Deep vein thrombosis : diagnostic and prognostic challenges

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Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis

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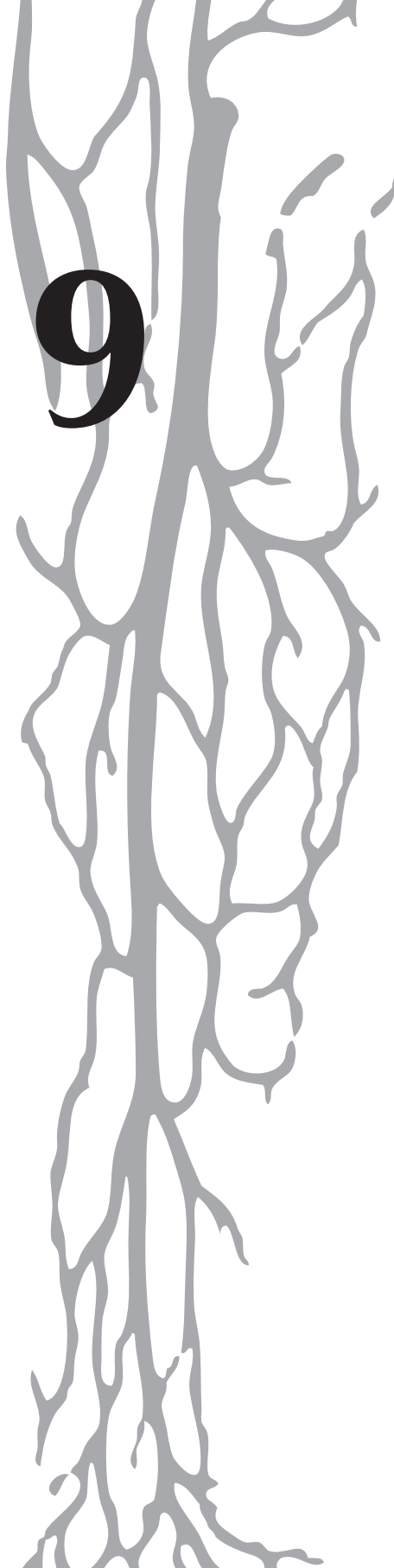

ABSTRACT

Background

Post-thrombotic syndrome (PTS) is a common and potential severe complication of deep venous thrombosis (DVT). Elastic compression stocking therapy may prevent PTS if worn on a daily basis, but stockings are cumbersome to apply and uncomfortable to wear. Hence, identification of predictors of PTS may help physicians to select patients at high risk of PTS.

Aims

To identify ultrasonography (US) parameters assessed during or after treatment of DVT of the leg, that predict post-thrombotic syndrome.

Methods

Systematic review and meta-analysis. Databases were searched for prospective studies including consecutive patients with DVT who received standardized treatment, had an ultrasonography during follow-up assessing findings consistent with vascular damage after DVT, and had a follow-up period of at least 6 months for the occurrence of PTS assessed by a standardized protocol.

Results

The literature search revealed 1156 studies of which 1068 were irrelevant after title and abstract screening by 3 independent reviewers. After full text screening, 12 relevant studies were included, with a total of 2684 analysed patients. Two US parameters proved to be predictive of PTS: residual vein thrombosis, for a pooled Odds Ratio (OR) of 2.17 (95%CI 1.79-2.63) and venous reflux at the popliteal level, for a pooled OR of 1.34(95%CI 1.03-1.75).

Conclusion

The US features reflux and residual thrombosis measured at least 6 weeks after DVT predict post-thrombotic syndrome. Whether these features may be used to identify patients who may benefit from compression therapy remains to be assessed in further studies.

INTRODUCTION

Post-thrombotic syndrome (PTS) is a common complication after deep vein thrombosis (DVT).[1,2] PTS may manifest with several signs and symptoms, ranging from mild pain or itching, to severe and difficult-to-treat venous ulcers.[3] Despite adequate anticoagulation treatment, PTS develops in 20-50% of patients following acute DVT with 5-10% of all PTS cases classified as being severe.[2] Since there are no reference laboratory or imaging tests, PTS is diagnosed only on clinical grounds using one of the available clinical scales.[4] The Villalta scale is the most widely used and is recommended by the International Society on Thrombosis and Haemostasis (ISTH) (**Table 1**).[5] The CEAP classification was originally developed for chronic venous disease, but is also often used for diagnosing PTS (**Table 2**).[6,7]

