in the postthrombotic syndrome." Archives of Surgery **120**(4): 424-426.	B
67.	Killewich, L. A., et al. (1989).	"Spontaneous lysis of deep venous thrombi: Rate and outcome." Journal of Vascular Surgery **9**(1): 89-97.	B
68.	Kolbach, D. N., et al. (2003)	"Therapy of acute deep vein thrombosis and prevention of the post-thrombotic syndrome: A survey among dermatologists in the Netherlands." Phlebologie **32**(2): 45-49.	A D
69.	Kolbel, T., et al. (2009)	"Chronic iliac vein occlusion: midterm results of endovascular recanalization." Journal of Endovascular Therapy **16**(4): 483-491.	D
70.	Krieger, E., B. van Der Loo, et al. (2004).	"C-reactive protein and red cell aggregation correlate with late venous function after acute deep venous thrombosis." Journal of Vascular Surgery **40**(4): 644-649.	B
71.	Kurtoglu, M., et al. (1998).	"Treatment of proximal deep venous thrombosis with low molecular weight heparin (Enoxaparin) (early results)." Dusuk molekul agirlikli heparin (Enoksaparin) ile proksimal derin ven trombozu tedavisi (erken sonuclarimiz)." Turkish Journal of Surgery **14**(5): 346-352. [Turkish]	A
72.	Kutsukata, N., et al. (2010)	"Surgical venous thrombectomy for Japanese patients with acute deep vein thrombosis: a review of 5 years' experience." Journal of Nippon Medical School = Nihon Ika Daigahu Zasshi **77**(3): 155-159.	A
73.	Labropoulos, N., et al. (1994).	"Venous reflux in patients with previous deep venous thrombosis: correlation with ulceration and other symptoms." Journal of Vascular Surgery **20**(1): 20-26.	C
74.	Lagerstedt, C., C. G. Olsson, et al. (1993).	"Recurrence and late sequelae after first-time deep vein thrombosis: Relationship to initial signs." Phlebology **8**(2): 62-67.	D
75.	Laiho, M. K., et al. (2004).	"Preservation of venous valve function after catheter-directed and systemic thrombolysis for deep venous thrombosis." European Journal of Vascular and Endovascular Surgery **28**(4): 391-396.	A
76.	LeSiege, C. J., et al. (1992)	"Importance of valvular incompetence after acute deep venous thrombosis." Journal of Cardiovascular Surgery **33**(6): 710-714.	C

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
77.	Lindhagen, J., et al. (1978)	"Ileofemoral venous thrombectomy." Journal of Cardiovascular Surgery **19**(3): 319-327.	A
78.	Lindhagen, A., et al. (1984).	"Deep venous insufficiency after postoperative thrombosis diagnosed with 125I-labelled fibrinogen uptake test." Br J Surg **71**(7): 511-515.	A D
79.	Lindhagen, A., et al. (1985).	"Venous function five to eight years after clinically suspected deep venous thrombosis." Acta Med Scand **217**(4): 389-395.	D
80.	Lindner, D. J., et al. (1986).	"Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis." Journal of Vascular Surgery **4**(5): 436-442.	C
81.	Lindow, C., et al. (2010)	"Long-term results after transfemoral venous thrombectomy for iliofemoral deep venous thrombosis." European Journal of Vascular & Endovascular Surgery **40**(1): 134-138.	A
82.	Lonner, J. H., et al. (2006).	"Postthrombotic syndrome after asymptomatic deep vein thrombosis following total knee and hip arthroplasty." American Journal of Orthopedics (Chatham, Nj) **35**(10): 469-472.	D
83.	Lurie, F., et al. (1999)	"Development of postthrombotic syndrome after acute unilateral iliofemoral thrombosis: Clinical dynamics and hemodynamic changes." Vascular Surgery **33**(1): 5-13.	A
84.	Luzzi R. et al (2014)	"The efficacy of sulodexide in the prevention of postthrombotic syndrome"	D
85.	Maleti (2006)	"Neovalve construction in postthrombotic syndrome." Journal of Vascular Surgery **43**(4): 794-799.	D
86.	Mant, M. J., D. T. Eurich, et al. (2008).	"Post-thrombotic syndrome after total hip arthroplasty is uncommon." Acta Orthopaedica **79**(6): 794-799.	C
87.	McAndrew, C. M., et al. (2010).	"Incidence of postthrombotic syndrome in patients undergoing primary total knee arthroplasty for osteoarthritis." Clinical Orthopaedics & Related Research **468**(1): 178-181.	C
88.	McNally, M. A., et al. (1994)	"Postphlebitic syndrome after hip arthroplasty. 43 patients followed at least 5 years." Acta Orthopaedica Scandinavica **65**(6): 595-598.	C
89.	Meissner, M. H., et al. (1997).	"Early outcome after isolated calf vein thrombosis."	B

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
90.	Mozafar and Talebianfar (2007)	"Long-term outcome of transfemoral thrombectomy in patients with acute iliofemoral vein thrombosis." Medical Journal of the Islamic Republic of Iran **21**(3): 154-157.	A
91.	Mudge, M. and L. E. Hughes (1978)	"The long term sequelae of deep vein thrombosis." British Journal of Surgery **65**(10): 692-694.	A
92.	Mudge, M. and L. E. Hughes (1984).	"Incisional hernia and post thrombotic syndrome - an observed association." Annals of the Royal College of Surgeons of England **66**(5): 351-352.	A
93.	Mudge, M., et al. (1988)	"A prospective 10-year study of the post-thrombotic syndrome in a surgical population." Annals of the Royal College of Surgeons of England **70**(4): 249-252.	C
94.	Neuhauser, B., et al. (2002).	"Results of loco regional rt-PA lysis therapy of deep upper or lower limb vein thrombosis - Follow-up after 12 months." 12-Monatsergebnisse nach lokoregionaler rt-PA-lysetherapie bei tiefer beinvenenthrombose." Phlebologie **31**(6): 137-140. [German]	C
95.	Noguchi, M., et al. (2003)	"Thrombus removal with a temporary vena caval filter in patients with acute proximal deep vein thrombosis." Heart and Vessels **18**(4): 197-201.	A
96.	Norris, C. S. and J. M. Darrow (1986).	"Hemodynamic indicators of postthrombotic sequelae." Archives of Surgery **121**(7): 765-768.	A
97.	Partsch, H. (1994).	"From thrombosis to post-thrombotic syndrome--plethysmography studies of venous function." Wiener Medizinische Wochenschrift **144**(10-11): 226-228. [German]	A
98.	Partsch, H., et al. (2004)	"Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome." International Angiology **23**(3): 206-212.	A
99.	Plate et al. (1990)	"Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula." European Journal of Vascular Surgery **4**(5): 483-489.	A
100.	Plate et al. (1997)	"Venous thrombectomy for iliofemoral vein thrombosis--10-year results of a prospective randomised study." Eur J Vasc Endovasc Surg **14**(5): 367-374.	A
101.	Prandoni, P., et al. (2004)	"Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial." Annals of Internal Medicine **141**(4): 249-256.	A

