Universitat de Girona
Facultat de Medicina

Efficacy evaluation of clinical prediction rules to reduce diagnostic time of venous thromboembolism in the emergency department

A quasi-experimental study

Final degree project

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1. Abstract

Background: venous thromboembolism (VTE) is a habitual urgency attended most frequently in emergency departments. It is the third cause of cardiovascular disease and its main manifestations are deep vein thrombosis and pulmonary embolism. VTE has severe complications and can be life-threatening. That is why a fast and accurate diagnosis is needed. To ensure it, there exist clinical prediction rules that combined with diagnostic algorithms, make diagnosis safer and reduces the number of false-positive and false-negative results. Nevertheless, it is been demonstrated that these diagnostic recommendations are not followed for physicians although they have been validated as the most accurate strategy.

Justification: lack of use of clinical prediction rules lead to a clinical practice that is not as safe as when they are used as well as an overuse of unnecessary diagnostic tests (that have important secondary effects such as radiation). One of the main causes for physicians to not using them may be the lack of awareness and training regarding clinical pre-test probability assessment with these scores. This is the reason why the study intervention will be the implementation of VTE diagnosis formation which will be carried in Hospital Universitari Josep Trueta.

Objectives: the main purpose of this study is to demonstrate if the use of clinical prediction rules (Wells score) reduces patients' time spent until they are correctly diagnosed. Secondarily, this study will assess whether the application of Wells score reduces the number of complementary requests in patients with suspected VTE.

Methodology: our study is designed as a quasi-experimental before and after evaluation that will be conducted in the emergency department of Hospital Universitari Josep Trueta between November 2019 – November 2022. Formation intervention will be implemented to physicians who work in the emergency department to improve VTE diagnostic process. A non-probabilistic consecutive sampling will be used and there will be needed a 316 patient's recruitment, needing 158 patient's recruitment in each period (pre and post-intervention). Time until achieving VTE diagnosis before and after the intervention will be assessed and compared to determine the impact of the intervention. Statistical analysis will be adjusted for possible confounding variables.

Keywords: *venous thromboembolism, deep vein thrombosis, pulmonary embolism, clinical prediction rules, Wells score, diagnostic algorithms, diagnosis formation, pre-test probability, emergency department*.

2. Abbreviations

APS: antiphospholipid syndrome

AST: aspartate aminotransferase

BNP: brain natriuretic peptide

CTEPH: chronic thromboembolic pulmonary hypertension

CTPA: computerized tomographic pulmonary angiography

CVD: cardiovascular disease

DOAC: direct oral anticoagulant

DVT: deep venous thrombosis

ED: emergency department

HUJT: Hospital Universitari Josep Trueta

INR: international normalized ratio

LDH: lactate dehydrogenase

LMWH: low-molecular weight heparin

NPV: negative predictive value

OCs: oral contraceptives

PE: pulmonary embolism

PNH: paroxysmal nocturnal haemoglobinuria

PPV: positive predictive value

PTS: post-thrombotic syndrome

RV: right ventricle

SPECT: single photon emission computed tomography

TTE: transthoracic echocardiography

UFH: unfractionated heparin

US: ultrasound

V/Q: ventilation-perfusion

VKA: vitamin K antagonist

VTE: venous thromboembolism

WHO: world health organisation

y.o.: years old.

3. Introduction

3.1. Concepts

Venous thrombosis is the process of clot formation within veins. This event is collectively referred to as venous thromboembolism (VTE), but it predominates in the blood vessels of the leg or the lungs. Therefore, VTE is manifested mainly as deep venous thrombosis (DVT) and pulmonary embolism (PE). Nevertheless, this event can take place in any venous system (1,2).

According to the world health organisation (WHO), DVT is a clinical-pathological process consisting of the formation of a thrombus within deep veins, usually in lower limbs. PE is defined as a partial or total occlusion of the pulmonary vascular system by an embolism (a thrombus that has been detached and has migrated, in this case, to lungs) that in more than 80% of cases comes from a DVT in the lower limbs. Therefore, and also according to WHO, PE can be considered as a possible complication of DVT (3,4).