Table 1. Villalta Scale[33]

	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paraesthesia's	0	1	2	3
Pruritus	0	1	2	3
Clinical Signs				
Pretibial oedema	0	1	2	3
Hyperpigmentation	0	1	2	3
Venous ectasia (venules or varicose veins)	0	1	2	3
Redness	0	1	2	3
Skin induration	0	1	2	3
Pain on calf compression	0	1	2	3
Venous Ulcer		Absent		Present
		Total score		
0-4			*No PTS*	
5-9			*Mild PTS*	
10-14			*Moderate PTS*	
≥15/venous ulcer present			*Severe PTS*	

Table 2. Clinical component CEAP Classification[6,7]

Class	Clinical Signs
0	No visible or palpable signs of venous disease
1	Telangiectasies or reticular veins
2	Varicose veins: distinguished from reticular veins by a diameter of ≥3 mm
3	Edema
4	Changes in skin and subcutaneous tissue secondary to CVD:
4a	Pigmentation or eczema
4b	Lipodermatosclerosis or atrophie blanche
5	Healed venous ulcer
6	Active venous ulcer

Note: CEAP indicates clinical, etiological, anatomic, pathophysiological

The pathophysiology of PTS is not completely understood, although chronic venous hypertension by residual venous obstruction and valvular reflux likely plays a major role.[8,9] Because treatment options for PTS are limited, its management relies on the prevention of its occurrence after DVT. It has been shown that elastic compression stocking (ECS) therapy may prevent PTS, provided patients are compliant to wearing the stocking on a daily base for 2 years.[10,11] Recently, a randomised controlled trial showed that stopping ECS after one year in compliant patients was not non-inferior to continuing ECS therapy for two years. In other words, ECS therapy should be ideally continued for two years after DVT.[12] However, stockings are costly, cumbersome to apply, and can be hot, constricting, and itchy. One randomized trial clearly indicated that adherence to prescribed daily ECS therapy in daily clinical practice is poor, which ultimately resulted in ineffective PTS prevention.[13] Hence, identification of predictors of PTS may help physicians to target PTS prevention to those patients with high risk of PTS who are likely to benefit most of the ECS therapy. Several risk factors for PTS at the time of the DVT diagnosis have been identified, such as proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[1] Whether ultrasound-measured chronic vein obstruction by residual clots and/or valvular reflux may be helpful in better predicting PTS remains controversial. Therefore the primary aim of this systematic review and meta-analysis was to identify ultra-sonographic parameters, assessed during or after treatment of proximal DVT of the leg, that predict post thrombotic syndrome.

METHODS

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) criteria.[14] All parts of

this study were performed by 3 independent reviewers (C.E.A.D., G.C.M. and G.M.), any disagreements were resolved by a fourth reviewer (F.A.K.)

Information sources and literature search

A literature search was performed of Pubmed, Embase, Web of Science, Cochrane, CINAHL and ScienceDirect in Oktober 2015. This search was updated in November 2016. The search strategy included (the synonyms of) the terms: 'deep venous thrombosis', 'post-thrombotic syndrome' and 'ultrasonography'. Full articles, abstracts and letters in the English language were eligible for this study.

Study selection

Studies were first screened by title and abstract. After excluding non-relevant studies, full-text articles were analysed for eligibility. All prospective studies including consecutive patients with DVT who received standardized treatment and had an ultrasonography during follow-up assessing findings consistent with vascular damage after DVT were eligible when they had a follow-up period of at least 6 months and assessed the occurrence of PTS. Occurrence of PTS had to be evaluated by a standardized protocol, i.e. the Villalta, Brandjes or CEAP score. Exclusion criteria were impossibility to create two by two tables of ultrasonography abnormalities and PTS, based on the study set-up, or the use of trombolytic therapy and/or thrombectomies. In articles randomizing patients between thrombolytic therapy and oral anticoagulation treatment, only the oral anticoagulation treatment group was included in the study.