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
102.	Prandoni, P., et al. (2012)	"Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: A randomized trial." Blood **119**(6): 1561-1565.	A
103.	Rathbun, S., et al. (2012).	"Expert: Exercise to prevent post-thrombotic syndrome elicited by recent thrombosis." American Journal of Hematology **87**: S190.	F
104.	Rosell Pradas, J., et al. (1990).	"Treatment of distal venous thrombosis of the lower extremity with "moderated" doses of heparin." Angiologia **42**(3): 100-104. [German]	E
105.	Saarinen, J., et al. (2002)	"Post-thrombotic symptoms after an isolated calf deep venous thrombosis." Journal of Cardiovascular Surgery **43**(5): 687-691.	A
106.	Schmutzler, R. (1990)	"The treatment of deep venous thrombosis. Thrombolysis vs heparin." Phlebologie **43**(4): 656-665; discussion 666. [French]	E
107.	Schulman, S., et al. (1986)	"Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase." Acta Med Scand **219**(4): 349-357.	A
108.	Schulman, S., P. Lindmarker, et al. (2006).	"Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months." Journal of Thrombosis & Haemostasis **4**(4): 734-742.	C
109.	Schwarzbach, M. H., et al. (2005)	"Surgical thrombectomy followed by intraoperative endovascular reconstruction for symptomatic ilio-femoral venous thrombosis." Eur J Vasc Endovasc Surg **29**(1): 58-66.	A
110.	Schmidt et al (1987)	"Haemodynamics of the postphlebitic syndrome." International Angiology **6**(2): 187-192.	A
111.	Sheridan, A. I. and L. R. Sauvage (1965)	"Treatment of iliofemoral venous thrombosis by thrombectomy." Pacific Medicine and Surgery **73**(6): 333-336	A
112.	Shi et al. (2011)	"Percutaneous mechanical thrombectomy for acute massive lower extremity deep venous thrombosis." Surgical Laparoscopy, Endoscopy & Percutaneous Techniques **21**(1): 50-53.	A F
113.	Shionoya, S., et al. (1989)	"Thrombectomy for acute deep vein thrombosis: prevention of postthrombotic syndrome." Journal of Cardiovascular Surgery **30**(3): 484-489.	A

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
114.	Sillesen, H., et al. (2005)	"Catheter directed thrombolysis for treatment of ilio-femoral deep venous thrombosis is durable, preserves venous valve function and may prevent chronic venous insufficiency." European Journal of Vascular & Endovascular Surgery **30**(5): 556-562.	B
115.	Skupin, M., M. Scherb, et al. (2002).	"Loco-regional lysis with thrombosis older than 10 days: experiences and outcome." Hamostaseologie **22**(2): 42-46. [German]	C
116.	Sottiurai, V. S., N. McHale, et al. (2007).	"Intermittent pneumatic compression of the lower limbs potentiates the effects of thrombolytic agents in postthrombotic syndrome: Non-randomized prospective study comparing systemic thrombolysis versus local thrombolysis." Angeiologie **59**(3): 55-63. [French]	B
117.	Ten Cate-Hoek et al. (2011)	"Individually tailored elastic compression therapy and post thrombotic syndrome, a randomized multicentre trial (ideal DVT study)." Journal of Thrombosis and Haemostasis **9**: 655.	A
118.	Torngren et al. (1996)	"The long-term outcome of proximal vein thrombosis during pregnancy is not improved by the addition of surgical thrombectomy to anticoagulant treatment." European Journal of Vascular and Endovascular Surgery **12**(1): 31-36.	A
119.	Toro et al. (2008)	"Long-term consequences of pelvic trauma patients with thromboembolic disease treated with inferior vena caval filters." Journal of Trauma-Injury Infection & Critical Care **65**(1): 25-29.	F
120.	Ulander et al. (2003)	"Long-term outcome of deep venous thrombosis during pregnancy treated with unfractionated heparin or low molecular weight heparin." Thrombosis Research **111**(4-5): 239-242.	A
121.	van Haarst, E. P., et al. (1996).	"The development of valvular incompetence after deep vein thrombosis: a 7 year follow-up study with duplex scanning." European Journal of Vascular & Endovascular Surgery **12**(3): 295-299.	A
122.	Villanueva, E. V., et al. (2001).	"Does the location of deep venous thrombosis affect the risk of developing postphlebitic syndrome?" Medical Journal of Australia **174**(2): 101-102.	D
123.	Wille-Jorgensen, P., et al. (1991).	"Postphlebitic syndrome and general surgery: an epidemiologic investigation." Angiology **42**(5): 397-403.	D
124.	Yamaki, T., et al. (2007).	"High peak reflux velocity in the proximal deep veins is a strong predictor of advanced post-thrombotic sequelae." Journal of Thrombosis & Haemostasis **5**(2): 305-312.	D

	Author and year	Title	Reason (Not meeting one or more inclusion criteria OR meeting an exclusion criteria as outlined in the methods section)
125.	Yin, M. Y., et al. (2011)	"Early and midterm outcomes of acute lower extremity deep venous thrombosis treated by catheter directed thrombolysis." Journal of Shanghai Jiaotong University (Medical Science) **31**(12): 1741-1745. [Chinese]."	A F
126.	Zenios etal (2003)	Post-thrombotic syndrome after total hip arthroplasty." HIP International **13**(3): 163-166.	D
127.	Zhao, J. and G. Dong (1995).	"Compositive treatment of acute deep vein thrombosis of lower extremity." Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] **33**(5): 310-312. [Chinese]	A
128.	Ziaja, K., et al. (2005).	"Long-term results of proximal deep vein thrombosis treatment - Anticoagulant treatment and compression therapy in post-thrombotic syndrome prevention." Chirurgia Polska **7**(2): 63-73.	A
129.	Ziegler, R. (2012).	"Deep vein thrombosis: Catheter-directed thrombolysis lowers the risk of a postthrombotic syndrome." Medizinische Monatsschrift fur Pharmazeuten **35**(6). [German]	F

Key: A - No relevant potential prognostic factor (n =72)

B - Outcomes not relevant (n =18)

C - Relevant data not reported separately (n = 15)

D - Population not relevant (n = 17)

E - No minimum follow up (n=3)

F - Wrong study design (n =13)

3.7 Unable to translate

Selection decisions on the following studies could not be made due to absence of a translator.

	Author	Title	Language
1.	Camilli, S., et al. (1996).	"Venous thrombectomy. La trombectomia venosa." Chronica Dermatologica **6**(6 SUPPL.): 111-127 [Italian]	Italian
2.	Fokin, A. A., et al. (1995).	"Use of cava-filter in the treatment of acute venous thrombosis in the end of pregnancy". Akusherstvo i Ginekologiia(1): 29-31.	Russian
3.	Ivanov, A. V. and A. B. Sakharov (2004).	"Prophylaxis and treatment of phlebothrombosis of deep veins of the lower extremities." Khirurgiia(1): 4-7.	Russian
4.	Ly, B., et al. (2004).	"Catheter-directed thrombolysis of iliofemoral venous thrombosis." Tidsskrift for Den Norske Laegeforening **124**(4): 478-480.	Norwegian
5.	Siragusa, S., et al. (1997).	"Clinical course and incidence of post-thrombophlebitic syndrome after profound asymptomatic deep vein thrombosis. Results of a transverse epidemiologic study." Minerva Cardioangiologica **45**(3): 57-66.	Italian

3.8 Articles translated and excluded

	Author	Title	Language
1.	Barras, J. P., M. T. Widmer, et al. (1991)	"Sequelae of venous thrombosis. Incidence in of the post-thrombosis syndrome after 5 years." " Journal des Maladies Vasculaires 16(2): 115-118.	French
2.	Denck, H. (1986).	"Indications for surgery in acute thrombosis of the leg and pelvic veins. Langenbecks Archiv fur Chirurgie 369: 599-602.	German
3.	Fasolini, F. G. and H. K. Streuli (1985)	"Thrombectomy versus conservative therapy of deep venous thromboses in the leg. Late results after 10 years. Thrombektomie Versus Konservative Therapie Tiefer Becken-Bein- Venenthrombosen. Spatergebnisse 10 Jahre Danach." Helvetica Chirurgica Acta 52(5): 735-738.	German
4.	Geier, B., C. Lindow, et al. (2009).	"Long-term results after venous thrombectomy in iliofemoral thrombosis. Langzeitergebnisse nach venoser thrombektomie bei iliofemoraler thrombose." Vasomed 21(3): 101-104.	German
5.	Gonzalez-Fajardo, J. A., M. Martin-Pedrosa, et al. (2010)	"Quality of life after deep venous thrombosis". Evaluacion de la calidad de vida en pacientes con sindrome postrombotico." Angiologia 62(4): 140-145.	Spanish
6.	Bellmunt-Montoya, S., et al. (2006).	"What awaits the patient following a diagnosis of deep vein thrombosis? A study of the factors predicting mortality, post-thrombotic syndrome and quality of life. [Spanish] ?Que le depara al paciente tras el diagnostico de trombosis venosa profunda? Estudio de factores pronosticos de la mortalidad, sindrome postrombotico y calidad de vida." Angiologia 58(1): 39-49.	Spanish
7.	Kalkowski, H., et al. (1984).	"Treatment of thrombotic occlusion of the pelvic and extremity veins. Comparison of three different types of treatment." Zentralblatt fur Chirurgie 109(2): 97-103.	German
8.	Kamphausen, M., et al. (2005)	"Clinical and functional results after transfemoral thrombectomy for iliofemoral deep venous thrombosis: a 5-year-follow-up."Zentralblatt fur Chirurgie 130(5): 454-461; discussion 461-452.	German
9.	Kurtoglu, M., et al. (1998).	"Treatment of proximal deep venous thrombosis with low molecular weight heparin (Enoxaparin) (early results)." Dusuk molekul agirlikli heparin (Enoksaparin) ile proksimal derin ven trombozu tedavisi (erken sonuclarimiz)." Turkish Journal of Surgery 14(5): 346-352.	Turkish