3.2. Epidemiology

Venous thromboembolic disease is an important cause of morbidity and mortality in patients that enter the hospitals because of medical or surgical causes and it's a major public health problem that affects millions of people all over the world. VTE is the third acute cardiovascular disease (CVD) in frequency, behind the acute myocardial infraction and ictus.

Although PE has higher mortality and morbidity than other VTE presentations, 85-90% of the PE is a consequence of non-treated DVT and 40-50% of DVT will lead to a PE (5,6).

The incidence of VTE is not well known. Detailed data about the annual number of VTE are difficult to obtain because VTE is hard to diagnose due to many factors such as its silent presentation in some cases or because sudden fatal PE can be its first manifestation. Also, less than half of autopsy-detected PE cases are diagnosed antemortem. On the other hand, these results are difficult to extrapolate to different populations because its incidence is influenced by external risk factors that variate between populations.

VITAE study took place on six different European countries (Spain included) in 2004. It determined that as for the main presentations of VTE, the estimated DVT attack rate was 148 per 100.000 person-years (65 per 100.000 for community-acquired DVT and 83 per 100.000 for hospital-acquired DVT) and the estimated PE attack rate was 95 per 100.000 person-years (28 per 100.000 for community-acquired PE and 67 per 100.000 for hospital-acquired PE).

In this study, the total estimated number of VTE related deaths in 2004 was 370.012:

- 7% as a result of diagnosed and treated VTE
- 34% from sudden fatal PE
- 59% from undiagnosed and untreated PE-related death

Deaths that occurred as a consequence of hospital-acquired VTE were 71% of the total number of VTE-related deaths (7).

Incidence of VTE in Spain is around 120 cases for 100.000 person/year.

It has been documented a constant increase in the number of cases due to the progressive increase of the prevalence of some of its risk factors such as advanced age, obesity, hospitalisation or surgery.

The majority of the deaths caused by VTE occur in a sudden way or during the first 2 hours after the event (6).

The incidence of this VTE seems to be lower among Asian and Native-Americans and higher among Blacks. It predominates in older age and the overall age-adjusted incidence rate is higher for men although during childbearing is higher in women (under 45 years) (8).

Survival after deep vein thrombosis and pulmonary embolism

Survival after VTE is significantly worse than expected for the same age and gender, and PE survival is even worse than DVT by itself (risk of early death in symptomatic PE is 18 times higher than the risk among DVT alone). For ¼ of patients with PE sudden death is the first symptom (8).

VTE recurrence

VTE is a chronic disease and about 30% of patients develop recurrence within the next 10 years (8). The risk of recurrence mostly depends on the presence or absence of prothrombotic risk factors at the time of the first VTE. Patients who experience a first episode of symptomatic unprovoked VTE tend to have a much higher risk of recurrence than patients with an intermittent risk factor like surgery (9).

The likelihood of recurrences is the highest in the first 6 to 12 months. There are some important predictors of recurrence like:

- Male gender
- Increasing patient age

- High body mass index
- Neurological disease with leg paresis
- Active cancer
- Initial presentation of the VTE
- Residual thrombosis after finishing the treatment
- D-dimer elevation after the cessation of the anticoagulation
- Thrombophilia

Some other predictors include idiopathic VTE, a lupus anticoagulant or antiphospholipid antibody, antithrombin, protein C or protein S deficiency.

As for the main chronic complications, post-thrombotic syndrome (PTS) occurs in up to 20-50% of patients after proximal symptomatic DVT of the lower limbs and up to 10% of them are severe. The appearance of PTS after a DVT on the upper limbs is about 15-20%. Symptomatic chronic thromboembolic pulmonary hypertension (CTEPH) can occur up to 3,8% of the cases after a PE (6,8).

3.3.Pathophysiology

Clotting cascade

Haemostasis is a regulated mechanism that allows the maintenance of blood flow under physiological conditions but also permits rapid and localized coagulation in the event of tissue damage. This phenomenon is possible because of a balance between vascular endothelium, platelets, the clotting cascade and fibrinolysis (10). Inhibitors have the goal of regulating and limit clot formation. If there is a deficient amount of antithrombotic factors or a raise in coagulation factors a thrombosis may occur because of an unbalance between them (11).