Data extraction

From each selected study, all extracted information was completed in pre-defined tables. The following information was extracted: 1) study characteristics: author, year of publication, study design, inclusion and exclusion criteria; 2) patient characteristics: number at baseline, number with complete follow-up, age, gender, history of VTE and presence of malignancy; 3) DVT characteristics: modality of diagnosis at baseline (whole leg/2 point CUS or venography), proximal (femoropopliteal) DVT or distal DVT(calf veins) and unprovoked or provoked VTE; 4) treatment of DVT: therapy, duration, use of compression stockings and percentage of adherence to compression therapy; 5) ultrasound measurements consistent with vascular damage after DVT: modalities, timing after initial thrombosis, 6) Outcome measure: duration of follow-up, PTS scoring system protocol, timing PTS scoring and number of patients with and without PTS combined with ultrasound abnormalities during follow-up (for completing two by two tables). If creating the two by two tables should be possible based on the study set-up but the needed data were not reported in the articles, authors were contacted and asked for additional data.

Quality assessment

Included studies were assessed for risk of bias with the QUIPS (Qualitiy in Prognosis Studies) tool.[15] This tool has been developed to evaluate the risk of bias in studies on prognostic factors based on 6 areas: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. All areas were scored as low risk of bias, moderate risk of bias or high risk of bias. Studies with one area with high risk of bias or with ≥2 areas of moderate risk of bias were overall scored as 'moderate risk of bias'. Studies with low risk of bias in all areas or ≤1 area with moderate risk of bias were overall scored as 'low risk of bias'.

Data synthesis and analysis

Patients who were lost to follow-up were excluded from the analysis. Odds ratio's (OR) were calculated to assess the relationship between the different ultrasound measurements consistent with vascular damage and the occurrence of post-thrombotic syndrome during follow-up. Data from the 2 by 2 tables were entered in Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. To assess study heterogeneity Cochran's chi-square test and the I^2 test for heterogeneity were used. The chi-square test is used to assess if the differences in results are by chance alone. I^2 calculates the percentage of the variability in the effect estimates that is due to heterogeneity rather than sampling error.[16] Statistically heterogeneity was considered present for a chi-square of $P<0.10$ and $I^2>50\%$. The presence of publication bias was evaluated using funnel plot analysis. Several sensitivity analysis were performed: for studies with a low risk of bias versus moderate risk of bias; studies with ultrasound assessment < 12 months after DVT versus ≥ 12 months after DVT and studies including only patients with proximal DVT

RESULTS

Study selection

With the literature search, 1156 potentially relevant studies were identified and screened for eligibility. Reasons of exclusion of 1068 studies after title and abstract screening are shown in **Figure 1**. Eighty-eight studies were retrieved for full text evaluation. After reading full text, 77 studies were excluded: 4 studies with a retrospective design, 6 studies with a follow-up less than 6 months, 2 studies in which DVT was not adequately diagnosed at baseline, 3 studies based on post-hoc analysis of a patient cohort already included in the meta-analysis, 19 were congress abstracts showing insufficient data on study design and outcome, 10 studies did not perform ultrasonography during follow-up, 24 studies did not have a standardized assessment of PTS and 9 studies did not