	Author	Title	Language
10.	Lopez-Azkarreta, I., et al. (2005).	"Prospective study of the risk factors for the development of post-thrombotic syndrome after proximal deep venous thrombosis." Medicina Clinica 125(1): 1-4.	Spanish
11.	Neuhauser, B., et al. (2002).	"Results of loco regional rt-PA lysis therapy of deep upper or lower limb vein thrombosis - Follow-up after 12 months." 12-Monatsergebnisse nach lokoregionaler rt-PA-lysetherapie bei tiefer beinvenenthrombose." Phlebologie 31(6): 137-140.	German
12.	Partsch, H. (1994).	"From thrombosis to post-thrombotic syndrome--plethysmography studies of venous function." Wiener Medizinische Wochenschrift 144(10-11): 226-228.	German
13.	Rosell Pradas, J., et al. (1990).	"Treatment of distal venous thrombosis of the lower extremity with "moderated" doses of heparin." Angiologia 42(3): 100-104.	German
14.	Schmutzler, R. (1990)	"The treatment of deep venous thrombosis. Thrombolysis vs heparin." Phlebologie 43(4): 656-665; discussion 666.	French
15.	Skupin, M., M. Scherb, et al. (2002).	"Loco-regional lysis with thrombosis older than 10 days: experiences and outcome." Hamostaseologie 22(2): 42-46.	German
16.	Sottiurai, V. S., N. McHale, et al. (2007).	"Intermittent pneumatic compression of the lower limbs potentiates the effects of thrombolytic agents in postthrombotic syndrome: Non-randomized prospective study comparing systemic thrombolysis versus local thrombolysis." Angeiologie 59(3): 55-63.	French
17.	Yin, M. Y., et al. (2011)	"Early and midterm outcomes of acute lower extremity deep venous thrombosis treated by catheter directed thrombolysis." Journal of Shanghai Jiaotong University (Medical Science) 31(12): 1741-1745.	Chinese
18.	Zhao, J. and G. Dong (1995).	"Compositive treatment of acute deep vein thrombosis of lower extremity." Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 33(5): 310-312.	Chinese
19.	Ziaja, K., et al. (2005).	"Long-term results of proximal deep vein thrombosis treatment - Anticoagulant treatment and compression therapy in post-thrombotic syndrome prevention." Chirurgia Polska 7(2): 63-73.	Polish
20.	Ziegler, R. (2012).	"Deep vein thrombosis: Catheter-directed thrombolysis lowers the risk of a postthrombotic syndrome." Medizinische Monatsschrift fur Pharmazeuten 35(6).	German

3.9 Data extraction form

Please note: Studies and data on potential prognostic factors will be excluded from this systematic review if;

1. Population studied were patients with upper limb DVT or in the paediatric age group

2. Studies investigated only the following factors before the year specified below;

    - *Physical activity before 2008*
    - *Inferior vena cava filter before 2008*
    - *Loco-regional thrombolysis before 2007*

3. Studies investigated only the following factors regardless of year published

    - *Anticoagulation with low molecular weight heparin,*
    - *Catheter directed thrombolysis,*
    - *Systemic thrombolysis,*
    - *Compression stockings,*
    - *Surgical thrombectomy*

Inclusion criteria

Study design	**Assessment**	**Comment**
Is it a prognostic model study/ a cohort study/ a case-control study/ a clinical trial	Yes/ No/ Unclear	
Population		
Were patients diagnosed with DVT? *NB: Please answer "Yes" if DVT is diagnosed in a sub population and data is extractable in relation to PTS*	Yes/ No/ Unclear	
Is it DVT of the lower limb? *Please answer "Yes" if , Iliac vein, Femoral vein, Popliteal vein, Fibular vein, Anterior tibial vein, Posterior tibial vein* *Please answer "Yes" if mixed population and data extractable*	Yes/ No / Unclear	
Are patients ≥ 18years *NB: Please answer Yes if mixed age population and data on ages ≥18 years is extractable*	Yes/ No/ Unclear	
Outcomes		
Did the study report any of the following outcome PTS/Chronic venous insufficiency/Venus stasis syndrome/Post-phlebitic syndrome	Yes/ No/ Unclear	
Follow up		
Were the patients followed up for a minimum of 3 months? *NB: Please answer yes if patients were assessed for outcome ≥3 months post DVT*	Yes/ No/ Unclear	
Prognostic factors		
Did the study assess other factors besides the following factors in relation to PTS? *Anticoagulation with low molecular weight heparin,* *Catheter directed thrombolysis,* *Systemic thrombolysis, Compression stockings, Surgical thrombectomy, Inferior-vena cava filters up to year 2007, Loco-regional thrombolysis up to year 2006 and Physical activity up to year 2007*	Yes/ No/ Unclear	
Effect sizes		
Are effect sizes reported and or is there sufficient reporting of data to calculate an effect size	Yes/ No/ Unclear	
Final decision (*please tick*)	Include (If answered "yes" to all questions above) Exclude (if answered "no" to one or more questions) Unclear (please specify):	

Study characteristics

General study characteristics *(please circle where appropriate)*	
Location of study	
Study aims	Reported/NR
Dates of recruitment	
Length of follow up of study	From ____ ____to _____ Median (range): n Mean: n
Length of time post DVT diagnosis to outcome measurement	From ____ ____to _____ Median (range): n Mean: n
Outcomes assessed	PTS/Chronic venous insufficiency/Venous stasis syndrome/Post-phlebitic syndrome Other *(please specify):*
Funding	Unclear NR Please State where reported:
Conflict of interest statement	Yes/No/NR

Baseline characteristics of patients for trials				
	Experimental arm/Group 1	Control arm/ Group 2	Other groups	Notes: Any Relationship with outcome? Yes/No/NR If Yes please state if statistically significant and p-values
Number of patients				
Age range (if reported) Mean				
Ethnicity No %				
Gender No %	Male: Female:	Male: Female:	Male: Female:	
No of patients screened for DVT				
No of patients recruited				
No of patients allocated				
No of patients evaluated				
No of drop outs				
Reasons for drop outs				
No of protocol violations				
Definition of DVT *Radiological/clinical/other* *Please circle all that applies and list all*				
Location of DVT				
Provoked/Unprovoked/NR				
Other DVT characteristics				
Additional diagnosis				
Status of patient at recruitment (Treated for DVT/Untreated for DVT) If treated: *Please state:* What treatment(s) Duration/treatment (weeks)				
Adverse event? Yes/No *If yes please state*				
Co morbidities? Yes/No (*If yes please state)*				

Baseline characteristics of patients for observational studies/Prognostic model studies			
	Outcome	No outcome	Notes: Any Relationship with outcome? Yes/No/NR If Yes please state if statistically significant and p-values
Number of patients			
Age range (if reported) Mean			
Ethnicity n/%			
Gender n/ %	Male: Female:	Male: Female:	
n of patients screened for DVT			
n of patients recruited			
n of patients evaluated			
n of drop outs			
Reasons for drop outs			
Definition of DVT *Radiological/clinical/other* *Please circle all that applies and list all*			
Location of DVT			
Provoked/Unprovoked/NR			
Other DVT characteristics			
Additional diagnosis			
Status of patient at recruitment (Treated for DVT/Untreated for DVT) If treated: *Please state:* What treatment(s) Duration/treatment (weeks)			
Adverse event? Yes/No (*If yes please state)*			
Co morbidities? Yes/No (*If yes please state)*			

