ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Μεταπτυχιακή Διπλωματική Εργασία

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απαιτήσεων για την απόκτηση του

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Επιβλέπων:

Αθανάσιος Γιαννούκας, Καθηγητής *Αγγειοχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*

Τριμελής Συμβουλευτική Επιτροπή:

1. Αθανάσιος Γιαννούκας, Καθηγητής *Αγγειοχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*
2. *Μιλτιάδης Ματσάγκας,* Καθηγητής *Αγγειοχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*
3. Γεώργιος Κούβελος, Επίκουρος Καθηγητής *Αγγειοχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*

Αναπληρωματικό μέλος:

Ελένη Αρναούτογλου, Καθηγήτρια *Αναισθησιολογίας, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*

ΕΥΧΑΡΙΣΤΙΕΣ

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Abstract

Background:

Post-thrombotic syndrome (PTS) is a common complication after deep vein thrombosis (DVT) of the lower limbs affecting patient's quality of life (QoL). Although anticoagulation is considered the standard treatment of DVT, the role of oral anticoagulants in PTS prevention is still controversial. This study aims to present existing evidence of different oral anticoagulation modalities for the treatment of DVT leading to the risk reduction of PTS.

Methods and Materials:

A systematic review of the literature was undertaken according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) searching in Pubmed, Cochrane, MEDLINE and CENTRAL databases including studies reporting oral anticoagulation for prevention of PTS after acute episode of DVT.

Results:

A total of 59.199 patients (in 8 studies, 6 retrospective and 2 randomized controlled studies) received treatment with oral anticoagulation and followed up for the development of PTS. In all studies rivaroxaban was compared to initial LMWH and treatment continued with warfarin. Among patients, 19.840 received rivaroxaban and 39.377, warfarin. The mean age of the patients was 56.5±7 y.o. (56.6 for rivaroxaban vs 57.8 for warfarin) and 48.4% were females. Mean duration of anticoagulation was comparable between treatments groups (6 months for rivaroxaban vs 7.8 months for warfarin). The mean follow up of patients was 33.5 months (range 12-61 months). The incidence of PTS was higher in warfarin group compared to rivaroxaban group (44.6% vs 28.9%) (p=<0.001). In addition patients treated with warfarin developed more severe PTS compared to patients treated with rivaroxaban (6.4% vs 3.7%) (p=0.024). Overall 11% of rivaroxaban treated patients and 12% of warfarin treated patients developed recurrent VTE event (p=0.32).

Conclusions: In conclusion, our study shows that treatment with rivaroxaban after acute DVT was associated with reduced risk of PTS compared to warfarin during mid-term follow up. Patients being treated with warfarin developed more severe PTS compared to patients treated with rivaroxaban.

Key words: Deep vein thrombosis, direct oral anticoagulants, post-thrombotic syndrome, oral anticoagulation, rivaroxaban, warfarin

Introduction

Post- thrombotic syndrome (PTS) is a frequent complication of deep vein thrombosis (DVT) of the lower limbs.[1] PTS refers to chronic clinical manifestations of venous insufficiency following proximal DVT (popliteal vein and above) affecting patient's quality of life (QoL) and reducing productivity. [2] PTS is associated with reduced ability to work with considerable consequences for both the patient and heath care systems.[3] Almost half of the patients with DVT (20-50%) will develop PTS , despite conventional anticoagulation therapy, with a combination of different signs and symptoms of variable severity.[4] Most often occurs within 24 months after an acute DVT episode, although some studies shown that the incidence increases up to 10 y. after the index event.[5,6]

1.1 Pathophysiology

The pathophysiology of PTS is attributed to venous hypertension due to valvular reflux caused by damaged valves and/or venous obstruction deriving from persistent residual vein thrombosis (RVT) and acute inflammatory response after acute venous thrombosis (Fig 1). [1] Vedovetto et al, reported that the relative risk of developing PTS was 1.9 (95% confidence interval (CI): 1.4–2.6) in patients with RVT alone, 1.1 (95% CI: 0.7–1.9) in patient with valvular reflux alone and 1.8 (95%CI: 1.3–2.7) in patients with both RVT and valvular reflux.[7] This study suggests that the lack of recanalization is a strong factor for PTS development, while valvular reflux has a limited effect. Another important factor to PTS development is the chronic inflammation affecting the venous wall and the microcirculation. Excessive capillary leakage and impairment of skin nutrition leads to skin changes and ulceration in more severe forms of PTS.[8] Inflammation also delays thrombus resolution and cause fibrosis in the vein wall.[9,10,11]

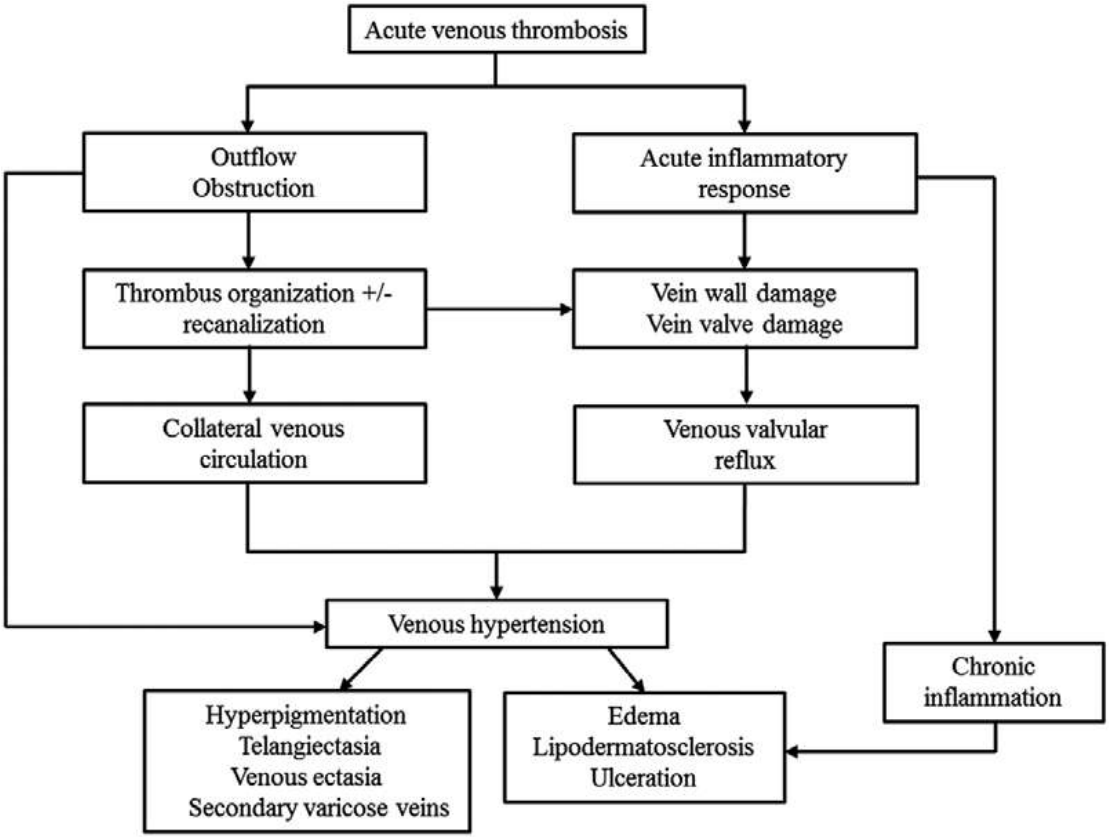


Fig 1. Pathophysiology of PTS

1.2 Risk factors for PTS

The following risk factors are associated with PTS development :

1) Proximal DVT (Most often ilio-femoral thrombosis followed by popliteal and infrapopliteal) [1]
2) Previous ipsilateral DVT, [1]
3) Iliofemoral vein obstruction, [12,13]
4) Increased body mass index, [14,15]
5) Recurrent DVT and obstruction of the collateral circulation, [15]
6) Sub-therapeutic anticoagulant therapy, poor International Normalized Ratio (INR) control, [14,16]
7) Increased -IL-6, CRP and ICAM-1 , [17,18]
8) Extensive clot on presentation, [19]

9) Less than 50% clot regression at 6months, RVT, [14,19]

10) Venous filling index (VFI) > 2.5 ml/sec at 6 months, [19]

11) <60% of the outflow volume depleted after 2 sec on presentation and/or at 6 months. [19]

Risk models for predicting PTS are described in Table 1. [20,21,22]

Rabinovich Model		Amin Model		Méan Model	
Points	**Risk of PTS (%)**	**Points**	**Risk of PTS (%)**	**Points**	**Risk of PTS (%)**
0	6	0-2	10	0-3	24
1	13	3-4	20	4-5	38
2	16	5	40	6	80
3	25				
4	30				

Méan model includes 11 symptoms (heaviness, cramps, pain, pain during calf compression, paresthesia, pruritus, edema, hyperpigmentation, erythema, skin induration, venous ectasia) and each of them is awarded with 1 point.