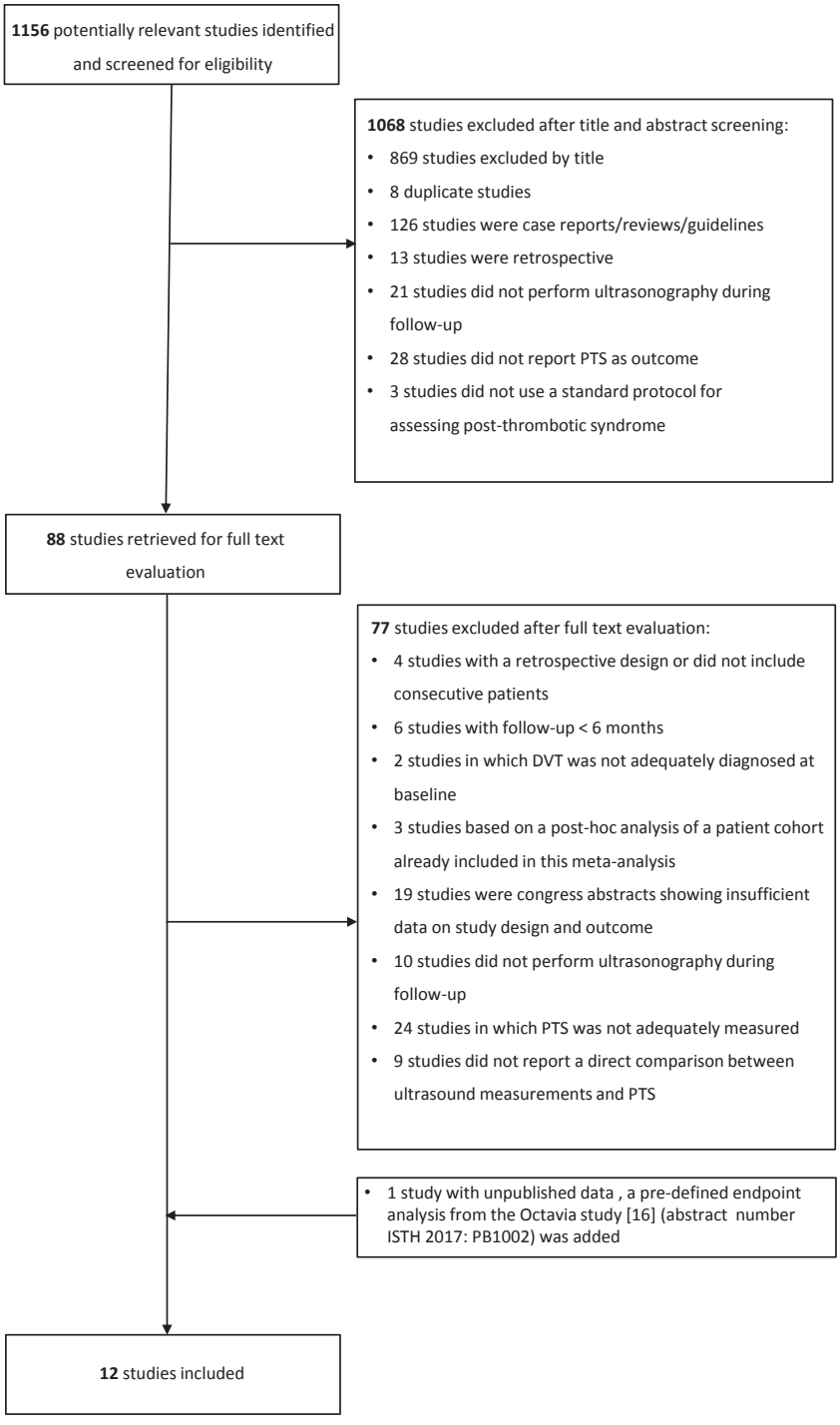

Figure 1. Flow-chart of study selection

report a direct comparison between ultrasound measurements and PTS. One study with unpublished data, a pre-defined endpoint analysis from the Octavia study (abstract number ISTH 2017: PB1002) was added to the list of included articles.[17] Finally, a total of 12 studies fulfilled all inclusion criteria and none of the exclusion criteria.[17-28] For 4 of these 12 studies, additional data was requested from the authors to complete the 2 by 2 tables, which was provided by two,[18,23] leaving 10 studies for the final meta-analysis.

Quality and patient characteristics of included studies

All included studies were prospective cohort studies including consecutive patients, diagnosed with DVT at baseline by compression ultrasonography. The quality of each selected study assessed by the QUIPS tool is presented in **Table 3**. The patient characteristics of the studies included in the meta-analysis are shown in **Table 4**. A total of 2684 patients were included with a mean age varying between 48 and 68 years. The percentage of male gender varied between 36% and 64%. Four [17,19,20,27] of the 10 studies included 8-19% of patients with a history of VTE. The percentage of patients with malignancy ranged between 0% and 12%.[17,19,25-28] Eight studies reported the number of patients with idiopathic DVT, which ranged between 16% and 55%.[17-21,23,25,28] Five studies included only patients with a proximal DVT.[17,18,20,23,26] Overall, 2374 patients (88%) had a proximal DVT, and 310 patients (12%) had a distal DVT. The duration of anticoagulation therapy ranged between 3 and 18 months. Nine out of 10 studies reported prescription of elastic compression stockings.[17-19,21,23,25-28] Three studies reported the percentage of adherence to the stockings, ranging from 52.2% to 88.4% (details table 4).[17,19,25]