Trial Characteristics *(please circle where appropriate)*	
Recruitment method	State (e.g. Consecutive inclusion)
Sample size n	
n Excluded (please state reasons)	
Trial design	Phase: Parallel/Cross-over/Factorial Single centre/multicentre: International/national If multicentre, how many centres? n Equivalent/Non-inferiority Multi-arm study? Yes/No If yes, how many? n
Treatment/ intervention	Please state:
Control	Please state:
Additional treatment/factor	Yes/No If yes, please state:
Compliance evaluated?	Yes/No If Yes, please state degree of compliance (%):
Number of arms	
Are treatment arms comparable?	Yes/No If No, please specify:
Flow diagram?	
Randomised?	Yes/No If Yes, please circle method of randomisation (Central/Methods NR/ Minimisation/ Inadequate)
Method of concealment of allocation	Adequate *(please specify)* Unclear/Not done/ Inadequate*(please specify)*
Blinding	Please circle: Single/Double/Triple/Not possible/Not done

Statistical methods used	Please state:
Observational study/ Prognostic model study characteristics	
Sample size	
n excluded (*please state reasons*)	
Recruitment method	
Type of observational study	Retrospective/prospective Case-control/cohort Longitudinal/cross sectional
Potential prognostic factor(s) assessed (*please list)*	
Any confounders?	Yes/No *If Yes Please state*
Any selective reporting?	
Statistical analysis method (*please state*)	

Outcome details

Outcomes assessed *(please state where relevant)*	
Please list outcomes and specify method of definition/measurement for each	
Timing of assessments for each outcome post DVT (months) and n of patients evaluated at each time point	

Potential prognostic factor details

Potential prognostic factor characteristics *(please duplicate rows if more factors identified)*			
	Definition/Method of measurement	Modifiable/ Non-modifiable	Notes, including; Clear definition or description of factor Dose, Length of exposure to factor, Time point of outcome measurement post DVT,
Factor 1 *(please state)*			
Factor 2 *(please state)*			
Factor 3 *(please state)*			
Factor 4 *(please state)*			

Potential prognostic factor versus outcome

Dichotomous data						
Outcome	Time	Exposed to factor		Not exposed to factor		Notes *(source: page/table no/ figure)*
		Observed events	Sample size	Observed event	Sample size	

Continuous data								
Outcome	Time	Exposed to factor			Not exposed to factor			Notes *(source: page/table no/ figure)*
		Sample size	Mean/mean change (incl. range)	Standard deviation	Sample size	Mean/mean change (incl. Range)	Standard deviation	

Quality assessment

Methodological quality summary for clinical trials					
Reviewer/date:			**Checked by:**		
	Clearly reported and appropriate	Unclear	Clearly reported and inappropriate	Not reported	Comments
Randomisation					
Treatment allocation					
Similarity of groups					
Blinding					
Transparent patient flow					
Completeness of trial					
ITT (less than 15% loss)					
Different dropout rates for different end points					
Summarised validity	Low risk of bias		Moderate risk of bias	High risk of bias	
Remarks:					

Methodological quality summary for observational studies					
Reviewer/Date:		**Checked by:**			
Contents *(please refer to tables below for guidance)*	Yes	Partly	No	Unsure	Comments
Study participation					
Study attrition					
Measurement of prognostic factors					
Measurement and controlling for confounding variables					
Measurement of outcomes					
Analysis approach					
Summarised validity	Low risk of bias	Moderate risk of bias	High risk of bias		
Remarks:					

Methodological quality for prognostic model studies					
Contents *(please refer to table below for guidance)*	Clearly described	Partly described	Not clearly described	Unsure	Comments
Introduction					
Patients					
Specimen characteristics					
Prognostic factor measurement					
Study design					
Statistical analysis approach					
Data					
Analysis and presentation					
Discussion					
Summarised validity	Low risk of bias		Moderate risk of bias	High risk of bias	
Remarks:					

Organisation

Organisational aspect		**Excluded**		**Included**	
Reviewer/date:		**Checked by:**			
Author/Year					
Journal/Source					
Country of origin					
Publication type	Full text/ Abstract/ Book Chapter/ Internal progress report/ Other - *please specify*				
Fate	Decision pending / Check references/ Use for discussion / Excluded without listing/ Excluded with listing Other- *please specify*				
Notes					

3.10 Quality assessment of prognostic model study

3.10.1 The Altman's Checklist

Introduction
State the marker examined, the study objectives, and any pre-specified hypotheses.
Materials and methods
Patients
Describe the characteristics (for example, disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.
Describe treatments received and how chosen (for example, randomised or rule-based).
Specimen characteristics
Describe type of biological material used (including control samples) and methods of preservation and storage.
Assay methods
Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.
Study design
State the method of case selection, including whether prospective or retrospective and whether stratification or matching (for example, by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.
Precisely define all clinical endpoints examined.
List all candidate variables initially examined or considered for inclusion in models.
Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.
Statistical analysis method
Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
Clarify how marker values were handled in the analyses; if relevant, describe methods used for cut-off point determination.

Results
Data
Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the number of patients and the number of events.
Report distributions of basic demographic characteristics (at least age and gender), standard (disease-specific) prognostic variables, and tumour marker, including numbers of missing values.
Analysis and presentation
Show the relation of the marker to standard prognostic variables.
Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (for example, hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analysed. For the effect of a tumour marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.
For key multivariable analyses, report estimated effects (for example, hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.
Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.
If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.
Discussion
Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study. Discuss implications for future research and clinical value

3.10.2 Application of the Altman's checklist

	Tick et al 2010[149]
Introduction	Clearly described
Patients	Clearly described
Specimen characteristics	Not applicable
Assay methods	PTS assessor was blind to outcome of measurement of variables included in model
Prognostic factor measurement	Clearly described
Study design	Clearly described and appropriate
Statistical analysis approach	Clearly described
Data	Partly described – Flow pattern of patients through study was not clearly described. Only number of patients at start of study and end of study described. Total number of patients at each time point during follow up was not presented. Missing data and distribution of demographic characteristics were however reported
Analysis and presentation	Partly described – Results of univariate analysis with corresponding confidence intervals were presented. However, confidence intervals and p-values were not reported for multivariate analysis. Individual effect size of predictor variables in multivariate analysis also not reported. There was discussion on the rationale to include some variables in the models
Discussion	Limitations and implications clearly described and appropriate
Summarised validity	High risk of bias

3.11 Quality assessment of prospective cohort studies with multivariate analysis

3.11.1 Application of the Hayden et al's checklist and blinding to PTS diagnosis

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Bouman et al 2012[150]	Yes	Partly	Yes	Yes	Yes	Yes	Partly	Moderate risk	Flow diagram was used to clearly describe patient flow through study/ 27% loss to follow up /PTS assessors were blind to duplex ultrasound result/ Factors adjusted for not reported

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Chitsike et al 2012[151]	Yes	Yes	NR	Yes	Partly	Yes	Partly	Moderate risk	Blinding not reported but part of larger study that reported blinding/ Important data on possible cofounders like extent of thrombosis not available/ Poor reporting of statistical significance of effect size
Galanaud et al 2013[152]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Low risk	Flow diagram used to clearly describe patient flow through study/ Blinding not reported but part of larger study that reported blinding

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Hach-Wunderle et al 2013[153]	Partly	Yes	NR	Yes	Yes	Yes	Partly	High risk	Reason for contacting only 488 out of 1388 eligible patients from TULIPA register for study not clear/ Flow diagram was used to clearly present patient flow through study/ Too many patients excluded from study/ Blinding not reported/ Poor reporting of statistical significance of effect size
Haenen et al 2001[154]	Yes	Yes	Yes	Yes	Yes	Yes	Partly	Moderate risk	No flow diagram to describe patient flow but well described/ PTS assessors blinded to plethysmography and USS duplex result/ Poor reporting of effect estimate
Haenen et al 2002[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	No flow diagram to describe patient flow but well described/ PTS assessors blinded to plethysmography and USS duplex result