The physiological haemostasis mechanism constitutes 4 phases:

1. Vasoconstriction of the involved area
2. Formation of a platelet aggregate on the injured surface
3. Fibrine formation and stabilization
4. Elimination of fibrine deposit

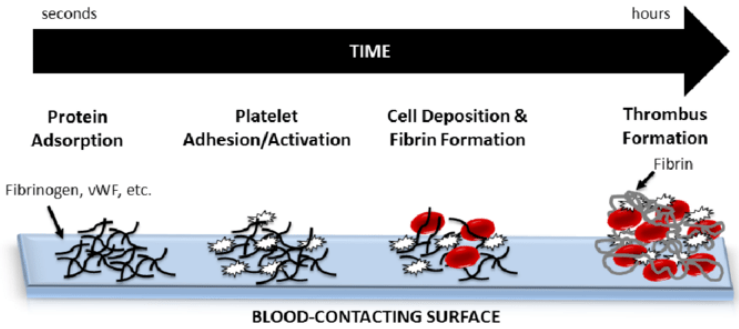

Figure 1. The sequence of events leading to thrombus formation on blood-contacting surfaces. Available from: Brisbois, Elizabeth. (2014). Novel Nitric Oxide (NO)-Releasing Polymers and their Biomedical Applications.

Clotting cascade is involved in thrombus formation (phases 2 and 3). It is a series of biochemical reactions leading to thrombus formation. It is divided into intrinsic and extrinsic pathways and they converge on a common pathway with the activation of factor X. Activated factor X with factor V generates prothrombin (factor II) that is split into thrombin. Thrombin converts fibrinogen (soluble) into fibrin (not soluble) as well as contributes on the stabilisation of fibrin. Fibrin promotes platelet aggregation and stabilisation of the clot. Therefore, it is in a therapeutic target for dissolving intravascular thrombus as well as minimizing bleeding in haemostatic disorders.

The intrinsic pathway is initiated by factor XII when it contacts with no physiological surfaces, for the prekallikrein action or the kininogen. The extrinsic pathway is initiated when blood contacts with damaged tissue, that produces tissue factor (expressed on damaged cells, subendothelium and monocyte's surface). It is activated by several stimuli like direct vascular injury, hypoxia, sepsis, malignancy or inflammation (11–13).

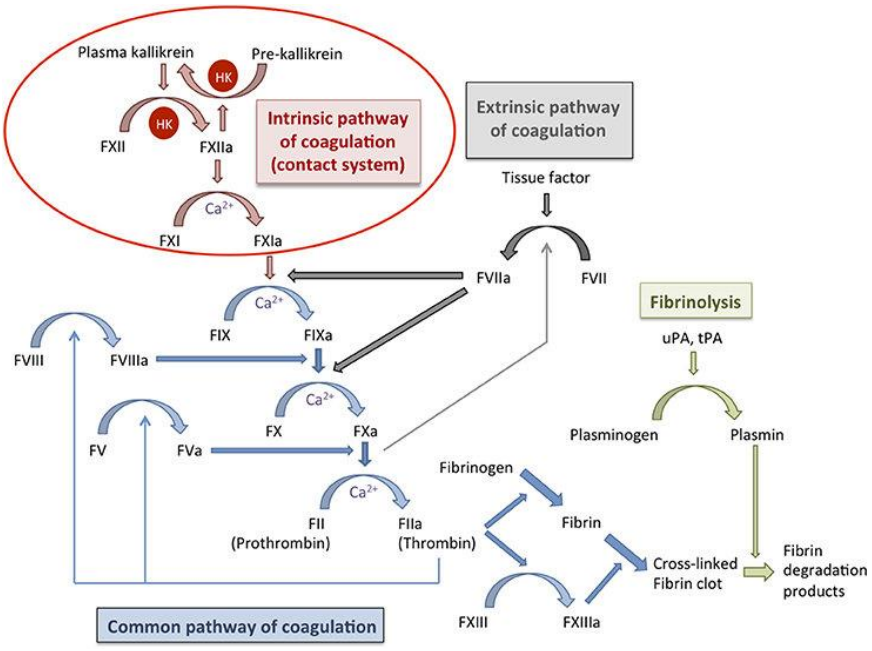

Figure 2. Schematic representation of the coagulation cascade and the fibrinolytic system.