Rabinovich Model		Amin Model		Méan Model	
Category	Points	Category	Points	Category	Points
BMI > 35	2	Age > 56	2	Age ≥ 75	1
Iliac vein thrombosis	1	BMI > 30	2	Prior varicose vein surgery	1
Villalta scale score in moderate/severe range at baseline	1/2	Varicose veins	4	Multi-level thrombus	1
		Iliofemoral DVT	1	Number of leg symptoms and signs (up to 11)	1 per symptom/sign
		Provoked DVT	1	Concomitant NSAID/antiplatelet	1
		History of DVT	1		
		Smoking	1		
		Female gender	1		

Table 1. PTS risk prediction models [23]

1.3 Symptoms and signs of PTS

The signs and symptoms of PTS include limb edema, various degrees of pain, heaviness, cramps, fatigue, itching, venous claudication, varicose veins due to venous stasis and skin changes.[24] Skin changes are hyperpigmentation, venous eczema, lipodermatosclerosis and in more severe forms of PTS, venous ulceration (Fig 2). Symptoms are provoked by standing position or walking and reduce by rest and elevation of the leg. Patients can experience similar symptoms as an acute DVT. In the exacerbation of PTS the limb is warm, painful with edema and redness. In some patients can present as venous claudication.[25]

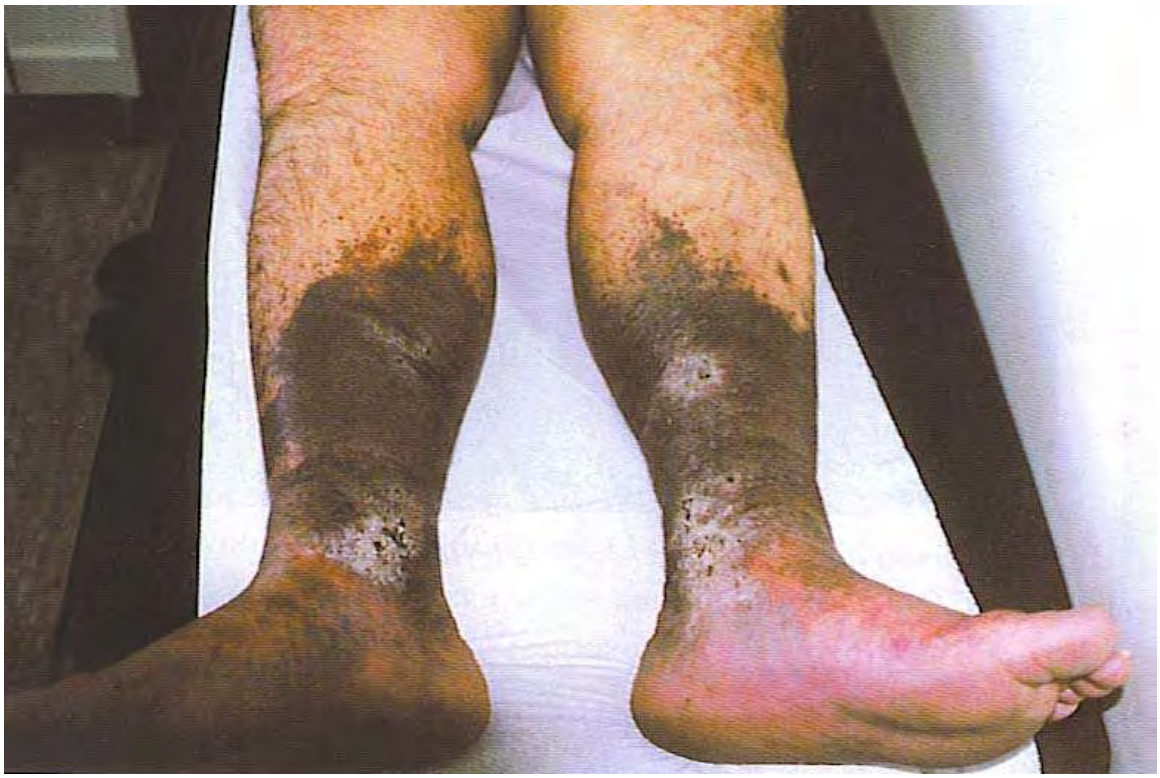


Fig 1. Skin changes in patient with PTS

1.4 Diagnosis of PTS

No standard criteria exist for PTS diagnosis. PTS diagnosis should be generally attributed when signs and symptoms occurs after the acute episode of DVT has passed (after 6 months). [26]

Numerous scores have been used to diagnose PTS. Specifically developed tools to PTS diagnosis are: Villalta scale [27], Brandjes scale [28], and Ginsberg measure [29]. Also Clinical- Etiological- Anatomic- Pathophysiological classification (CEAP)[30], Venous Clinical Severity Score (VCSS) [31], and Widmer scale [32] are used for PTS diagnosis, although these scores are typically developed for chronic venous disease.

1.4.1 Villalta Scale

Is the commonest scoring system used for diagnosis and grading of PTS in clinical studies (Table 2). It's incorporates the assessment of 5 venous symptoms and 6 signs as well as the presence of ulcer in a limb previous affecting from DVT. [27] When the score is >5, PTS is considered present (Fig 3). The Villalta scale is recommended by the International Society on Thrombosis and Haemostasis for diagnosis and grading of PTS.[26]

Severity of PTS (range 0- 33 points)

SCORE (points)	PTS severity
<5	no PTS
5-9	mild
10-14	moderate
>14	severe
Ulcer	severe

Symptoms/clinical signs	*None*	*Mild*	*Moderate*	*Severe*
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent			Present

Table 2. Villalta scale

1.4.2 Brandjes scale

The Brandjes scale, combines subjective symptoms and objective signs (Table 3). [28] Each sign and symptom is scored one point, and venous ulcer with 4 points. PTS is present when the score is ≥3.

PTS severity

Score (points)	PTS Severity
>3	Moderate
>4	Severe

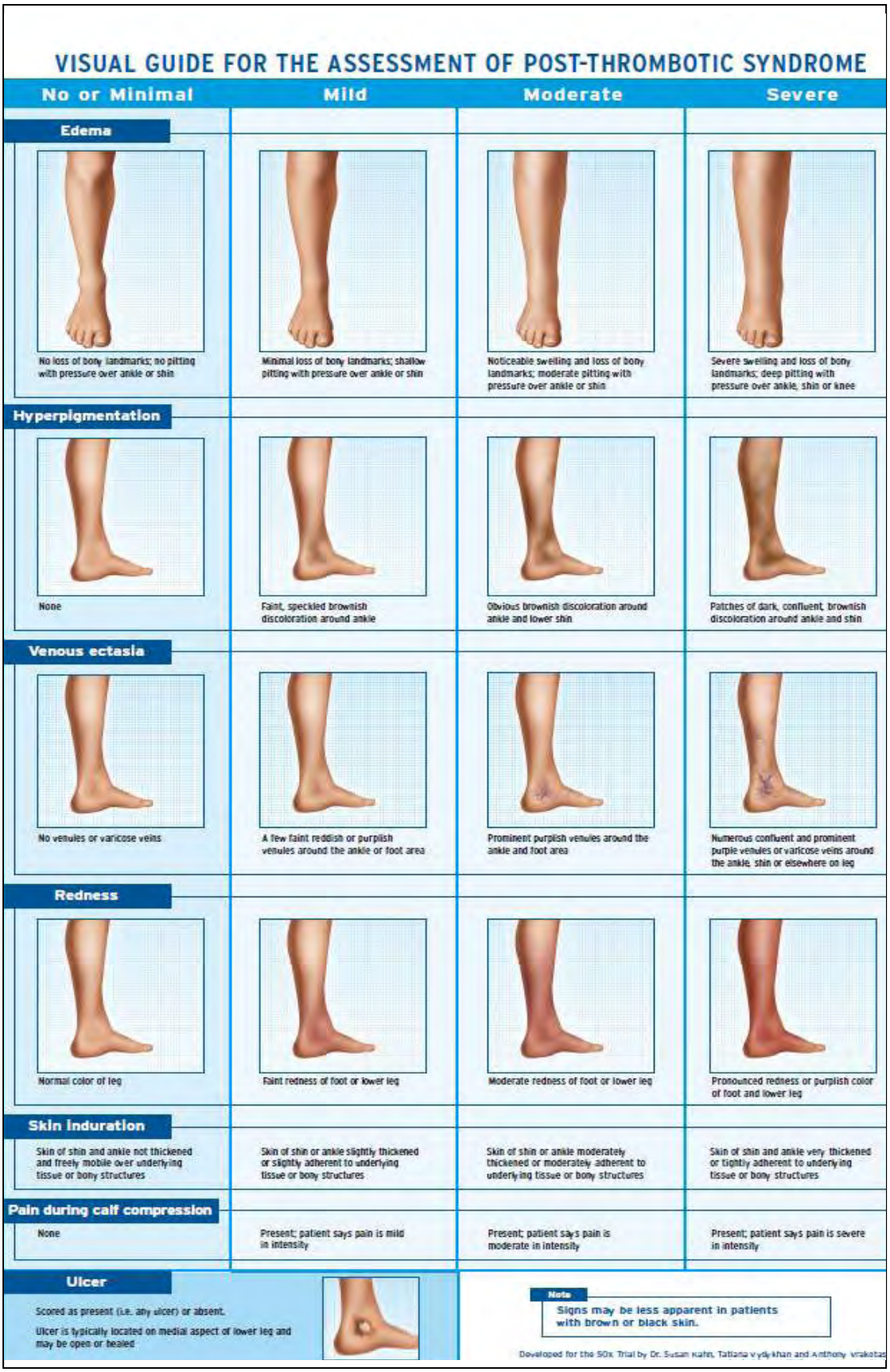


Fig 3

Symptoms	Score
Symptoms (Mild to Moderate PTS)	
Calf pain (spontaneous)	1 point
Thigh pain (spontaneous)	1
Calf pain on standing/walking	1
Thigh pain on standing/walking	1
Edema	1
Heaviness	1
Symptoms (Severe PTS)	
Pain	1
Calf edema	1
Daily activities Impairment	1
Signs (Mild to Moderate PTS)	
Circumference of the calf increased by 1 cm	1
Circumference of the ankle increased by 1 cm	1
Hyperpigmentation	1
Venectasia	1
Varicose veins	1
Phlebitis	1
Signs (Severe PTS)	
Circumference of the calf increased by 1 cm	1
Hyperpigmentation, Venectasia	1
Venous Ulceration	4