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Kahn et al 2005[155]	Yes	Partly	Yes	Yes	Yes	Yes	Yes	Moderate risk	PTS assessors were blind to thrombophilia status/ 37% lost to follow up
Kahn et al 2008[47]	Yes	Partly	Yes	Yes	Yes	Yes	Yes	Moderate risk	Used flow diagram to present patient flow/ PTS assessors blinded to patient's response to subjective component of the diagnostic scale/ 33% lost to follow up
Latella et al 2010[156]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	No flow diagram to present patient flow but adequately described/ PTS assessors blinded to ECS use and to patient's response to subjective component of the diagnostic scale

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Lopez-Azkarreta et al 2004[157]	Yes	Partly	NR	Yes	Partly	Yes	Partly	High risk	Blinding not reported/ Confounders measured but not reported/ Poor reporting of statistical significance of effect size
Monreal et al 1993[158]	Yes	Yes	NR	Yes	Partly	Partly	Yes	High risk	No flow diagram to describe patent flow but well described/ No blinding reported/ 21% lost to follow up at 5years and 58% by 8 years/Poor reporting of statistical significance of effect size /Adjusted for only age and gender.

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Prandoni et al 1996[159]	Yes	Yes	Yes	Yes	Partly	Yes	Partly	Moderate risk	No flow diagram of patient but flow clearly described/ 31% lost to follow up/PTS assessors blinded to clinical details of patient/Did not report on factors adjusted for/Poor reporting of statistical significance of effect size
Rabinovich et al 2015[168]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Low risk	Flow diagram used to present patient flow/No blinding reported
Roberts et al 2013[160]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Low risk	Flow diagram used to present patient flow/ no blinding reported,
Roumen-Klappe et al 2005[161]	Partly	Yes	Yes	Yes	Yes	Yes	Partly	Moderate risk	Consisted mostly of older patients/No flow diagram to present patient flow but well described /Assessors for PTS were blinded to venous exam result/ Did not give complete details of logistic regression analysis done

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Roummen-Klappe et al 2009[162]	Yes	Yes	Yes	Yes	Yes	Yes	Partly	Low risk	No flow diagram to present patient flow but well described/Assessors for PTS were blinded to venous exam result/ Poor reporting of significance of effect size
Roumen-Klappe et al 2010[163]	Yes	Yes	Yes	Yes	Yes	Yes	Partly	Low risk	No flow diagram to present patient flow but well described/ Assessors for PTS were blinded to venous exam result/ Poor reporting of significance of effect size
Shbaklo et al 2009[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	No flow diagram to describe patent flow but well described/ PTS assessors blind to patient's response to subjective component of scale

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Shrier et al 2009[165]	Yes	Partly	Yes	Yes	Yes	Yes	Partly	Moderate risk	Flow diagram used to present patient flow/ PTS assessors blinded to patient's response to subjective component of the diagnostic scale/ Only 67% of patients completed follow up /Poor reporting of statistical significance of effect size
Stain et al 2005[166]	Partly	Yes	NR	Yes	Yes	Yes	Partly	Moderate risk	Consisted of mostly younger patients/Flow diagram used to present patient flow/ No blinding reported/ Poor reporting of statistical significance of effect size
Ten-Cate Hoek et al 2010[169]	Yes	Yes	Yes	Yes	Yes	Yes	Partly	Low risk	Flow diagram used to present flow of patients through study/Assessor of PTS blinded to findings on Doppler scan/ Did not report on the magnitude of effect size or effect estimates

Author and year	Study participation	Study attrition	Blinding	Measurement of prognostic factors	Measurement and controlling for confounding variables	Measurement of outcomes	Analysis approach	Summarised validity (Risk of bias classified as Low risk/Moderate risk/High risk)	Comments
Tick et al 2008[13]	Yes	Partly	Yes	Yes	Yes	Partly	Partly	High risk	Large sample size/Interviewers blinded to treatment of patients/ Atypical PTS assessment (face to face interview or over phone-subjective symptoms only) / Poor reporting of statistical significance of effect size
Yamaki et al 2010[167]	Yes	Yes	NR	Yes	Unclear	Yes	Yes	Moderate risk	Used flow diagram to present patient flow/ No blinding reported/ Factors adjusted for in multivariate analysis not clear

Key: NR – Not reported (Additional component "Blinding added" to Hayden et al's checklist[140])

Appendix 4: Identification and assessment of the utility of PTS diagnostic methods used in the previously conducted reviews

Methods of PTS diagnosis first used to diagnose PTS by identified primary studies

Browse et al's definition of PTS – This was developed by Browse et al[207] to diagnose PTS in their study. The components of this rating scale included subjective symptoms and objective signs assessed at one time point. A score of one was assigned to aches and pains, and varicose veins; a score of two was assigned to, swelling above the ankle, skin pigmentation and ankle flare; a score of three was assigned to venous claudication; a score of four was assigned to lipodermatosclerosis; and a score of five was assigned to the presence of a venous ulcer. It had a minimum score of zero and a maximum score of 15. Scores were further grouped as mild (zero to three), moderate (four to nine) and severe (10 - 15).

Monreal et al's definition of PTS – Monreal et al[158] diagnosed PTS using an unnamed scoring system devised by Kakkar and Lawrence to detect chronic venous insufficiency in their own study.[43] This rating scale took into account patient symptoms as well as clinical signs. A score of zero was given for absence of symptoms and signs; a score of one was given for minor pain, aches or minor oedema defined as increase in leg or thigh circumference < 2cm; a score of two was given for moderate pain, aching, venular flare or marked oedema defined as increase in leg or thigh circumference > 2cm; a score of three for chronic pain, aching, induration and pigmentation and a score of four for

ulceration. The scale has a minimum score of zero and a maximum score of 10. PTS was said to be absent with a score of zero. A score of one to three was classified as mild PTS and a score of four to 10 was classified as severe PTS.

Mehdipour et al's definition of PTS – In 2009, Mehdipour and colleagues conducted a study on PTS during which they also devised their own method for PTS diagnosis.[198] Clinical and anatomical considerations were given to their definition so that signs of PTS and radiological findings were both considered. Essentially their method combined radiological assessment on Doppler ultrasound and the Widmer classification. PTS was rated mild if there was pitting oedema to mid-calf and venous reflux on Doppler ultrasound, it was rated moderate when there was skin changes such as hyperpigmentation and or lipodermatosclerosis and severe if there was an active ulcer or a healed ulcer.

Sharifi et al's definition of PTS – Sharifi et al added a component assessing patients' symptoms to Mehdipour et al's definition of PTS (described above).[193,199] To make a diagnosis of PTS in the studies by Sharifi et al,[193,199] a patient must have developed at least two new symptoms (leg burning, pain, aches, discomfort, restlessness and tingling) in addition to the signs described under Mehdipour's classification of mild, moderate and severe PTS.

Singh and Masuda's definition of PTS – Singh and Masuda conducted a retrospective study[209] that required patients to be diagnosed with PTS retrospectively. They acknowledged that data available to them did not report on all the details required to use available standardised scales. They therefore improvised and developed a PTS diagnostic criterion for their study which classified PTS into asymptomatic, mild, and

moderate to severe. Mild PTS was defined as a patient having mild pain and or occasional swelling while moderate to severe PTS was defined as moderate pain, chronic swelling or multiple symptoms (slight varicose veins, slight discolouration). A patient was classified as asymptomatic, in the absence of these symptoms.

Widmer et al 1985's definition of PTS – The 1985 study by Widmer and colleagues developed this tool to detect PTS[235] in their study. A score of two was assigned to a patient with signs of corona phlebectatica (dilated veins around the ankle), cyanosis and or a slight difference in leg circumference, a score of three was assigned to a patient with leg oedema, score of four was assigned to skin changes and pronounced circumference difference and a score of seven for the presence of leg ulcer. A total score of greater than 10 indicated the presence of PTS.