Assessment of ultrasound abnormalities

During follow-up, compression ultrasound was performed in 2510 (94%) of the patients. The time between DVT diagnosis at baseline and follow-up ultrasound varied between 6 weeks,[25] 3 months,[20] 6 months[26-28]) and 12 months[17,19] (**Table 5**). In one study the timing of ultrasound was dependent on the treatment duration: ultrasound was performed 6 weeks after stopping anticoagulation treatment with variable total treatment duration.[21] Different ultrasound measurements were performed including reflux, patency, residual vein thrombosis and 'the thrombosis score'. Reflux was defined as a valve closure time >0.5 seconds,[18,26-28] > 1second[17,19,25] or >1.5 seconds[21] after calf or thigh compression. Compression was accomplished by a Valsalva manoeuvre,[19] or performed by manual compression of the calf for at least 10 seconds followed by sudden release[17,19,21] or by using a compression unit.[18,25-28] Patency was defined as flow in the pelvic and femoral vein and complete compressibility of the femoral vein.[18] Residual vein thrombosis was defined as the persistence of thrombotic material resulting in a diameter of 4 mm or more,[20,26] or when a previously thrombosed deep venous segment was incompletely compressible.[21] The thrombosis score was based on the number of veins with throm-

bosis and the degree of occlusion, measured as diameter of the clot during maximal compression, giving 1 point when the diameter was 2-3 mm, 2 points for 4-5 mm and 3 points when ≥ 6 mm.[23,25] Since the measurements of patency and the thrombosis score are comparable with that of residual vein thrombosis, these 2 terms were combined in the 'residual thrombosis' group for the purpose of this meta-analysis, with 'absence of patency' or a thrombosis score ≥1 defined as presence of residual thrombosis. The incidence of residual vein thrombosis in the included studies ranged between 10% and 75%. The reported incidence of reflux ranged between 12% and 78%. Two studies reported on the combination of residual thrombosis and reflux, with an incidence of 14% and 22% respectively.[26,28]

Table 3. Study quality assessment (QUIPS Tool)

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall
Haig *et al.*[18]	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Latella *et al.*[19]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Mol *et al., unpublished data*[17]	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Prandoni *et al.*[20]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Roberts *et al.*[21]	🟡	🔴	🟡	🟢	🟢	🟢	🟡
Roumen-Klappe *et al.**[22]	🟡	🔴	🟡	🟢	🟢	🟢	🟡
Sartori *et al.*[23]	🟢	🟢	🟡	🟢	🟢	🟢	🟢
Ten Cate-Hoek*[24]	🟢	🟡	🔴	🔴	🟢	🟢	🟡
Tick *et al.*[25]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Vedovetto *et al*[26]	🟡	🟡	🟢	🟢	🟢	🟢	🟡
Yamaki *et al. (2011)*[27]	🟡	🟡	🟢	🟢	🟢	🟢	🟡
Yamaki *et al.* (2016)[28]	🟢	🟡	🟢	🟢	🟢	🟢	🟢

🟢: low risk of bias; 🟡: moderate risk of bias; 🔴: high risk of bias. * not included in final meta-analysis because data for two by two tables could not be extracted from the manuscript and could not be provided by the authors.

Table 4. Patient characteristics of the included studies

Study	Total study population	Mean age (years)	Percentage of men	Percentage VTE in history	Percentage Malignancy	Idiopathic/ risk factor (n/n)	Distal/ proximal DVT (n/n)	Mean duration of anticoagulation therapy	Compression stocking use	Percentage adherent to stockings
Haig *et* al.[18]	99 (standard therapy group)	50	62	Exclusion criterion	NR	26/73	0/99	6 months	Yes	NR
Latella *et al.*[19]	387	56.3	51	19	12.4	211/176	154/233	34.1 weeks	Yes	52.2% (not further specified)
Mol *et al* [17]	518	57	59	14	9.6	215/303	0/518	6 months	Yes	88.4% (7 days/week in the first year)
Prandoni *et al*[20].	869	63	58	12	Exclusion criterion	444/425	0/869	At least 3 months	NR	NR
Roberts *et al*[21].	114	47.8	52.6	Exclusion criterion	Exclusion criterion	47/67	57/57	3 months (distal DVT)/6 monhts (proximal DVT)	Yes	NR
Sartori *et al.*[23]	59	62.8	56	Exlusion criterion	Exclusion criterion	22/36	0/59	3 months	Yes	NR
Tick *et al.*[25]	111	48	53	Exclusion criterion	5.0	34/77	18/93	6 months	Yes	67% (≥ 6 days/week)
Vedovetto *et al.*[26]	290	67.7	49	Exclusion criterion	14	Not reported	0/290	6 months	Yes	NR
Yamaki *et al.* (2011)[27]	121	65.8	42.1	5	15	Not reported	29/92	at least 3 months	Yes	NR
Yamaki *et al.* (2016)[28]	116	61.3	36	Exclusion criterion	13	19/97	52/64	18 months	Yes	NR