Table 3. Brandjes scale

1.4.3 Ginsberg measure

According to the Ginsberg measure PTS is defined by the presence of persisting daily leg pain and swelling for at least 30 days in addition to valvular incompetence and occurs at least 6 months after an acute episode of DVT. [29] Symptoms and signs exacerbated after walking or standing and are relieved by rest and leg elevation. Symptoms need to be accompanied by documented valvular incompetence in order patients to be diagnosed with PTS. Although Ginsberg measure does not grade PTS severity, it correlates well with quality of life scores.[33]

1.4.4 Clinical -etiological -anatomical -pathophysiological (CEAP) Classification

The CEAP classification categorizes venous disease according to clinical, etiological, anatomical and pathophysiological aspects (Table 4). [30] Although CEAP classification was developed to diagnose chronic venous disease (CVD), several studies in the past, have been used CEAP for PTS diagnosis. Additionally CEAP classification does not grade PTS severity. [34]

Table 4. Clinical Etiological Anatomical Pathophysiological Classification (CEAP)

CEAP classification	
Clinical classification	
C0	No visible or palpable signs of disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophic blanche
C5	Healed venous ulcer
C6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Etiologic classification	
Ec	Congenital
Ep	Primary
Es	Secondary (post-thrombotic)
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic	
Pr	Reflux
Po	Obstruction
Pr, o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

1.4.5 Venous Clinical Severity Score (VCSS)

VCSS combines CEAP classification with additional criteria such as severity of symptoms and signs, usage of compression therapy, number and duration of ulcers (Table 5).[31] PTS is absent when the score is ≤3 and as present when the score is ≥8 .

1.4.6. Widmer Classification

The Widmer classification was developed in 1985. CVD is classified into 3 classes (class I: edema, class II: white skin atrophy or lipodermatosclerosis and class III: ulcer). [32,35] Additional is used for PTS diagnosis and to assess the effectiveness of compression therapy. [32,35]

Table 5. VCSS

Attribute	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain	None	Occasional	Daily	Daily limiting
Varicose Veins	None	Few	Confined to calf or thigh	Involves calf and thigh
Venous Edema	None	Limited to foot/ankle	Extends above ankle/below knee	Extends to knee and above
Skin Pigmentation	None	Limited, to perimalleolar	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 calf
Inflammation	None	Limited, to perimalleolar	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 calf
Induration	None	Limited, to perimalleolar	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 calf
No. Active Ulcers	None	1	2	>3
Active Ulcer Size (largest active)	None	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Ulcer Duration (longest active)	None	<3 months	>3 mo but <1 yr	Not healed for >1 year
Compression Therapy	None	Intermittent use of stockings	Wears stockings most days	Fully compliance: stockings

Scales	Clinical signs included?	Patient symptoms included?	Specific for PTS
CEAP	Yes	No	No
VCSS	Yes	Yes	No
Widmer	Yes	No	No
Brandjes	Yes	Yes	Yes
Ginsberg	Yes	Yes	Yes
Villalta	Yes	Yes	Yes

1.4.7 Imaging examinations for PTS diagnosis

Duplex ultrasonography (DUS) must be performed in every patients with signs and symptoms of PTS in order to exclude an acute episode of DVT or to seek evidence for a previous episode. The deep veins of the lower limbs are investigated for lack of compressibility or presence of valvular incompetence.[35,36] Others imaging techniques includes non invasive magnetic resonance and computed tomography, and invasive such as intravascular ultrasound and venography especially when iliac vein obstruction is suspected.

1.5 Prevention of PTS

Pharmacological or mechanical thromboprophylaxis is recommended to prevent PTS.[37] Appropriate duration and intensity of anticoagulation therapy prevents recurrent DVT and occurrence of PTS. [38] When Vitamin K Antagonist (VKAs) is administrated, regular international normalized ratio (INR) monitoring to avoid sub-therapeutic levels, is recommended to reduce the risk of PTS. [39]

1.5.1 Compression therapy for prevention of PTS

Compression therapy increases venous return and reduces ambulatory pressure.[40] Additionally, helps in ulcer healing by reducing the levels of vascular endothelial growth factor and TNF-a. [41] Compression modalities include elastic compression stockings (ECS), bandaging and intermittent pneumatic compression. ECS has been considered a mainstay for PTS prevention. [38] Only one randomized placebo-controlled trial (SOX trial), found no significant benefit of ESC on PTS prevention. [42] In accordance to this study the American College of Chest Physicians recommends against routinely usage of compression stockings for PTS prevention after an acute episode of DVT (Grade 2B). [43] In patients with symptoms, a trial of ECS is often justified.[43] The SOX trail was criticized for its methodology as the compliance of patients in ESC usage was not recorded. A sub- study of the RCT, IDEAL-DVT,

reported that, the usage of ECS, reduces the risk of residual venous obstruction and the risk of PTS. [44]

1.5.2 Anticoagulation for PTS prevention

Patients with venous thromboembolism (VTE) are treated with anticoagulants in order to prevent clot extension and embolization. [43] Anticoagulation also reduces the risk of PTS development. [45] The latest PTS guidelines, do not recommend a particular anticoagulant over another, although the quality and type of anticoagulation may influence the risk of PTS. [39]

1.5.2.1 Vitamin- K Antagonists (VKAs)

For more than half a century, VKAs have been recommended as the standard treatment for DVT. [46] VKAs inhibit the synthesis of coagulation factor II, VII, IX and X (Fig 4). Numerous studies have documented that, the quality of VKA treatment plays an important role in PTS development. [16,47] Sub-therapeutic anticoagulation with VKAs has been related with a 3-fold higher risk of PTS in patients who had an INR less than 2.0 for more than 50% of the treatment duration. [16,47] About 30% of the patients, especially in the first weeks of treatment have sub-therapeutic INR . [16,47]

1.5.2.2 Direct oral anticoagulants

Direct oral anticoagulants (DOACs) have become the new standard treatment for VTE. [43] DOACs can be given in fixed doses without routine monitoring. The following DOACs are licensed for VTE treatment: dabigatran, which inhibits thrombin, and rivaroxaaban, edoxaban and apixaban, which inhibits FXa (Fig 4). The main characteristics of DOACs are described in table 6. The latest guidelines by the American College of Chest Physicians (ACCP), recommends DOACs over VKAs for the treatment of VTE (Grade 2B) in patients without cancer.[43] Theoretically, DOACs may also reduce the incidence of PTS compared to VKA, due to their more reliable dosing and predictable pharmacodynamics. It remains unknown whether DOACs, are equivalent to low molecular weight heparins (LMWH) with respect to PTS prevention. Nevertheless, little is known regarding the role of DOACs, with respect to PTS prevention as in most of the studies that investigated the use of DOACs for DVT therapy, PTS prevention was not an outcome.

	Dabigatran	Rivaroxaban	Apixaban	Edoxapan
Mechanism of Action	FIIa inhibitor	FXa inhibitor - both free and Prothrombinase-bound FXa	FXa inhibitor - both free and Prothrombinase-bound FXa	FXa inhibitor - both free and Prothrombinase-bound FXa
Half-time	15-17h	5-9h Age >80y.o: 11-13h -	8-15 h	10-14 h
T-max	2 h	2.5-4 h	1-3 h	1-2 h
Binding to plasma proteins	35%	95%	87%	80%
Elimination	Renal 80%	Renal 66%	Renal 27%	Renal 35%
	Hepatic 20%	Hepatic/Faecal 28%	Faecal 46-56% Hepatic 2-3%	Hepatic/Faecal 46-56%
Quantitative assay	dTT or ECT	Anti-FXa assay	Anti-FXa assay	Anti-FXa assay
Reversal agents	Idarucizumab - humanized, monoclonal	Andexanet alfa - modified Factor Xa molecule that bind to FXa inhibitors		
	Ciraparantag- synthetic small molecule	Ciraparantag- synthetic small molecule		
Comments	CrCl<30ml/min	CrCl <15ml/min	CrCl <15ml/min	CrCl <15ml/min
Contraindications		Liver impairment	Liver impairment	Liver impairment