Appendix 5: Correlation of PTS diagnostic methods in proportion of PTS diagnosed (systematic review of primary studies)

5.1 Search strategy (EMBASE AND MEDLINE)

	Search terms applied to; EMBASE (1947 – August 2014) MEDLINE (1946 – August 2014)
1.	PTS.ti,ab.
2.	postthrombotic syndrome.ti,ab.
3.	post-thrombotic syndrome.ti,ab.
4.	postthrombotic syndrome/
5.	postphlebitic syndrome.ti,ab.
6.	or/1-5
7.	scale$.ti,ab.
8.	score$.ti,ab.
9.	scoring.ti,ab.
10.	definition$.ti,ab.
11.	classification.ti,ab.
12.	measure$.ti,ab.
13.	questionnaire$.ti,ab.
14.	Villalta or Ginsberg or Brandjes or Widmer or CEAP or VCSS.ti,ab.
15.	or/7-14
16.	6 and 15
17.	limit 16 to "diagnosis (best balance of sensitivity and specificity)" – applied only to EMBASE

5.2 Excluded studies and reasons for exclusion

Excluded studies	Reason(s) for exclusion
Galanaud, J. P., et al. (2012). "Comparison of the Villalta post-thrombotic syndrome score in the ipsilateral vs. contralateral leg after a first unprovoked deep vein thrombosis." Journal of Thrombosis and Haemostasis 10(6): 1036-1042.	C
Gillet, J. L., et al. (2006). "Clinical presentation and venous severity scoring of patients with extended deep axial venous reflux." J Vasc Surg 44(3): 588-594.	A
Kahn, S. R., et al. (2014). "Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial." Lancet 383(9920): 880-888.	C
Kakkos, S. K., et al. (2003). "Validation of the new venous severity scoring system in varicose vein surgery." J Vasc Surg 38(2): 224-228.	A
Kolbach Dinanda, N., et al. (2003) Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane Database of Systematic Reviews	B
Krasowski, G., et al. (2003). "Evaluation of the CEAP classification, as a comparative scale determining the severity of the postthrombotic syndrome	A
Lattimer, C. R., et al. (2013). "Validation of the Villalta scale in assessing post-thrombotic syndrome using clinical, duplex, and hemodynamic comparators." Journal of Vascular Surgery: Venous and Lymphatic Disorders 2(1): 8-14.	A
Meissner, M. H., et al. (2002). "Performance characteristics of the venous clinical severity score." Journal of Vascular Surgery 36(5): 889-895.	A
Monreal, M., et al. (1993). "Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study." Journal of Internal Medicine 233(3): 233-238.	C
Rabinovich, A., et al. (2015). "Inflammation markers and their trajectories after deep vein thrombosis in relation to risk of post-thrombotic syndrome." Journal of Thrombosis & Haemostasis 13(3): 398-408.	C
Roberts, L. N., et al. (2013). "Presenting D-dimer and early symptom severity are independent predictors for post-thrombotic syndrome following a first deep vein thrombosis." British Journal of Haematology 160(6): 817-824.	C
Rodger, M. A., et al. (2008). "Inter-observer reliability of measures to assess the post-thrombotic syndrome." Thrombosis and Haemostasis 100(7): 164-166.	C
Rosfors, S., et al. (2010). "A follow-up study of the fate of small asymptomatic deep venous thromboses." Thrombosis Journal [Electronic Resource] 8: 4.	C
Roumen-Klappe, E. M., et al. (2009). "Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study." Journal of Thrombosis & Haemostasis 7(4): 582-587.	C
Roumen-Klappe, E. M., et al. (2009). "Multilayer compression bandaging in the acute phase of deep-vein thrombosis has no effect on the development of the post-thrombotic syndrome." J Thromb Thrombolysis 27(4): 400-405.	C
Roumen-Klappe, E. M., et al. (2010). "Obesity is related to venous outflow resistance and to the risk of post-thrombotic syndrome." Pathophysiology of Haemostasis and Thrombosis 37: A122.	C

Key: A – Wrong population, B – Systematic review, C - No comparisons between two different PTS diagnostic methods made

5.3 QUADAS 2 checklist (explanation)

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Reference: Whiting, P. F., et al. (2011). "QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies." Ann Intern Med 155(8): 529-536.

5.4 QUADAS 2 checklist application

STUDY	RISK OF BIAS				OVERALL RISK OF BIAS
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	
Gabriel 2004[178]	High	Not clear	NA	Low	Moderate
Jayaraj 2014[251]	High	Low	NA	Not clear	Moderate
Kahn 2006[250]	High	Not clear	NA	Low	Moderate
Kolbach 2005[40]	High	High	NA	Low	High

Appendix 6: Expert opinion on potential prognostic factors and methods of PTS diagnosis (e-Delphi study)

6.1 Participant invite letter

Dear **name of participant**,

As you are an expert in the field of venous thromboembolism, Professor David Fitzmaurice and I would like to invite you to participate in this study in which we aim to identify the prognostic factors that may be associated with the development of post-thrombotic syndrome after deep vein thrombosis of the lower limb.

There is not enough evidence on the prognostic factors that may be associated with the development of post-thrombotic syndrome and there is no gold standard yet for post-thrombotic syndrome diagnosis despite the presence of multiple diagnostic methods. Therefore we rely on the knowledge and experience of professionals like you to help improve the evidence on prognostic factors for post-thrombotic syndrome and post-thrombotic syndrome diagnosis.

Our aims are;

· To identify prognostic factors associated with the development of post-thrombotic syndrome after deep vein thrombosis of the lower limb

· To identify the best method for diagnosing post-thrombotic syndrome from current methods

If you decide to participate, we will ask you to answer 3-5 questions in a survey over 3 rounds. The length of time required to answer the questions will vary across rounds but

it should take no more than 10 minutes to complete questions for each round. Links to questions for each round will be sent out via emails with an interval of 6 to 8 weeks. In the second and third rounds, you will be updated on opinions of other experts in the field and the rationale behind their opinions.

I have attached a participant information sheet which has more details of the study.

If you decide to participate please reply to this email, or email us at hoo115@bham.ac.uk .

If there are colleagues who are also specialists in the field of venous thromboembolism and post-thrombotic syndrome who you think might be able to contribute to this study, please forward this email to them.

Please do not hesitate to contact me if you have any questions.

With kind regards

Halima Olakareem

Post graduate researcher

Public health building

University of Birmingham

Edgbaston campus

B15 2TT

Hoo115@bham.ac.uk

6.2 Information sheet for participant

Title of study

Identification of prognostic factors associated with the development of post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT) of the lower limb – an e-Delphi study

Aims of the study

1. To identify prognostic factors associated with the development of PTS after DVT of the lower limb

2. To identify the best methods for diagnosing PTS

Why you have been invited to participate

We have invited you to participate in this study because you have been identified as an expert in the management of venous thromboembolism. Other experts like you in the field of venous thromboembolism will also be participating in this study. This will include haematologists, clinical nurse specialists, vascular surgeons, general practitioners and interventional radiologists.

How will the study be conducted and what participation involves?

Participation will involve answering a set of questions on 3 occasions as this study will comprise a 3 round survey. Links to questions for each round will be sent to you via emails with an interval of 6 to 8 weeks between rounds. It is very important that you answer the questions as soon as you can, preferably within two week of receiving the

link. The length of time it will take you to answer the questions will vary across rounds, but it should take no more than 10 minutes to complete the questions for each round.

If you do not complete the questions within two weeks of being sent a link, you will be sent a two weekly reminder via email until you are able to complete the questions or until analysis for that round begins, this will be approximately 6 weeks after you have first received the link to the questions.

If we are unable to get responses from you from one round of the survey, you will be contacted for a second round. A similar reminder schedule (two weekly) will be employed the second time. We will not be able to include your input in our analysis if you do not respond to at least two rounds of this survey.