Note: NR: not reported

Table 5. Outcome of included studies

Study	Total study population (n)	CUS performed (n)	Time between DVT and follow-up ultrasound	Collected ultrasound abnormalities	CUS positive for residual thrombosis (n (%))	CUS positive for reflux (n (%))	CUS positive for residual thrombosis and reflux (n(%))	Time between DVT and PTS scoring	PTS score	PTS diagnosed (n (%))
Haig *et al.*[18]	99	95	6 months	Reflux, patency	45 (47)	74 (78)	NR	24 months	Villalta	53 (55)
Latella *et al.*[19]	387	233	12 months	Reflux		109 (47)	NR	24 months	Villalta	116 (50)
Mol *et al* [17]	518	516	12 months	Residual vein thrombosis, reflux	220 (43)	354 (69)	NR	24 months	Villalta	84 (16)
Prandoni *et al.*[20]	869	869	3 months	Residual vein thrombosis	429 (49)		NR	36 months	Villalta	343 (39)
Roberts *et al.*[21]	114	114	6 weeks after stopping anticoagulation therapy	Reflux, residual vein thrombosis	56 (49)	19 (17)	NR	Median: 11 months	Villalta	61 (54)
Sartori *et al.*[23]	59	59	90 days after DVT	Thrombosis score	44 (75)		NR	Day 180	Villalta	13 (22)
Tick *et al.*[25]	111	97	6 weeks	Reflux and thrombosis score	64 (66)	29 (30)	NR	1 year	CEAP	49 (51)
Vedovetto *et al.*[26]	290	290	6 months	Residual vein thrombosis and popliteal valve incompetence	75 (26)	36 (12)	42 (14)	3 years	Villalta	119 (41)
Yamaki *et al. (2011)*[27]	121	121	6 months	Reflux, residual thrombosis	12 (10)	31 (26)	NR	Mean 66.4 months	CEAP	25 (21)
Yamaki *et al.* (2016)[28]	116	116	6 months	Reflux, residual thrombosis	21 (18)	16 (14)	26 (22)	6 years	Villalta	19 (16)

Note: NR: not reported

Assessment of PTS

The time between DVT at baseline and scoring of PTS differed between the studies, ranging from 6 months,[23] 11 months[21] and 12 months[17-19,25] to 3[26] and 6 years,[27,28] respectively. Most (8 out of 10) studies used the Villalta score for diagnosing PTS. The diagnosis PTS was established when the Villalta score was ≥5 points at 1 visit[17,18,21,28] or 2 consecutive visits.[19,20,23,26] The symptoms were scored by the patient and the signs by the treating physician. In one study a full colour visual guide was used to score the clinical signs.[17] In another study, the doctors who scored the clinical signs of the Villalta score were blinded to the symptoms reported by the patient and the ultrasound abnormalities.[19] Two studies used the CEAP score to diagnose PTS. The first study defined a CEAP score ≥3 as diagnostic for PTS;[25] the second used a cut-off of ≥4.[27] The incidence of PTS in the included studies ranged between 16% and 55%. Overall, 882 out of all 2510 patients (35%) with a complete follow-up developed PTS.

Outcome of the meta-analysis

The results of 9 studies measuring residual thrombosis were pooled, as were 8 studies measuring reflux as predictive value of PTS and the results of 2 studies measuring the combination of residual thrombosis and reflux. The meta-analysis showed that residual vein thrombosis measured 6 weeks to 12 months after DVT was predictive for PTS with an OR of 2.2 (95%CI 1.8-2.6) (**Figure 2a**). From 966 patients with residual thrombosis, a total of 421 (44%) developed PTS, compared with 343 (26%) of 1311 patients without residual thrombosis for a positive likelihood ratio (LR+) of 1.53 (95%CI 1.4-1.7) and negative likelihood ratio of (LR-) of 0.70 (95%CI 0.6-0.8). The heterogeneity between these studies was high as indicated by an I^2 of 65% and a Chi^2 of P=0.004. Funnel plot analysis showed no indication for publication bias.

Sensitivity analyses including studies with measurement of residual thrombosis <12 months after DVT showed an even higher predictive value with an OR of 2.5 (95%CI 2.0-3.1), with an I^2 of 49% and Chi^2 of P=0.06. Sensitivity analysis of studies with a low risk of bias, moderate risk of bias and studies including only patients with proximal DVT showed similar predictive values.