Available from: (14).

Virchow's triad

Virchow's triad is a set of interdependent factors that lead to venous thrombosis: venous stasis, blood hypercoagulability and vascular wall injury (11).

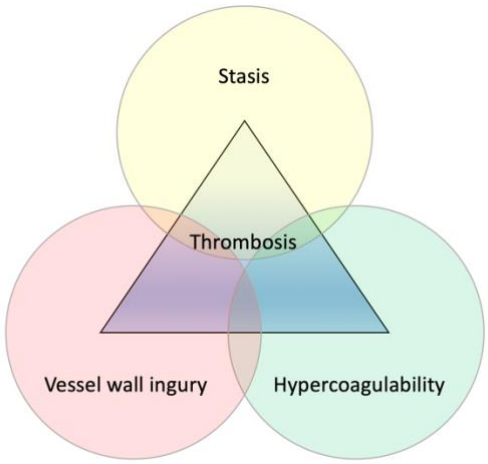

Figure 3. Virchow's triad

Blood stasis: the majority of venous thrombi originate in regions with slow blood flow. As blood flow slows, there is increased contact between blood and vessel wall irregularities as well as a decreased mixing of anticoagulants with the blood. Therefore, blood stasis leads to activation of the coagulation system resulting in a local state of hypercoagulability.

Vascular wall injury: it disrupts the normal endothelial cell layer, leading to a procoagulant surface. After an injury, there are changes in the clotting system like an increase in components of von Willebrand factor and platelet aggregability that could contribute to the state of hypercoagulability.

Hypercoagulability: it is a state developed when there is an unbalance between procoagulant and anticoagulant substances, favouring procoagulant ones. If the cause of this unbalance is an inherited defect, the hypercoagulability state remains all life. On the contrary, if it is a transient factor there is a hypercoagulability state as long as the risk factor is present (15,16).

Valves

Venous thrombosis is believed to begin in the venous valves. The functionality of these is to boost the blood circulation in the lower limbs. These areas are also predisposed to stasis (one of the components of Virchow's triad) and hypoxia, and a frequent location for thrombosis initiation. It has also been found that several of the important vessel-based antithrombotic proteins (like thrombomodulin and endothelial protein C receptor) were regionally expressed on the valves. The expression has an interindividual variation and can be influenced by the environmental factors like hypoxia or inflammation, causing downregulation of antithrombotic proteins and up-regulation of procoagulant activity that may contribute to the induction of the thrombosis. The expression of P-selectin on endothelium, that recruit leukocytes or leukocyte microparticles containing tissue factor, is also up-regulated by hypoxia. These microparticles that contain tissue factor contribute to thrombus formation, in fact, can serve as a substratum for the initiation of

the thrombotic response. The p-selectin inhibitor prevents thrombus development and helps clot resolution (17).

3.4.Risk factors

Risk factors for VTE can be divided into hereditary or acquired, and they can be found simultaneal in the same patient. In fact, the three items of Virchow's triad can be found at the same time in many patients with VTE (18).

Inherit risk factors

They mainly refer to a hypercoagulable state caused by alteration on proteins that normally prevent VTE. Inherit thrombophilia is a genetic predisposition to VTE due to a defect on some factor of clotting cascade (15). The most frequent causes are factor V Leiden mutation and the prothrombin gene mutation (50-60%) and the following are defects in protein S, protein C and antithrombin III (19). Most common inherit thrombophilia are also those with a moderate risk of thrombosis and the uncommon ones have a higher risk (15).

Acquired risk factors

Previous thromboembolism: it is a major risk factor for the recurrence of VTE. The amount of risk for recurrence depends on the type of risk factors presented in the moment of the previous episode, being higher if there were permanent risk factors and lower if they were reversible (20). The localisation of the first VTE apparently is a predictor of the site of future episodes of VTE (21).