Table 6. Main characteristics of DOACs

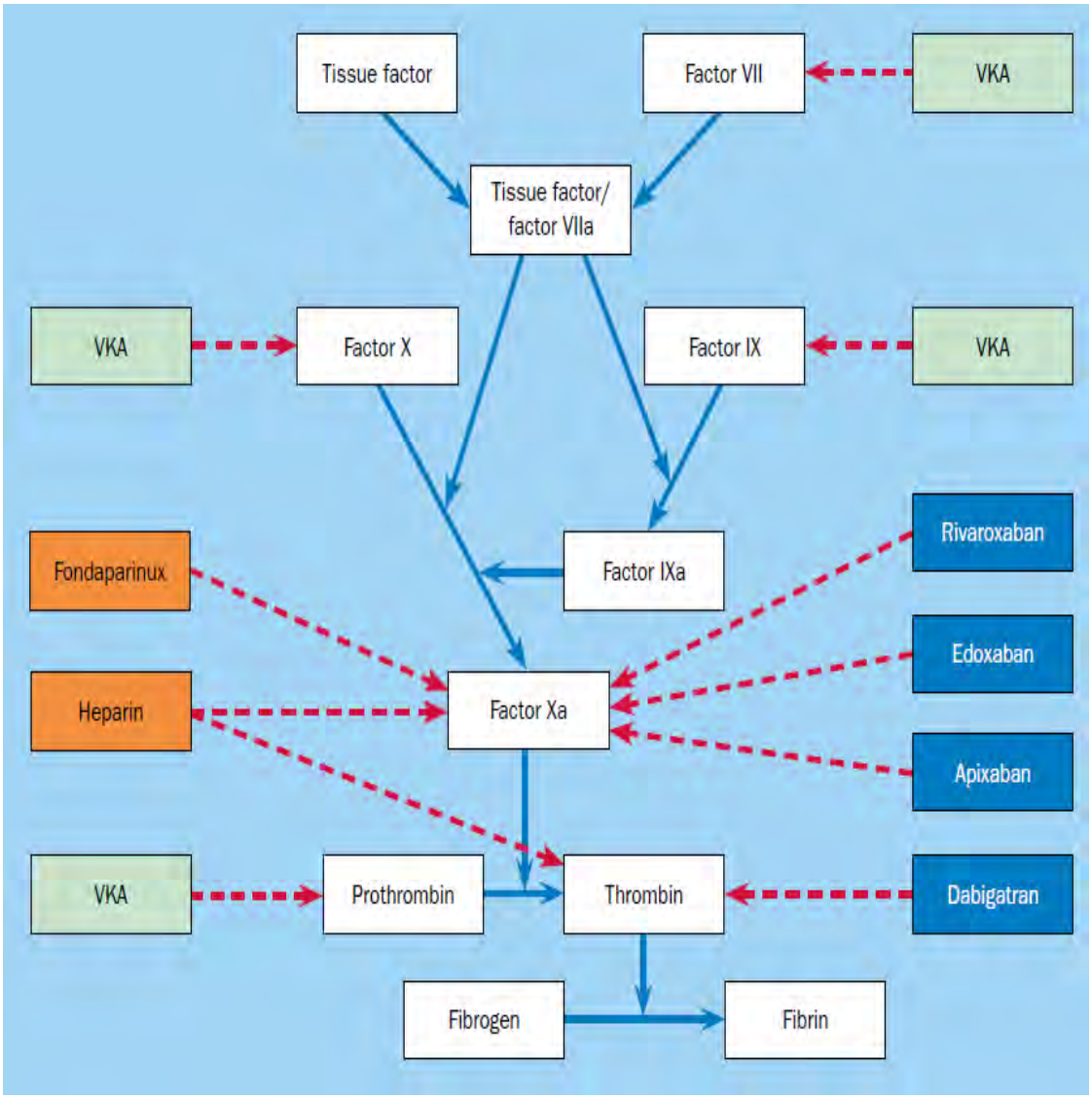


Fig 4. Anticoagulants and their targets in coagulation cascade

Table 7. Comparison of DOACs with VKAs [48]

	Warfarin	DOACs
Drug interactions	Many	Some interaction with CYP3A4 and P-glycoprotein inhibitors (see main text)
Dosing	Once daily	May require twice daily (apixaban, dabigatran)
Dietary restrictions	Requires consistent level of vitamin K intake[12]	None
Onset/offset of action	Slow	Quick – removes need for heparin bridging and simplifies periprocedural management
Reversal agents	Well-established, effective reversal agents (vitamin K, prothrombin complex concentrates)	Idarucizumab for dabigatran. No reversal agent currently licensed for factor Xa inhibitors (but in development)
Dependence on renal function	None	Contraindicated in severe renal failure

1.5.2.3 Low Molecular Weight Heparins

LMWHs are polysulphated glycosaminoglycans derived from unfractionated heparin by enzymatic or chemical depolymerisation. The molecular weight is on average 4-5 kDa (range 2-9 kDa). [49,50] LMWH inhibits factor Xa over thrombin (Fig 4). [49,50] Fondaparinux is a synthetic pentasaccharide, which binds antithrombin (Fig 4). It has a molecular weight of 1.7 kDa and 700 U/mg anti-Xa activity , which is 7-fold higher than that of LMWHs. [50]

LMWHs have anticoagulant and anti-inflammatory properties.[51,52,53] Experimental studies have shown that LMWHs reduces venous wall inflammation, [51] enhances endothelisation [52] and reduces fibrosis[53] and these anti-inflammatory properties could have a role in preventing PTS. Hull et al [54], compared long term LMWH (≥3 months) with VKAs for DVT treatment and showed a more favored recanalization and lower incidence of venous ulceration with LMWHs. Another study which compared tinzaparin to VKAs showed 23% reduction in signs and symptoms of PTS at three months. [55]

1.5.3 Thrombolysis and Endovascular Therapies

Systemic (ST), pharmacomechanical (PCDT) and catheter-directed thrombolysis (CDT) thrombolysis are techniques that aim in removal of thrombus.[56] All these techniques aimed the “open vein” theory in which an earlier and more complete thrombus removal improves venous outflow, preserve valve and decrease venous hypertension.[57,58] However, the evidence of the above techniques for PTS prevention is insufficient to support its routine use in all patients with DVT.[38,59]

ST has been related with an increased risk of bleeding, especially intracranial haemorrhage. [60] During CDT a thrombolytic agent is administrated, direct at the place of thrombosis , while special designed devices is used to macerate and aspirate the thrombus.[61] With the use of smaller amount of fibrinolytic, CDT aims to reduce the thrombus load and the risk of bleeding. In the CaVenT trial, including patients

with iliofemoral vein thrombosis, PTS occurred in 43% of the CDT group and 71% of the control group at 5 years follow up. [62] Bleeding complications occurred in 9.6% of the patients.[63] In the ATTRAC trial, patients with proximal DVT were randomized to PCDT or anticoagulation alone. The study did not demonstrate any significant difference in the rates of PTS at 24 months, although more bleeding complications occurred in the PCDT group. [64] Nevertheless, the study showed that the severity of PTS was reduced in patients with PCDT. [65] The CAVA trial randomized patients with proximal DVT to ultrasound-accelerated CDT or anticoagulation alone. [66] PTS at one year occurred in 29% of the patients allocated to CDT treatment and in 35% of the patients receiving standard anticoagulation alone with no difference in QoL measures. The study concluded that PCDT does not reduce the risk of PTS, 1 year after acute iliofemoral DVT.

1.6 Treatment of PTS

ECS are the cornerstone of PTS treatment. [39] The goals of ECS usage is symptoms relief (particularly limb swelling) and improvement of daily activities. Usually, 20–30 mmHg graduated ECS are recommended with progression to 40 mmHg if not effective. Venous-return assist devices can be performed in patients that are unresponsive to ECS.[23] Lifestyle interventions include weight loss, physical exercise, moisturizing creams and elevation of the limb at rest. [23] Physical exercises improve calf muscle pump function and reduce residual venous refill index. Weight loss reduces intra-abdominal pressure and thus reduces venous hypertension. [14] Elevation of legs enhances microcirculatory flow and aids venous drainage by reducing hydrostatic pressure. [68] Venoactive drugs are commonly used to treat chronic venous disease symptoms, although, data supporting their use in PTS is limited. The most recent Cochrane review shows that venoactive drugs are not superior to placebo or ECS. [69,70]

Interventional techniques (endovascular, open and/or hybrid procedures) may be considered in selected group of patients with more severe PTS. [39] Possible

interventions include iliac vein stenting, saphenopopliteal or saphenotibial bypass, femoro-femoral bypass, valve reconstruction, great saphenous vein ablation or stripping for reflux, and hybrid procedures.[71]

Chapter 2

2. 1 Aim

PTS is a common complication after DVT of the lower limbs affecting patient's quality of life. While anticoagulation is the standard treatment of DVT, the role of oral anticoagulants in PTS prevention is still controversial. This study aims to present existing evidence of different oral anticoagulation modalities for the treatment of DVT leading to the risk reduction of PTS.

2.2 Materials and Methods

2.2.1 Literature search strategy

We conducted a comprehensive search of the literature including Pubmed, Cochrane Library, Embase, Web of Science between January 1, 1980 and June 1, 2020. The P.I.C.O model (Table 8) was used to find the relevant evidence in the literature.[72] The following keywords were used for our search "post-thrombotic syndrome" and "oral anticoagulation" or "post-thrombotic syndrome" and "direct oral anticoagulants" or treatment of deep vein thrombosis". All the associated studies based on the title and abstract were primarily selected, followed by a secondary selection taking into account the full text of publications. To identify further articles a manual screening of the reference lists of selected articles was also undertaken.

2.2.2 Study selection

Two investigators (CK and PN) independently searched for eligible studies. Selected abstracts were subsequently reviewed to see if they meet the inclusion criteria. Duplicate data were examined for similarities, and if necessary, they excluded.

Inclusion criteria were:

1) original studies (case-control or randomized control studies)
2) studies including patients undergoing treatment for DVT with oral anticoagulants

Exclusion criteria were:

1) case reports

2) review articles

3) studies including catheher-directed thrombolysis for the treatment of DVT

4) studies which did not report the outcome of interest (PTS)

5) language other than English

6) ongoing trials, without final results.