Reflux was predictive for PTS as well, with an OR of 1.3 (95%CI 1.03-1.7) (**Figure 2b**). From a total of 668 patients with reflux, 218 (33%) developed PTS. From 909 patients without reflux, 306 (34%) developed PTS, for a LR+ of 0.97 (95% CI 0.9-1.1) and LR- of 1.02 (0.9-1.1). These studies showed less heterogeneity with an I^2 of 33% and a Chi^2 of p=0.17. Funnel plot analysis was not indicative for publication bias (Appendix II). Sensitivity analyses of studies that assessed reflux at 12 months after DVT, studies with low risk of bias and studies including only patients with proximal DVT showed similar results, but with less heterogeneity.

The meta-analysis on the combination of residual thrombosis and reflux showed an OR of 2.35 (95%CI 1.35-4.11), with an I^2 of 37% and Chi^2 of p=0.21 (**Figure 2c)**. From the patients with both residual thrombosis and reflux, 32 (47%) of 68 developed PTS. Of the patients without residual thrombosis or reflux, 106 of 338 (31%) developed PTS, for a NNT of 6.3, LR+ of 1.73 (95%CI 1.1-2.7) and LR- of 0.89 (95%CI 0.8-1.0).

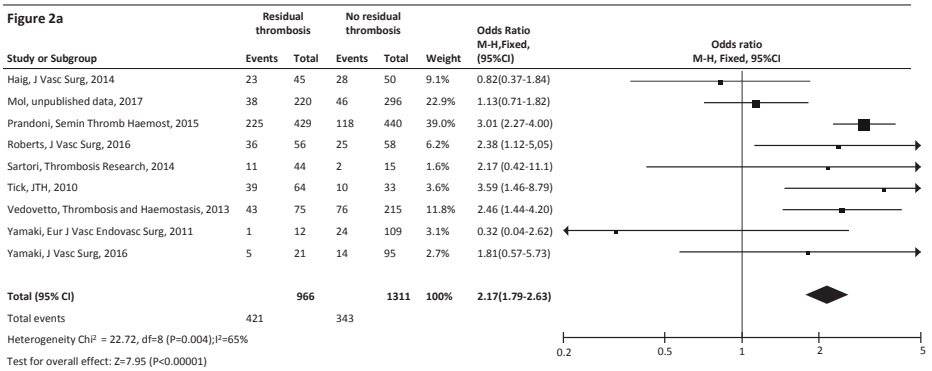

Figure 2a. Forrest plot of meta-analysis of residual thrombosis measured during or after treatment of acute DVT as predictive factor for PTS

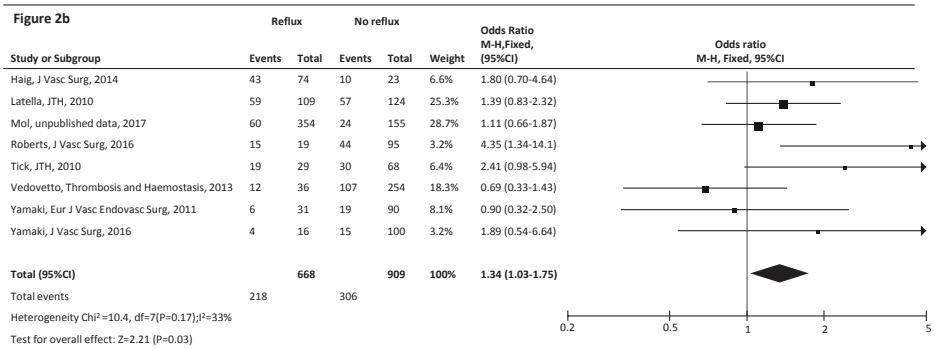

Figure 2b. Forrest plot of meta-analysis of reflux measured during or after treatment of acute DVT as predictive factor for PTS

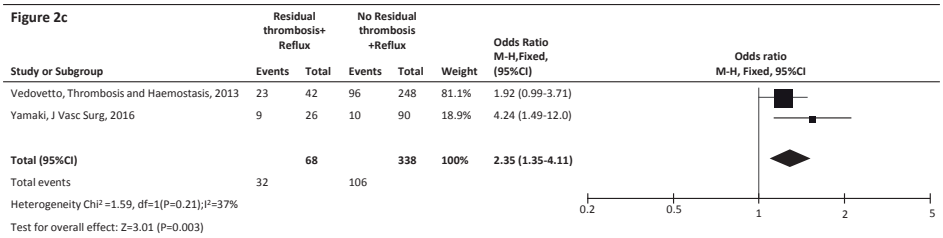

Figure 2c. Forrest plot of meta-analysis of the combination of residual thrombosis and reflux during or after treatment of acute DVT as predictive factor for PTS.