Malignancy: patients with cancer can have a hypercoagulable state because of the production of tissue factor and cancer procoagulant, that are substances with procoagulant activity (15). On 10% of cancer patients, a clinical VTE happens and approximately 20% of patients with symptomatic DVT have a known malignancy. VTE is also the second cause of death of cancer patients. Nevertheless, VTE can precede the diagnosis of malignancy. Most common sites of cancer diagnosed after VTE occurred are lung, pancreas, colon and rectum, kidney and prostate (22,23)

Surgery: thrombotic risk increased particularly in the following: orthopaedic, major vascular, neurosurgery and cancer surgery (24).

Trauma: the increased risk of thrombosis in all types of major injury can be due to a decreased venous blood flow in the lower limbs, decreased fibrinolysis, immobilisation and the release of tissue factor and the depletion of anticoagulant substances (25). Intravenous drug use as a minor

trauma (it also causes irritation and infections) is associated with a high prevalence of DVT in young people who inject drugs right into their femoral veins (26).

Pregnancy: is a hypercoagulable state and also can cause obstruct venous return by the bigger size of the uterus, leading to an increased risk of thrombosis (27).

Drugs:

- Oral and transdermal contraceptives: oral contraceptives (OCs) are the most important cause of thrombosis among young woman because of its widespread use (28).
- Hormone replacement therapy (29).
- Tamoxifen: there is an increased thrombotic effect when added to chemotherapy (30).
- Glucocorticoids (31)
- Antidepressants (32)

Immobilization: venous stasis associated with bed rest or prolonged immobilization is an important risk factor as well as prolonged sitting (seated immobility thromboembolism) and extended travel (economy class syndrome when air travel) (33,34).

Antiphospholipid syndrome (APS): the presence of antiphospholipid antibodies directed to plasma proteins. It may be associated with systemic lupus erythematosus or other rheumatic diseases (35).

Renal diseases: such as chronic renal disease, nephrotic syndrome and renal transplantation (36–38).

Age: a higher incidence of VTE with increasing age is found (39).

Hematologic risk factors: among them heparin-induced thrombocytopenia, hyperviscosity, myeloproliferative neoplasms and paroxysmal nocturnal haemoglobinuria (PNH) (19,40,41).

Inflammatory bowel disease (42).

Table 1. VTE risk factors. Adapted from: (43).

Strong risk factors	Moderate risk factors	Weak risk factors
Fracture (hip or leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Prolonged immobility
Major general surgery	Chemotherapy	Increasing age
Major trauma	Congestive heart or respiratory failure	Laparoscopic surgery
Spinal cord injury	Hormone replacement therapy	Obesity
	Malignancy	Pregnancy, antepartum
	Oral contraceptive therapy	Varicose veins
	Paralytic stroke	
	Postpartum	
	Previous VTE	
	Thrombophilia	

3.5. Diagnosis

The diagnosis of the VTE is complicated because it is a disease with a very unspecific and variate symptomatology. Besides, most symptomatic patients do not have VTE, and serial testing is often unnecessary. Is necessary an accurate diagnosis of VTE because untreated VTE can have severe consequences. Several diagnostic strategies can be found but current recommended VTE diagnostic algorithms use a combination of clinical prediction rules (such as Wells or Geneva score) with complementary studies like D-dimer test or imaging tests. The effectiveness of the scores has been validated (44–46).

Clinical characteristics can be used to classify patients with suspected VTE according to the grade of probability (pre-test probability) before doing other tests. The combination of clinical characteristics and non-invasive testing improves the diagnostic process. If both pre-test probability for VTE and test results are low and normal respectively, the post-test probability of VTE is low enough to rule out the VTE diagnosis without doing any further testing in a save way. Furthermore, when there is a discordance between pre-test probability and the test results may be necessary to do additional testing (47).

Bayes theorem explains that with a reasonably sensitive and specific test, is more probable to have a false-positive result when the pre-test probability is low and a false-negative result when pre-test probability is high. Concordant results tend to be correct.