P	Patient, Population or Problem	Patients after DVT
I	Intervention, Prognostic factor or Exposure	Treatment with oral anticoagulation
C	Comparison or Intervention (if appropriate)	Among Vit-K antagonists and Direct oral anticoagulants (DOACs)
0	Outcome you would like to measure or achieve	Incidence and severity of PTS
	What type of questions are you asking?	Are DOACs effective treatment in the prevention of PTS? Do DOACs reduce the severity of PTS?
	Type of study you want to find	Any study reporting the incidence of PTS after treatment of deep vein thrombosis with oral anticoagulation

Table 8. P.I.C.O. model

2.2.3 Data extraction and quality assessment

The extracted information included publication date, sample size, patient's demographics, duration of treatment and follow up, incidence of proximal DVT, incidence of unprovoked DVT, recurrent VTE events, incidence and severity of PTS.

The primary outcome was the incidence of PTS and secondary outcome the severity of PTS.

This systematic review was performed according to PRISMA guidelines.[73]

2.3 Statistical analysis

Comparisons among rivaroxaban and warfarin were undertaken in terms of VTE recurrence, incidence of PTS and severity of PTS. Data were analyzed using descriptive and inductive methods. Nominal variables were presented as frequency and relative frequency, while for scale variables we calculated mean values and standard deviation. For the fitting in the normal distribution, we used the Kolmogorov-Smirnov test. Mean value inter-group differences were assessed with independent sample t-test and ANOVA, while intra-group differences were assessed with repeated measures ANOVA. A p-value <.05 was considered significant. Statistical analysis was performed by SPSS 22.0 for Windows software (IBM Corp, Armonk, NY).

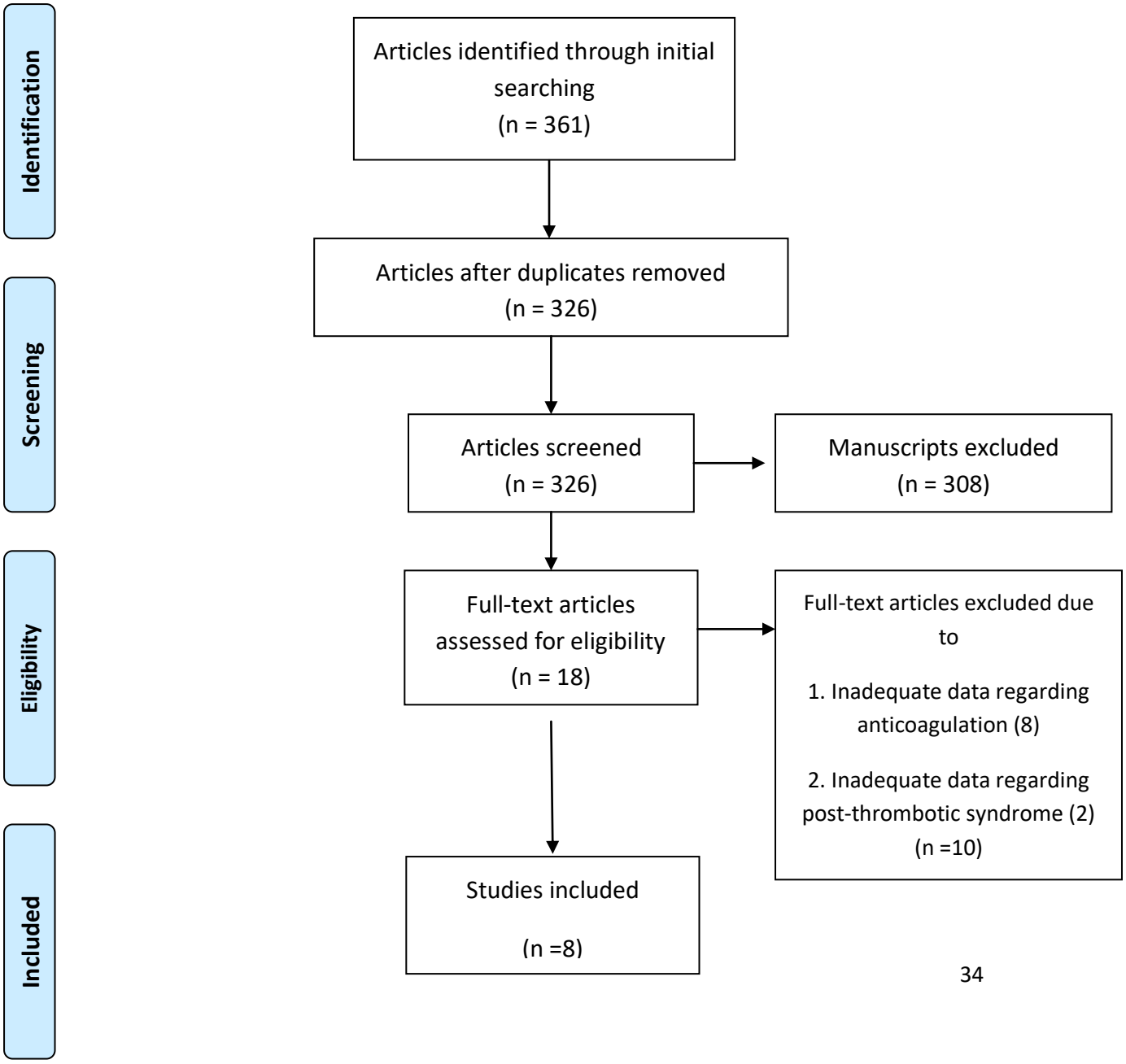
Chapter 3

3.1 Results

3.1.1 Study selection

A total of 361 papers were identified. 18 articles were assessed full for eligibility. Only 8 studies (6 retrospective and 2 randomized controlled studies) met the criteria for inclusion in the review. [74-81] Figure 5 highlight the detailed literature search according to PRISMA guidelines.

Fig 5. Prisma flow diagram



3.1.2 Baseline characteristics

A total of 59.199 patients received treatment with oral anticoagulation and followed up for the development of PTS. In all studies rivaroxaban was compared to initial LMWH and treatment continued with warfarin (table 9). Table 10 shows the baseline characteristics for each study. Among patients, 19.840 received rivaroxaban and 39.377, warfarin. The mean age of the patients was 56.5±7 y.o. (56.6 for rivaroxaban vs 57.8 for warfarin) and 48.4% were females. Mean duration of anticoagulation was comparable between treatments groups (6 months for rivaroxaban vs 7.8 months for warfarin). The mean follow up of patients was 33.5 months (range 12-61 months).

3.1.3 Efficacy outcomes

Efficacy outcomes are summarized in table 11. Five studies recorded the incidence of VTE recurrence. [74,75,76,80,81] Overall 11% of the patients treated with rivaroxaban and 12% of the patients treated with warfarin developed recurrent VTE event (p=0.32). The incidence of PTS was higher in warfarin group compared to rivaroxaban group (44.6% vs 28.9%) (p<.001). In addition patients treated with warfarin developed more severe PTS compared to patients treated with rivaroxaban (6.4% vs 3.7%) (p=.024).

Table 9. Summary of studies characteristics

Authors	Journal	Publication Date	Study Design	Comparison
Cheung W et al [74]	Thrombosis Haemostasis	2016	RCT post-hoc	Rivaroxaban vs Warfarin
Jeraj L et al [75]	Thrombosis Research	2017	Retrospective	Rivaroxaban vs Warfarin
Coleman C et al [76]	Clinical and Applied Thrombosis/ Heamostasis	2018	Retrospective	Rivaroxaban vs Warfarin
Soogard M et al[77]	The American Journal of Medicine	2018	Retrospective	Rivaroxaban vs Warfarin
Ulte K et al [78]	Thrombosis Research	2018	Retrospective	Rivaroxaban vs Warfarin
de Athayde Soares R et al [79]	Surgery	2019	RCT	Rivaroxaban vs Warfarin
Pradoni P et al [80]	Internal and Emergency Medicine	2020	Retrospective	Rivaroxaban vs Warfarin
Ferreira T et al [81]	Vascular Pharmacology	2020	Retrospective	Rivaroxaban vs Warfarin

Abbreviations: RCT, randomized controlled study

Table 10. Summary of patient's characteristics

Authors	Female/ Male	Mean Age	Treatment duration	Proximal DVT	Unprovoked DVT	Diagnosis of PTS	Follow up
Cheung W							
Rivaroxaban (n=162)	71/91	54.9±3	6 m	92 (57%)	101 (62%)	Villalta score	60 m
Warfarin (n=174)	68/106	55.6±2	12 m	117 (67%)	114 (65%)		
Jeraj L							
Rivaroxaban (n=61)	24/37	59 (50-70)	6 m	61 (100%)	37 (61%)	Villalta score	36 m
Warfarin (n=39)	19/20	59 (50-68)	6 m	39 (100%)	25 (56%)		
Coleman C							
Rivaroxaban (n=10463)	5126/5337	NR	6 m	NR	NR	MacDougal algorithm	16 m
Warfarin (n=26494)	13008/13486	NR		NR	NR		
Soogard M							
Rivaroxaban (n=8567)	5504/3063	64.2	NR	NR	6897 (80.5%)	MacDougal algorithm	30 m
Warfarin (n=11390)	4000/7390	64	NR	NR	8643 (75.9%)		
Ulte K							
Rivaroxaban (n=161)	52/109	60±14	6 m	101 (63%)	87 (54%)	Villalta score	25 m
Warfanin (n=148)	64/84	63±14	6 m	92 (62%)	76 (51%)		