You will receive a summary of our findings at the end of every round. This will reflect the input from you as well as the other participants. These findings will be aggregated to safeguard everyone's anonymity.

It is very important to the success of this study that you complete all the rounds and answer all the questions. If participants drop out of this study either because they feel that other participants do not agree with their opinion or for other reasons, there could be overestimation of how much the final participants have agreed on the issues being discussed. This may in turn compromise the reliability of the results from this study.

At the end of the study, you will be sent a summary of our overall findings via email.

Anonymity and confidentiality

All efforts will be made to ensure participating experts are anonymous to each other. However, because the study will be limited to experts in the United Kingdom within the

field of venous thromboembolism and PTS which is small and as we have employed the snowball technique in identifying experts, there is the risk that you might be identified accidentally. All participants including you will be requested to tick a box before commencing the survey stating that the identity of any participant in this study will be kept confidential if accidentally discovered.

Your responses to this email will be treated in the strictest of confidence.

Your right to withdraw from the study

You have the right to withdraw at any stage of the study, (before or during) at no risk to you by notifying us via email. However please note that each round will last approximately 3 months with data analysis occurring in the last month. You can withdraw your data for each round if you withdraw within the first two months of a round starting. Data can no longer be withdrawn after this time period, as analysis of collated data for that round would have started.

If you withdraw within the first two month of a round commencing, your data for that round will be removed from analysis unless you consent to your data being included in the analysis.

Anticipated benefits of this project

It is hoped that a consensus will be reached on what the prognostic factors associated with the development of PTS are as well as what the best methods for diagnosing PTS is/are from your opinions and that of other experts.

Prognostic factors identified by this method may in turn be used as a set of outcomes in future clinical trials while the method of diagnosis with the highest level of consensus may be advocated for use in clinical practice and research in the future.

Contacts

In the events of any questions, please contact the facilitators at the following address;

Halima Olakareem
School of Public Health
The University of Birmingham
Edgbaston
Birmingham B15 2TT

David Fitzmaurice
Primary care clinical sciences
The University of Birmingham
Edgbaston
Birmingham B15 2TT

Sabi Redwood
School of Public Health
The University of Birmingham
Edgbaston
Birmingham B15 2TT

Thank you

6.3 Round 1 questionnaire

Thank you for taking the time to complete this survey.

The objectives of the survey and what to expect through the survey process are described in the participant information sheet attached to your invitation email.

Please feel free to express your opinions based on your knowledge and experience of post- thrombotic syndrome.

All information you have provided cannot be traced back to you except by the facilitator of this study for feedback purposes.

The survey should take approximately 10 minutes to complete.

1. I consent to participate in this survey after reading the participant information sheet
Yes
No

2. I confirm that I will keep the identity of other participants if accidentally discovered confidential
Yes
No

3. Please state your area of specialty

4. Please provide a brief description of your current employment position

5. Please select your age range
21 or younger
22-34
35-44
45-54
55-64
65 or older

6. Please select your level of expertise in the knowledge of the recognition of post-thrombotic syndrome

Very high

High

Medium

Low

7. Please select your level of expertise in the knowledge of the management of post-thrombotic syndrome

Very High

High

Medium

Low

8. Please provide your name and preferred email address for future correspondence (only the facilitator of this study will have knowledge of these details to facilitate feedback through the e-Delphi rounds)

The questions below are open ended questions

9. Please list factors that may determine whether patients develop post-thrombotic syndrome or not after deep vein thrombosis. For each factor listed please give reasons

10. Please list methods used for diagnosing post-thrombotic syndrome in your current practice.

11. Any further comments and/or remarks (this question does not require a response)

6.4 Round 2 questionnaire

Welcome to Round 2 of the Delphi survey on prognostic factors associated with the development of for Post Thrombotic Syndrome (PTS) after a deep vein thrombosis (DVT) of the lower limb.

Potential prognostic factors and methods of diagnosing PTS listed by respondents from round 1 of the survey are listed below (in descending order of proportions of respondents that have listed them). In addition, potential prognostic factors and methods for diagnosing PTS not explicitly identified by experts, but resulting from a review of the evidence, are also listed.

On the Likert scale, please indicate your level of agreement with the statement on each potential prognostic factor and method for diagnosing PTS. After each statement, you will have an opportunity to make free texts comments in the box provided.

Your details and the information you provide will remain anonymous except to the facilitator of this study who will use this information for feedback purposes only.

The survey should take approximately 10 minutes to complete.

1. Name

Potential prognostic factors listed by respondents:

Below are the potential prognostic factors associated with the development of PTS after a DVT of the lower limb as listed by respondents in round 1 of the e-Delphi study.

Proportions of respondents that have listed the factors are presented in percentages. Please indicate your level of agreement with the statements below.

2. Location and extent of DVT – a proximal DVT / an extensive clot increases the risk of PTS (listed by 82% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

3. A BMI >25 increases the risk of PTS (listed by 45.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

4. Sub-therapeutic anticoagulation during treatment of DVT increases the risk of PTS (listed by 36% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

5. Reduced mobility increases the risk of PTS (listed by 32% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

6. Older Age increases the risk of PTS (listed by 32% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

7. Ipsilateral recurrent DVT increases the risk of PTS (listed by 27% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

8. Recurrent DVT increases the risk of PTS (listed by 27% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

9. Compression therapy reduces the risk of PTS (listed by 27% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

10. Residual vein thrombosis increases risk of PTS (listed by 27% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

11. Poor treatment compliance post DVT including anticoagulation and compression therapy increases the risk of PTS (listed by 23% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

12. Previous ipsilateral varicose veins increases the risk of PTS (listed by 18% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

13. Underlying thrombotic disease such as thrombophilias and antiphospholipid syndrome increases the risk of PTS (listed by 14% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

14. Good quality of initial anticoagulation after DVT reduces the risk of PTS (listed by 14% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

15. A delay before presentation and treatment of DVT increases the risk of PTS (listed by 14% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

16. Longer duration of anticoagulation therapy reduces the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

17. Female gender increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

18. Venous valvular damage /venous reflux increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

19. D-dimer levels; high D-dimer levels post completion of anticoagulation and a high initial D-dimer level post DVT increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

20. Pregnancy increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

21. Previous ipsilateral dermatological conditions increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

22. Arteriosclerosis and other arterial disease which will impair blood supply to the skin increases the risk of PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

23. Smoking increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

24. Intravenous drug users tend to have increased risk PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

25. Infection increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

26. Diabetes increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

27. Persistent DVT symptoms following initiation of treatment (when evaluated 2 to 4 weeks post initiation of treatment) increases risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

28. Previous lymphoedema increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

29. Pre-existing PTS symptoms increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

30. Congenital vascular anomalies increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

31. Systemic thrombolysis after acute DVT reduces the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

32. Reduced calf muscle pump function increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

33. An occlusive thrombi increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

34. Use of hormones increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

35. Multiple asymptomatic DVT increases the risk of PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Other potential prognostic factors from a review of the evidence only:

Presented below are additional factors not mentioned by respondents but identified from a review of the evidence on potential prognostic factors associated with the development of PTS.

Please indicate your level of agreement with the sentences on these factors as well.

Thank you

36. Calf swelling >3cm during index DVT increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

37. An unprovoked DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

38. Loco-regional thrombolysis for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

39. Catheter-directed thrombolysis for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

40. Surgical thrombectomy for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

41. Physical activity as part of index DVT treatment reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

42. Use of inferior vena cava filters during treatment of index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

43. Male gender increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

44. A high thrombosis score on Doppler ultrasound in the first three months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

45. High venous outflow resistance on strain-gauge plethysmography in the first three months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

46. High reflux velocity on Doppler ultrasound increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

47. A high retension index from near-infrared spectroscopy six months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

48. High Villalta scores one month post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

49. Absence of a pathway to assess for PTS risk after DVT increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

50. Cancer increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

51. High levels of CRP at presentation of index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

52. High levels of interleukin 6 at presentation and 4months post index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

53. High levels of ICAM 1 4months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

54. A high near infrared spectrometry venous retension index 6months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Methods of diagnosing PTS used by respondents in current practice

Below are the methods used for diagnosing PTS in the current practice of respondents as listed in round 1 of the e-Delphi survey.