D-dimer

D-dimer is a degradation product of cross-linked fibrin and it is detectable since its formation until 7 days later (48). It is elevated with acute VTE as well as with other non-thrombotic events like haemorrhage, malignancy, major surgery, trauma, sepsis, pregnancy and so (49). D-dimer has a high sensitivity but its specificity is low, so the potential value of this test is a negative result to rule out the diagnosis (due to its high negative predictive value (NPV)) rather than a positive result to confirm it. This means that in a patient with a low pre-test probability is safe to reject VTE without doing further tests whereas in a patient with a high pre-test probability is recommended doing additional tests like a lower limbs ultrasound (US) in the case of DVT suspicion (50,51).

There are several lab techniques to detect D-dimer, and the ones recommended are those with the highest sensitivity and NPV. Conventional ELISA is the standard technique with a sensitivity >95% and specificity around 40%. Other techniques to D-dimer determination are VIDAS ELISA, immunofiltration or agglutination (51–53).

The physiological elevation of the D-dimer with the age limits its utility. That is why D-dimer adjusted by age appears so that the result of age x 10μg for each year (when the patient is over 50 years) is the cut point. The conventional cut point is 500μg (used for patients under 50) (54–56).

DVT diagnosis

Signs and symptoms

DVT signs and symptoms are nonspecific and when isolated, they are not enough to establish DVT diagnosis (44,57) *(See Diagnosis).*

Table 2. Signs and symptoms of DVT. Adapted from: (6).

Sign or symptom	Sensibility (%)	Specificity (%)
Pain	62-91	3-87
Inflammation	56-84	26-74
Homans' sign	13-48	39-84
Increase of limb diameter	35-97	8-88
Superficial veins dilatation	-	82
Increase of limb temperature	72	>80

Clinical prediction rules

There are validated clinical prediction rules that help to classify patients with DVT suspicion into low, moderate or high pre-test probability (they can be also classified into likely or unlikely). These clinical scores incorporate signs, symptoms and risk factors. The utility of pre-test probability increases with their incorporation into diagnostic algorithms (53).

Table 3. Wells score for DVT. Adapted from: (53)

Clinical variable	Score
Active oncologic disease	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous months requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 2cm larger than that on the asymptomatic leg (measured 10cm below the labial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis at least as likely as DVT	-2

0p: low risk

1-2p: moderate risk

≥3p: high risk

Imaging tests

Venous US is the diagnostic test of choice for DVT. Nevertheless, US effectiveness is linked to the symptomatology, localisation, size of the thrombus as well as the DVT prevalence. The specificity and sensibility for proximal DVT are high (98% and 96% respectively) but it decreases if is a distal DVT and on asymptomatic patients. The venography has been set apart to some specific cases like a discordance between pre-test probability and US, post-thrombotic syndrome, recurrent VTE, obesity or extrinsic compression. Basically is used when other tests are not able to confirm or rule out DVT diagnosis (58,59). The most recommended modality of US is compression US to assess the lower limbs. The most sensitive and specific diagnostic US sign for a first episode of DVT is the absence of compressibility of a venous segment. Doppler can be used to identify vessels and in case there is a doubt of the compressibility on some segment (60).

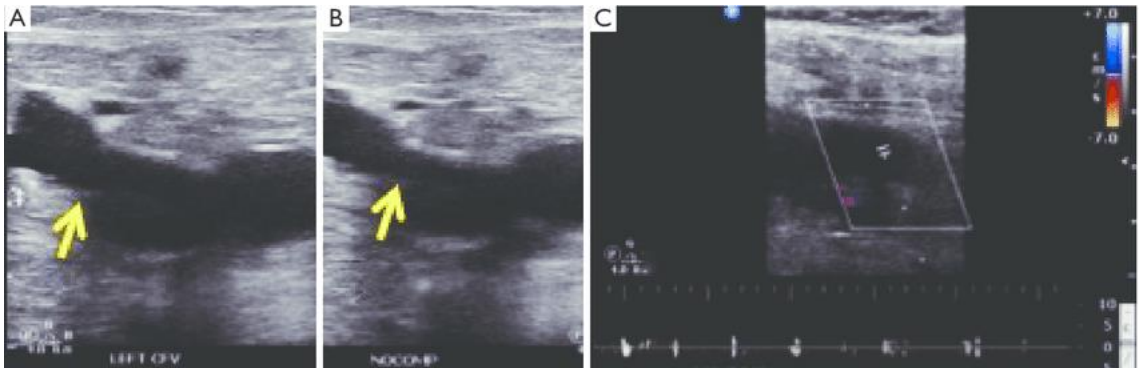

Figure 4. Acute deep vein thrombosis on ultrasound. Available from: (61).