Table II. Continue

Authors	Female/ Male	Mean Age	Treatment duration	Proximal DVT	Unprovoked DVT	Diagnosis of PTS	Follow up
de Athayde Soares R							
Rivaroxaban (n=46)	26/20	54.9±3	6 m	46 (100%)	20 (43.5%)	Villalta score	12 m
Warfarin (n=38)	17/21	5.6±2.3	6 m	38 (100%)	21 (55.3%)		
Pradoni P							
Rivaroxaban (n=309)	144/165	65±15.6	13.2±10.7	309 (100%)	228 (73%)	Villalta score	36 m
Warfarin (n=1036)	528/508	60.2±17	10±11.3	1036 (100%)	494 (47%)		
Ferreira T							
Rivaroxaban (n=71)	39/32	42 (33-56)	6 m	71 (100%)	34 (48%)	Villalta score	61 m
Warfarin (n=58)	49/9	44 (29-52)	7 m	58 (100%)	22 (38%)		

Abbreviations: DVT, deep venous thrombosis; m, months; NR, not reported; PTS, post-thrombotic syndrome

Table 11. Efficacy outcomes

Authors	Recurrent VTE	Incidence of PTS	Severe PTS
Cheung W			
Rivaroxaban (n=162)	34 (21%)	45 (29%)	5 (11%)
Warfarin (n=174)	29 (17%)	66 (40%)	6 (9%)
Jeraj L et al			
Rivaroxaban (n=61)	4 (7%)	15 (25%)	NR
Warfarin (n=39)	3 (8%)	19 (49%)	NR
Coleman C			
Rivaroxaban (n=10463)	NR	3.69 /100 p.y.	1.1/100 p.y.
Warfarin (n=26494)	NR	4.73 / 100 p.y.	1.38/100 p.y.
Soogard M			
Rivaroxaban (n=8567)	0.96 (95% CI	0.53 /100 p.y.	NR
Warfarin (n=11390)	0.83-1.23) for Rivaroxaban	0.55/ 100 p.y.	NR
Ulte K			
Rivaroxaban (n=161)	6 (3.7%)	71 (45%)	9 (6%)
Warfanin (n=148)	12 (8.1%)	88 (55%)	15 (10%)
de Athayde Soares R			
Rivaroxaban (n=46)	NR	4 (8.7%)	0
Warfarin (n=38)	NR	11 (28.9%)	4 (10.5%)
Pradoni P			
Rivaroxaban (n=309)	29 (9.4%)	87 (28.2%)	12 (3.8%)
Warfarin (n=1036)	123 (13.8%)	443 (42.8%)	61 (5.8%)
Ferreira T			
Rivaroxaban (n=71)	10 (14%)	36 (50.7%)	4 (5.6%)
Warfarin (n=58)	12 (20.7%)	40 (69%)	10 (17.2%)

Abbreviations: p.y., person-years; VTE, venous thromboembolism

Chapter 4

4.1 Discussion

The current systematic review investigated different oral anticoagulation modalities for the treatment effects of DVT leading to the risk reduction of PTS. Specifically assess the risk of PTS in patients being treated with DOACs and VKA. This study demonstrated that rivaroxaban is more effective in prevention of PTS compared to warfarin. Rivaroxaban also provided a more favorable outcome in terms of the severity of PTS.

We have only indentified studies comparing rivaroxaban versus warfarin. Rivaroxaban was administered 15 mg twice daily for 21 days, followed by 20 mg once daily, while subcutaneous LMWH was administered initially and then followed by warfarin (target INR 2–3).

The majority of studies included in this review were retrospectives.[75,76,77,78,80,81] Two registries [76,77] used the International Classification of Diseases (ICD-10) codes to indentified patients treated for DVT. Although both studies included a significant number of patients, were excluded from final analysis due to incomplete data and high risk of bias. In a registry by USA rivaroxaban was associated with a significant risk reduction of PTS compared to warfarin (23%).[76] In the Danish registry rivaroxaban was associated with decreas risk of PTS compared with warfarin within 3 years follow-up (0.53 per 100 p.y. versus 0.55 per 100 p.y., respectively).[77]

Four of the studies included in the analysis were non-randomized; [75,78,80,81] all of these studies indicated that rivaroxaban was more effective in reducing pevalence of PTS compared to warfarin. Also 2 RCTs were included in the present analysis; a post-hoc subgroup analysis of patients who participated in the Einstein DVT trial [74] and a study by de Athayde Soares et al. [79] The Einstein DVT trial compared the efficacy and safety of rivaroxaban with subcutaneous enoxaparin followed by VKA in 3449 patients with DVT. [82] After the completion of the study, all centers were invited to collect assessments for PTS and to participate in this sub-study. In total, 336 patients were included of whom 174 (52 %) had been treated with

enoxaparin/warfarin and 162 (48%) with rivaroxaban. The trial concluded that rivaroxaban group was associated with a numerically lower but statistically non-significant risk of PTS compared to enoxaparin/warfarin group. [74] In a small RCT by de Athayde Soares et al [79], rivaroxaban treated patients had lower incidence of PTS and a better total vein recanalization rate at 1 year follow up compared to warfarin treated patients.

Six studies reported the severity of PTS. [74,76,78,79,80,81] Our analysis shows that, patients with PTS being treated with warfarin developed more often severe PTS compared to patients treated with rivaroxaban (6.4% vs 3.7%). Only the study by Cheung W et al, [74] reported higher incidence of more severe PTS, although not statistically significant, in patients being treated with rivaroxaban. Coleman et al, [76] reported that rivaroxaban was associated with a lower risk of PTS with venous ulcer (1.11 events per 100 p.y with rivaroxaban vs 1.38 events per 100 p.y, with warfarin).

Recurrent VTE is a risk factor for PTS. [39] Numerous studies have reported that, rivaroxaban is associated with reduced occurrence of recurrent VTE.[83,84,85] In our study, rivaroxaban was as effective as warfarin in reducing the incidence of recurrent VTE events. In our study the incidence of recurrent VTE were similar in both groups.

The exact mechanism underlying the effect of rivaroxaban in reducing PTS is not fully understood. The rapid onset of anticoagulant activity and the stable pharmacokinetics and profibrinolytic effects may play an important role. [86] In addition binding and inhibition of FX man play also a role. [86] A recent study has reported that, that rivaroxaban was associated with a more rapid reduce in thrombus load within the first 21 days than enoxaparin.[87] Moreover; experimental studies have demonstrated the anti-inflammatory properties of rivaroxaban due to the inhibition of thrombin generation which may contribute to the prevention of PTS development. [88,89] Local inflammation may damage the vessel wall and valves causing venous hypertension and PTS.[90]

Appropriate dosage, intensity and duration of anticoagulation have been suggesting as factors that may play an important role in PTS prevention. [16,47] Van Dongen et al [16] demonstrated that the risk of PTS increases by 2.7-fold if the INR

range (INR 2-3) is insufficient during the first 3 mths of treatment with VKA (subtherapeutic INR>50% of treatment period). An adequate anticoagulation, especially during the first 7 days after a DVT episode, is also an important factor for PTS prevention. [47] The Einstein DVT trial demonstrated that, 21% of VKAs treated patients were below the therapeutic INR levels .[82] A large Danish survey including 310.300 patients being treated with VKA reported that, around 70% of patients were in therapeutic range, whereas another study from USA shows that only 54% of the patients achieved continuing target levels of INR. [91,92] Erkens et al, [93] reported that patients treated with VKAs, spend only about 50% of their time in the target level of anticoagulation (INR 2-3), with a strong tendency toward subtherapeutic INR (42% in 0-1 month, 35% in 1-3 months and 24.1% in 1-6 months). All the aforementioned studies reflected an overall poor anticoagulantion control in patients being treated with VKAs, particularly in the first 4 weeks after the event.[93] In this period, delayed clot lysis and stimulated connective tissue growth due to thrombin generation, may cause permanent fibrosis and venous damage.[94] DOACs have more stable pharmacodynamics with early achievement and persistence of anticoagulation effect compared to VKA and this may be one of the reasons explaining why patients treated with rivaroxaban in our study were associated with reduced risk of PTS.

Another potential factor for PTS development is the presence of RVT detected on duplex, 3 to 6 months after an episode of DVT. [95,96,97] Pradoni et al,[80] reported that the degree of residual thrombus in the rivaroxaban group, decreased from 50% to 40%, at 3 months and continuous to decreased even to 20% at 6 months after the episode of DVT. The study concluded that vein recanalization progressively increases over time in patients treated with DOACs in contrast to those treated with warfarin.[98] Ferreira et al,[81] demonstrated a significant low rate of RVT in patients treated with rivaroxaban (24.4%) compared to patients treated with VKAs (64.6%). Others reported that, the incidence of total recanalization 1 year after the episode was significantly higher in rivaroxaban group than in warfarin group, whereas partial or absent venous recanalization was higher in the warfarin group.[79] The earlier and more complete recanalization correlates with lower risk of PTS development. [99] DOACs may produce an earlier vein recanalization due to more rapid and stable

antithrombotic effect by facilitate endogenous thrombolysis, preventing further thrombus growth and reducing damage of venous valve.[94]

The main limitation our study was the lack of large randomized studies. Most of the studies were retrospectives. Two studies were registries and sampling biases are always important limitations these studies. The definition of PTS used in these registries was based of PTS symptoms and not to clinical diagnosis as the Villalta score. This may have impact in the incidence of the PTS reported by these studies. Nevertheless, even when the Villalta score is used, PTS diagnosis is based on the subjective symptoms reported by patients and objective signs documented by the investigator, and therefore observation bias could not be excluded. Although all of the studies included patients with proximal DVT (iliofemoral and/or femoropopliteal DVT) the incidence of PTS in accordance to the location of thrombosis was not recorded. Patients with iliofemoral DVT develop more often and more severe PTS. [1] INR measurements and times in therapeutic rages were not available in all studies, and consequently the compliance of patients with warfarin treatment and the incidence of PTS could not be analyzed. Another possible limitation was that the follow up duration of the included studies varied. Two studies,[76,79] reported outcomes with less than 2 years follow up. These patients could develop PTS if the duration of follow-up was longer. Nevertheless, it is unlikely that we underestimated the PTS incidence in the rivaroxaban group, since more patients with short follow- up (less than 2 years) were treated with warfarin (10.547 vs 26.540, respectively). In our literature search, only studies with rivaroxaban were indentified and conclusions about others DOACs cannot be exported. All these limitations, potentially increases the heterogeneity of our analysis.