DISCUSSION

Despite heterogeneity between the selected studies, this systematic review and meta-analysis showed that both residual thrombosis and reflux, measured by ultrasonography during or after treatment of acute DVT, is predictive of PTS. The combination of residual thrombosis and reflux showed the largest predictive value (OR 2.35 [95%CI 1.3-4.1]), although this was based on only 2 studies with a total of 406 patients. Moreover, residual thrombosis showed a good predictive value with an OR of 2.17 (95% CI 1.8-2.6) based on meta-analysis of 2307 patients, and reflux showed a predictive value to a lesser extent with an OR of 1.34 (95%CI 1.0-1.7) based on 1577 patients.

Our findings are biologically plausible. After DVT, recanalization of the thrombosed veins occurs by a combination of fibrinolysis, thrombus organization and neovascularization.[9] Inflammation plays a major role in case of incomplete recanalization, leading to residual vein thrombosis. This remaining thrombus causes damage to the venous valves,[29] resulting in incompetent valves and reflux. Both reflux and residual thrombosis are associated with a higher risk of venous hypertension.[8] Although the pathophysiology of PTS is not fully understood yet, venous hypertension, causing an absence of pressure decrease in the venous system of the legs during walking, which plays a major role in the cause of PTS development.[30]

What are the potential implications of our findings? Our meta-analysis supports the practice of using ultrasonography to identify patients at higher risk of PTS. These patients could thus be counselled with regard to PTS prevention. One cohort study investigated a tailored stocking therapy in 125 patients after acute DVT based on ultrasound findings. Ultrasound was performed one week before planned cessation of anticoagulation therapy.[24] If ultrasound showed no reflux and the Villalta score was ≤4, patients were allowed to discontinue their elastic compression therapy. In case of reflux or a Villalta score ≥5 points, patients were advised to continue this therapy for a total of 2 years. This study showed an overall incidence of PTS of 21% (95%CI 14-29), which is very much comparable to the reported incidence in another randomized controlled trial, suggesting that this strategy was safe.[11] An additional outcome study however, randomizing patients between stopping ECS therapy in case of absence of reflux and/or residual thrombosis and continuing ECS for two years is needed to confirm this hypothesis.

Some limitations should be considered for the interpretation of the results of this meta-analysis. Firstly, the heterogeneity between these studies was large, especially for the studies measuring residual vein thrombosis ($I^2$of 65% and Chi^2 of P=0.004). Therefore, this meta-analysis is not conclusive. The heterogeneity can be explained by the differences in study design and study populations. Especially treatment duration and timing of ultrasound examinations as well as the criteria for a PTS diagnosis were different between all studies. Moreover, the ultrasound measurement techniques and

PTS score thresholds varied among the studies. Sensitivity analyses of studies which assessed residual vein thrombosis <12 months after DVT showed a slightly lower heterogeneity: I^2 49%, Chi^2 p=0.06. However other sensitivity analyses did not result in a lower heterogeneity. Secondly, we found in our meta-analysis an absolute small predictive value of reflux for PTS, leading to a high NNT of 100. Although there were only two studies which assessed the combination of the presence of both residual thrombosis and reflux as predictive factors, these showed the largest predictive value (OR: 2.35 (95%CI 1.35-4.11)) but a relatively low LR+ of 1.73 (95%CI 1.1-2.7). Whereas our findings may encourage patients with residual thrombosis and reflux to be adherent to ECS therapy, it remains unclear whether ECS therapy can be safely stopped in patients without both residual thrombosis and reflux.

Further studies are needed to establish the role of residual vein thrombosis and reflux after acute DVT in predicting PTS, in conjunction with other known risk factors for PTS being proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[1] Ideally, these risk factors should be investigated in a large study and summarized in a clinical prediction score. Two of such scores, consisting of readily accessible baseline characteristics have recently been suggested, but both lack adequate external validation.[31,32]

In conclusion, our systematic review and meta-analysis showed that residual vein thrombosis and reflux, assessed by ultrasound during or after treatment of acute DVT are predictive for PTS. Even with the heterogeneity between the included studies, the shown associations may be helpful in the identification of patients at high risk for PTS.

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