Proportions of respondents that have listed the factors are presented in percentages. Please indicate your level of agreement with the statements below.

55. Subjective clinical assessment – using signs and symptoms is a reliable way of diagnosing PTS (listed by 100% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

56. Doppler ultrasound is a reliable method for diagnosing PTS (listed by 41% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

57. Magnetic resonance venography is a reliable method for diagnosing PTS (listed by 23% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

58. Objective clinical assessments – for example using tape measure to assess swelling of limbs and microlife twin cuff device to measure ankle brachial pressure index is a reliable method for diagnosing PTS (listed by 14% of repondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

59. Villata score is a reliable method of diagnosing PTS (listed by 14% of repondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

60. Specialist advice is a reliable method for diagnosing PTS (listed by 9% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

61. Clinical etiological anatomical and pathophysiological (CEAP) score is a reliable method for diagnosing PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

62. Venous clinical severity score is a reliable method for diagnosing PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

63. Ankle brachial index with Doppler ultrasound is a reliable method of diagnosing PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

64. Venography (ascending venography or descending venography) is a reliable method for diagnosing PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

65. Abdomino-pelvic CT is a reliable method for diagnosing PTS (listed by 4.5% of respondents)

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Other methods for diagnoses of PTS identified from a review of the evidence

Below are additional PTS diagnostic measures not mentioned by respondents but identified from a review of the evidence.

Please indicate your level of agreement with each of the following statements.

66. Venous disability score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

67. Venous segmental disease score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

68. Brandjes score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

69. Widmer classification is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

70. Ginsberg measure is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

71. Ambulatory venous pressure is a reliable method for measuring PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

72. Plethysmography (air plethysmography or photoplethysmography) is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

73. Patient reported outcome questionnaire is a reliable method of diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

74. Any further comments and/or remarks (this question does not require a response)

Thank you for taking the time to complete Round 2.

6.5 Round 3 questionnaire

Welcome to the Round 3 of the e-Delphi survey on prognostic factors associated with development of Post Thrombotic Syndrome (PTS) after a Deep Vein Thrombosis (DVT) of the lower limb.

Potential prognostic factors and methods of diagnosing PTS have been grouped according to levels of agreement from the previous round (explained in detail in your invite email). Statements with low levels of agreement from the previous round have been removed from this round.

This is the final round to get your opinions on potential prognostic factors associated with the development of PTS and the methods of diagnosing PTS for this e-Delphi study.

On the Likert scale, please indicate your level of agreement with the statement on each potential prognostic factor and method for diagnosing PTS. After each statement, you will have an opportunity to make free texts comments in the box provided.

Your details and the information you provide will remain anonymous except to the facilitator of this study who will use this information for feedback purposes only.

The survey should take approximately 10 minutes to complete.

1. Name

Statements on potential prognostic factors with HIGH LEVELS OF AGREEMENT

On the following pages, statements on potential prognostic factors with HIGH LEVELS OF AGREEMENT from the previous round are presented in no particular order.

Please reconsider the statements and indicate your level of agreement with the statements.

Statements on potential prognostic factors with HIGH LEVELS OF AGREEMENT

2. Location and extent of DVT – a proximal DVT / an extensive clot increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

3. A BMI >25 increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

4. Reduced mobility increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

5. Ipsilateral recurrent DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

6. Recurrent DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

7. Residual vein thrombosis increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

8. Poor treatment compliance post DVT including anticoagulation and compression therapy increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

9. Venous valvular damage /venous reflux increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

10. Persistent DVT symptoms following initiation of treatment (when evaluated 2 to 4 weeks post initiation of treatment) increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

11. Previous lymphoedema increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

12. Cancer increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

13. Pre-existing PTS symptoms increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

14. Calf swelling >3cm during index DVT increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

15. Systemic thrombolysis after acute DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

16. Loco-regional thrombolysis for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

17. Catheter-directed thrombolysis for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

18. Physical activity as part of index DVT treatment reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

19. An occlusive thrombi increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

20. Multiple asymptomatic DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Statements on potential prognostic factors with MODERATE LEVELS OF AGREEMENT

On the following pages, statements on potential prognostic factors with MODERATE LEVELS OF AGREEMENT from the previous round are presented in no particular order.

Please reconsider the statements and indicate your level of agreement with the statements.

Statements on potential prognostic factors with MODERATE LEVELS OF AGREEMENT

21. Compression therapy reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

22. Older age increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

23. Sub-therapeutic anticoagulation during treatment of DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

24. An unprovoked DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

25. Previous ipsilateral varicose veins increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

26. Underlying thrombotic disease such as thrombophilias and antiphospholipid syndrome increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

27. Good quality of initial anticoagulation after DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

28. D-dimer levels; high D-dimer levels post completion of anticoagulation and a high initial D-dimer level post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

29. A delay before presentation and treatment of DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

30. Female gender increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

31. Pregnancy increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

32. Intravenous drug use increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

33. Arteriosclerosis and other arterial disease which will impair blood supply to the skin increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

34. Smoking increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

35. Infection increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

36. Diabetes increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

37. Use of hormones increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

38. Congenital vascular anomalies increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

39. Reduced calf muscle pump function increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

40. Surgical thrombectomy for treatment of index DVT reduces the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

41. Use of inferior vena cava filters during treatment of index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

42. Male gender increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

43. High venous outflow resistance on strain-gauge plethysmography in the first 3 months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

44. High reflux velocity on Doppler ultrasound increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

45. A high retension index on near-infrared spectroscopy six months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

46. High Villalta scores one month post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

47. Absence of pathway to assess PTS risk after DVT increases risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

48. High levels of CRP at presentation of index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

49. High levels of interleukin 6 at presentation and 4months post index DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

50. High levels of ICAM 1 4months post DVT increases the risk of PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Statement on methods of PTS diagnosis with a HIGH LEVEL OF AGREEMENT

On the following page, the only statement on method of PTS diagnosis with a HIGH LEVEL OF AGREEMENT from the previous round is presented.

Please reconsider the statement and indicate your level of agreement with the statement.

Statement on methods of PTS diagnosis with a HIGH LEVEL OF AGREEMENT

51. Subjective clinical assessment – using signs and symptoms is a reliable way of diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

Statements on methods of PTS diagnosis with MODERATE LEVELS OF AGREEMENT

On the following two pages, statements on methods of PTS with MODERATE LEVELS OF AGREEMENT from the previous round are presented in no particular order.

Please reconsider the statements and indicate your level of agreement with the statements.

Statements on methods of PTS diagnosis with MODERATE LEVELS OF AGREEMENT

52. Doppler ultrasound is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

53. Magnetic resonance venography is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

54. Objective clinical assessments – for example using tape measure to assess swelling of limbs and microlife twin cuff device to measure ankle brachial pressure index is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

55. Villata score is a reliable method of diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

56. Specialist advice is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

57. Clinical etiological anatomical and pathophysiological (CEAP) score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

58. Venous clinical severity score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

59. Ankle brachial index with Doppler ultrasound is a reliable method of diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

60. Venography (ascending venography or descending venography) is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

61. Abdomino-pelvic CT is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

62. Brandjes score is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

63. Widmer classification is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

64. Ginsberg measure is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

65. Ambulatory venous pressure is a reliable method for measuring PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

66. Plethysmography (air plethysmography or photoplethysmography) is a reliable method for diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

67. Patient reported outcome questionnaire is a reliable method of diagnosing PTS

Strongly disagree

Disagree

Neither agree nor disagree

Agree

Strongly agree

Additional comments:

68. Any further comments and/or remarks (this question does not require a response)

Thank you for taking the time to complete the Round 3 and previous rounds of the e-Delphi survey. We will contact you shortly with the findings of the survey via e-mail.

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