Chapter 5

5.1 Conclusions

In conclusion, our study shows that treatment with rivaroxaban after acute DVT was associated with reduced risk of PTS compared to warfarin during mid-term follow up. Patients being treated with warfarin developed more severe PTS compared to patients treated with rivaroxaban.

Chapter 6

6.1 References

1. Kahn SR. How I treat postthrombotic syndrome. Blood 2009; 114:4624– 4631

2. Galanaud JP, Kahn SR. The postthrombotic syndrome: a 2012 therapeutic update. Curr Treat Options Cardiovasc Med 2013; 15:153–163

3. O'Donnell TF Jr, Browse NL, Burnand KG, Thomas ML. The socioeconomic effects of an iliofemoral venous thrombosis. J Surg Res 1977;22:483-488

4. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A *et al*. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997;82:423-8

5. Schulman S, Lindmarker P, Holmström M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolismtreated withwarfarin for 6weeks or 6 months. J Thromb Haemost 2006;4(4):734–742

6. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5 year follow-up results of an open label, randomized controlled trial. Lancet Haematol 2016;3(2):64–71

7. Vedovetto V, Dalla Valle F, Milan M, et al. Residual vein thrombosis and transpopliteal reflux in patients with and without the postthrombotic syndrome. Thromb Haemost 2013; 110:854–855

8. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488-98

9. Deatrick KB, Elfline M, Baker N, et al. Postthrombotic vein wall remodeling: preliminary observations. J Vasc Surg 2011; 53:139–146

10. Henke PK, Varma MR, Moaveni DK, et al. Fibrotic injury after experimental deep vein thrombosis is determined by the mechanism of thrombogenesis. Thromb Haemost 2007; 98:1045–1055

11. Deatrick KB, Obi A, Luke CE, et al. Matrix metalloproteinase-9 deletion is associated with decreased mid-term vein wall fibrosis in experimental stasis DVT. Thromb Res 2013; 132:360–366

12. Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007;46:979-90

13. Meissner MH, Eklof B, Smith PC, Dalsing MC, DePalma RG, Gloviczki P *et al*. Secondary chronic venous disorders. J Vasc Surg 2007;46(Suppl S):68S-83S

14. Galanaud JP, Holcroft CA, Rodger MA, et al. Predictors of post-thrombotic syndrome in a population with a first deep vein thrombosis and no primary venous insufficiency. J Thromb Haemost 2013; 11:474–480

15. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009;145:286-95

16. van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrom-botic syndrome. J Thromb Haemost 2005;3:939-42

17. Shbaklo H, Holcroft CA, Kahn SR. Levels of inflammatory markers and the development of the post-thrombotic syndrome. Thromb Haemost 2009;101:505-12.

18. Roumen-Klappe EM, Janssen MC, Van Rossum J, Holewijn S, Van Bokhoven MM, Kaasjager K *et al*. Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study. J Thromb Haemost 2009;7:582-7

19. van Rij AM, Hill G, Krysa J, et al. Prospective study of natural history of deep vein thrombosis: early predictors of poor late outcomes. Ann Vasc Surg 2013;27:924–931

20. Rabinovich A, Ducruet T, Kahn SR, Shapiro S, Tagalakis V, Johri M, Chagnon I, Solymoss S, Opatrny L, Miron MJ, et al. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. J Thromb Haemost 2018; 16: 262–270

21. Amin EE, Van Kuijk SMJ, Joore MA, Prandoni P, Ten Cate H, Ten Cate-Hoek AJ. Development and validation of a practical two-step prediction model and clinical risk score for post-thrombotic syndrome. Thromb Haemost. 2018;118: 1242–1249

22. Méan M, Limacher A, Alatri A, Aujesky D, Mazzolai L. Derivation and validation of a prediction model for risk stratification of post-thrombotic syndrome in elderly patients with a first deep vein thrombosis. Thromb Haemost. 2018; 118; 1419–1427

23. Makedonov I, Kahn SR, Galanaud JP. Prevention and Management of the Post Thrombotic Syndrome. J. Clin. Med. 2020, 9, 923; doi:10.3390/jcm9040923

24. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164:17-26

25. Browse NL, Burnand KG, Irvine AT, Wilson NM. Diseases of the Veins. London, UK: Arnold; 1999

26. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7(5):879–883

27. Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome. Haemostasis. 1994;24:158

28. Brandjes DPM, Buller HR, Heijboer H, Hulsman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349:759–762.

29. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, Gent M. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med. 2001;161:2105–2109

30. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC, Wakefield TW; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004;40:1248–1252

31. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, Meissner MH, Rutherford RB; American Venous Forum Ad Downloaded from Hoc Outcomes Working Group. Revision of the Venous Clinical Severity Score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg. 2010;52:1387–1396

32. Widmer LK, Stathelin HB, Nissen C, da Silva A. Venen-, Arterien-, Krankheiten, koronaire Herzkrankhei bei Berufstatigen. Bern, Switzerland: Verlag Hans Huber; 1981

33. Kahn SR, Desmarais S, Ducruet T, Arsenault L, Ginsberg JS. Comparison of the Villalta and Ginsberg clinical scales to diagnose the post-thrombotic syndrome: correlation with patient-reported disease burden and venous valvular reflux. J Thromb Haemost. 2006;4:907–908

34. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. J Vasc Surg. 2013;57:254–261

35. Kolbach D, Sandbrink M, Neumann H, Prins M. Compression therapy for treating stage I and II (Widmer) post-thrombotic syndrome. Cochrane Database Syst Rev. 2003:CD004177

35. Olowoyeye OA, Awosanya GO, Soyebi KO. Duplex ultrasonographic findings in patients with suspected DVT. Niger Postgrad Med J. 2010;17:128–132

36. Gaitini D. Multimodality imaging of the peripheral venous system. Int J Biomed Imaging. 2007;2007:54616

37. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH; American College of Chest Physicians. Prevention of VTE in non surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl):e195S–e226S

38. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl):e419S–e494S

39. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, Gupta DK, Prandoni P, Vedantham S, Walsh ME, Weitz JI on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies A

scientific statement from the American Heart Association. Circulation 2014;130: 1636–1661

40. Partsch B, Partsch H. Calf compression pressure required to achieve venous closure from supine to standing positions. J Vasc Surg 2005;42(4):734–738

41. Murphy MA, JoyceWP, Condron C, Bouchier-Hayes D. A reduction in serum cytokine levels parallels healing of venous ulcers in patients undergoing compression therapy. Eur J Vasc Endovasc Surg 2002;23(4):349–352

42. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, Tagalakis V, Houweling AH, Ducruet T, Holcroft C, Johri M, Solymoss S, Miron M-J, Yeo E, Smith R, Schulman S, Kassis J, Kearon C, Chagnon I, Wong T, Demers C, Hanmiah R, Kaatz S, Selby R, Rathbun S, Desmarais S, Opatrny L, Ortel TL, Ginsberg JS; SOX Trial Investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo controlled trial. Lancet 2014;383:880–888

43. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores CL. Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. CHEST 2016; 149(2):315-352

44. Amin EE, Bistervels IM, Meijer K, Tick LW, Middeldorp S, Mostard G, Van De Poel M, Serné EH, Otten HM, Klappe EM et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. Blood 2018, 132, 2298–2304

45. Galanaud JP, Righini M, Quéré I. Compression stockings to prevent post-thrombotic syndrome. Lancet 2014; 384: 129

46. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. J Thromb Haemost 2013; 11: 402–411

47. Chitsike RS, Rodger MA, Kovacs MJ, et al. Risk of postthrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. J Thromb Haemost. 2012;10(10):2039-2044

48. Wilson MT, Docherty KF, Gardner RS. Use of direct oral anticoagulants in thromboembolic disease. Drug Review 2016; (8): 15-22

49. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; 126: 188S-203S

50. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:24S-43S

51. Downing LJ, Strieter RM, Kadell AM,Wilke CA, Greenfield LJ, Wakefield TW. Low dose low-molecular-weight-heparinis is anti-inflammatory during venous thrombosis. J Vasc Surg 1998;28(5):848–854

52. Moaveni DK, Lynch EM, Luke C, Sood V, Upchurch GR, Wakefield TW, Henke PK. Vein wall re-endothelialization after deep vein thrombosis is improved with low molecular weight heparin. J Vasc Surg 2008;47:616–624

53. Obi AT, Diaz JA, Ballard-Lipka NL, Roelofs KJ, Farris DM, Lawrence DA, Henke, PK, Wakefield TW. Low-molecular-weight heparin modulates vein wall fibrotic response in a plasminogen activator inhibitor 1-dependent manner. J Vasc Surg Venous Lymphat Disord 2014; 2: 441–450

54. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. Am J Med 2011;124(8):756–765

55. Hull RD, Pineo GF, Brant R, et al; LITE Trial Investigators. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. Am J Med 2009;122(8):762–769

56. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis (Review) summary of findings for the main comparison. Cochrane Database Syst. Rev. 2016.

57. Vedantham S. Valvular dysfunction and venous obstruction in the postthrombotic syndrome. Thromb Res. 2009;123:S62–S65

58. Comerota AJ, Grewal N, Martinez JT, Chen JT, Disalle R, Andrews L, Sepanski D, Assi Z. Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. J Vasc Surg. 2012;55:768–773

59. Meissner MH, Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Lohr JM, McLafferty RB, Murad MH, Padberg F, Pappas P, Raffetto JD, Wakefield TW; Society for Vascular Surgery; American Venous Forum. 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;55:1449–1462

60. Goldhaber SZ, Meyerovitz MF, Braunwald E, Green D, Vogelzang RL, Citrin P, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. Am. J. Med. 1990;88: 235–240

61. Vedantham S, Grassi CJ, Ferral H, et al. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. J Vasc Interv Radiol 2009; 20: S391

62. Haig Y, Enden T, Grøtta O, Kløw NE, Slagsvold CE, Ghanima W, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol. 2016;3: 64–71

63. Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Ja MR, Cohen DJ, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017; 377:2240–2252

64. Comerota AJ, Kearon C, Gu CS, Julian JA, Goldhaber SZ, Kahn SR, et al. Endovascular Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis: Analysis from a Stratified Multicenter Randomized Trial. Circulation 2019; 139: 1162–1173

65. Kahn SR, Julian JA, Kearon C, Gu CS, Cohen DJ, Magnuson EA, Comerota AJ, et al. Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2020; 8:8–23

66. Notten P, Cate-Hoek AJ, Arnoldussen C, Strijkers R, de Smet A,Tick LW, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. Lancet Haematol 2019, doi.org/10.1016/S2352-3026(19)30209-1

67. Mastoris I, Kokkinidis DG, Bikakis I, Archontakis-Barakakis P, Papanastasiou CA, Jonnalagadda AK, Schizas D, Bakoyiannis C, Palaiodimos L, Faillace RT. Catheter-directed thrombolysis vs. anticoagulation for the prevention and treatment of post-thrombotic syndrome in deep vein thrombosis: An updated systematic review and meta-analysis of randomized trials. Phlebology 2019, DOI: 10.1177/0268355519835618

68. Abu-Own A, Scurr JH, Coleridge Smith. Effect of leg elevation on the skin microcirculation in chronic venous insuffciency. J Vasc Surg 1994; 20: 705–710

69. Morling JR, Broderick C, Yeoh SE, Kolbach DN. Rutosides for treatment of post-thrombotic syndrome. Cochrane Database Syst. Rev. 2018

70. Cohen JM, Akl EA, Kahn SR. Pharmacologic and compression therapies for postthrombotic syndrome: A systematic review of randomized controlled trials. Chest 2012; 141: 308–320

71. Schleimer K, Barbati ME, Grommes J, Hoeft K, Toonder IM, Wittens CHA, Jalaie H. Update on diagnosis and treatment strategies in patients with post- thrombotic syndrome due to chronic venous obstruction and role of recanalization. J Vasc. Surg Venous Lymphat. Disord. 2019; 7: 592–600

72. The University Illinois at Chicago. What is the PICO Model? [Internet]. Available from: http://researchguides.uic.edu/c.php?g=252338&p=1683349 [cited Dec 6, 2019]

73. Liberati A, Altman DG, Tetzlaff J, et al.: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009, 339:2700. 10.1136/bmj.b2700

74. Cheung YW, Middeldorp S, Prins MH, Pap AF, Lensing AWA, ten Cate-Hoek AJ, Villalta S, Milan M, Beyer-Westendorf J, Verhamme P, Bauersachs RM, Prandoni P on behalf of the Einstein PTS Investigators Group. Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis. A post-hoc analysis. Thromb Haemost 2016; 116: 733–738

75. Jeraj L, Jezovnik MK, P. Poredos. Rivaroxaban versus warfarin in the prevention of post-thrombotic syndrome. Thromb Res. 2017;157:46-48

76. Coleman CI, Beyer-Westendorf J, Bunz TJ, Mahan CE, Spyropoulos AC. Postthrombotic syndrome in patients treated With rivaroxaban or warfarin for venous thromboembolism. Clinical and Applied Thrombosis/Hemostasis 2018;24(4): 575-582

77. Søgaard M, Nielsen BP, Skjøth F, Kjældgaard JN, Coleman CI, Larsen TB. Rivaroxaban vs warfarin and risk of post-thrombotic syndrome among patients with venous thromboembolism. AM J Med. 2018;131(7):787-794

78. Utne KK, Dahm A, Wik HS, Jelsness-Jørgensen LP, Sandset PM, Ghanima W. Rivaroxaban versus warfarin for the prevention of post-thrombotic syndrome. Thromb Res 2018; 163:6-11

79. de Athayde Soares R, Matielo MF, Brochado Neto FC, Nogueira MP, Almeida RD, Sacilotto R. Comparison of the recanalization rate and post-thrombotic syndrome in patients with deep venous thrombosis treated with rivaroxaban or warfarin. Surgery 2019;166(6):1076-1083

80. Prandoni P, Ageno W, Ciammaichella M, Mumoli N, Zanatta N, Imberti D, Visonü A, Bucherini E, Di Nisio M, Noventa F for the DOAC-PTS Investigators. The risk of post-thrombotic syndrome in patients with proximal deep vein thrombosis treated with the direct oral anticoagulants. Intern Emerg Med. 2020;15(3):447-452

81. Ferreira T, Hubera SC, de Moraes Martinelli B, Lemos AJ, Menezes FH, Orsi AF, Bittar LF, de Oliveira LFG, Sodre RL, Mello TT, Rielli G, Colella MP, de Paula EV, Yamaguti-Hayakawa GG, Montalvão S, Annichino-Bizzacchi JM. Low prevalence of post-thrombotic syndrome in patients treated with rivaroxaban. Vascul Pharmacol. 2020;124:106608 https://doi.org/10.1016/j.vph.2019.106608

82. The Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499–2510

83. Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol. 2016;3(1):12-21

84. Kucher N, Aujesky D, Beer JH, et al. Rivaroxaban for the treatment of venous thromboembolism. The SWIss Venous ThromboEmbolism Registry (SWIVTER). Thromb Haemost. 2016;116(3):472-479

85. Larsen TB, Skjøth F, Kjældgaard JN, Lip GYH, Nielsen PB, Søgaard M. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. Lancet Haematol. 2017;13(17):1-8

86. Haas S. New oral Xa and IIa inhibitors: updates on clinical trial results, J. Thromb. Thrombolysis 2008;25(1): 52–60

87. Agnelli G, Gallus A, Goldhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation. 2007;116(2):180-187

88. Ellinghaus P, Perzborn E, Hauenschild P, et al. Expression of pro-inflammatory genes in human endothelial cells: Comparison of rivaroxaban and dabigatran. Thromb Res. 2016;142:44-51

89. Terry CM, He Y, Cheung AK. Rivaroxaban improves patency and decrease inflammation in a mouse model of catheter thrombosis. Thromb Res 2016;144:106-112

90. Bouman AC, Smits JJM, Ten Cate H, Ten Cate-Hoek AJ. Markers of coagulation, fibrinolysis and inflammation in relation to post-thrombotic syndrome. J Thromb Haemost. 2012;10(8):1532-1538

91. Holm T, Lassen JF, Husted SE, Heickendorff L. The quality of routine oral anticoagulant therapy in a large geographical area. A survey of 310,300 inhabitants. Dan Med Bull. 2002;49(3):252-255

92. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation. 2014;129(13):1407-1414

93. Erkens PM, ten Cate H, Bu¨ller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLoS One. 2012;7(9):e42269

94. Baglin T. Prevention of post-thrombotic syndrome: a case for new oral anticoagulant drugs or for heparins? J Thromb Haemost 2012; 10(8):1702–1703
95. Prandoni P, Frulla M, Sartor D, Concolato A, Girolami A. Vein abnormalities and the post-thrombotic syndrome. J Thromb Haemost. 2005;3:401-402
96. Dronkers CEA, Mol GC, Maraziti G, et al. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: A systematic review and meta-analysis. Thromb Haemost. 2018;118: 1428-1438
97. Jeraj L, Kaja M, Poredos P. Insufficient recanalization of thrombotic venous occlusion and risk for postthrombotic syndrome. J Vasc Interv Radiol. 2017;28:941-944
98. Prandoni P, Ageno W, Mumoli M et al. Recanalization rate in patients with proximal vein thrombosis treated with the direct oral anticoagulants. Thromb Res 2017;153:97–100
99. Ramacciotti E, Volpiani GG, Dávila R, Resende Aguiar VC, Silveira Magella FM, Fareed J. Early recanalization of veins in patients with DVT treated with rivaroxaban: do we need to move from bedside to bench again? International Angiology 2018;37: 1–3