As an example, *Figure 4* shows an acute DVT ultrasound. Greyscale ultrasound examination of the left common femoral vein (CFV) demonstrates an enlarged (arrow in A), non-compressible vein (arrow in B) with low-level intraluminal echoes. Corresponding colour flow and spectral Doppler (C) suggests no flow within the vein.

Duplex US (compression US plus doppler for the evaluation of the entire venous system of the lower limb) was thought to be the most suitable but recent studies have demonstrated that serial 2-point US plus D-dimer is equivalent to whole leg colour-coded doppler US. The 2-point US assesses the compressibility of the common femoral vein at the groin and to popliteal vein in the popliteal fossa (58,62). Several advantages of this technique are (62–64):

- Simplicity (the technique can be learned in less than 2h and performed by non-radiology personal).
- Reproducibility
- Broad availability

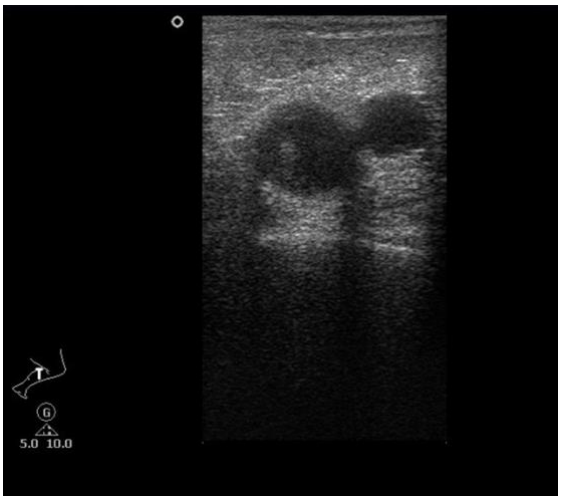

Figure 5. Left femoral vein distended and non-compressible. Case courtesy of Dr Hidayatullah Hamidi, Radiopaedia.org

The main disadvantage is the need of serial 2-point US (repeat the procedure) within a week to detect a possible extension to the proximal veins (64–66). Despite its main limitation, this technique is considered of choice for the first assessment on a patient with DVT suspicion on the emergency department (ED) due to its multiple suitable features in this environment (6,67). Also, the colour-coded doppler US requires top-quality US equipment and experienced personal and implies that patients have to wait further to benefit from this procedure (68,69).

The US diagnostic signs are (67,70,71):

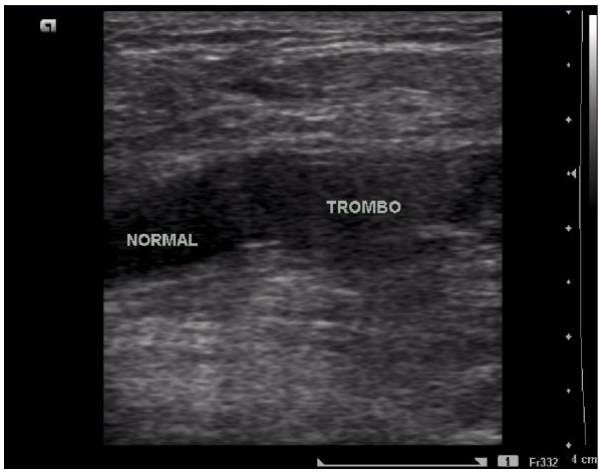

Figure 6. Femoral vein distended, not compressible, and filled by heterogenous hypoechogenic material without flow. Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org

- The full collapse of vein walls is not possible (the most direct and reliable sign).
- Direct vision of the thrombus in the vein. Does not distinguish between an acute and a chronic thrombus so it is helpful to consider that in acute DVT it is usually occlusive, not echogenic and continuous. On the contrary, chronic DVT thrombus tends to nonocclusive, discontinuous and echogenic. It also helps to compare with previous US if present
- Increase in diameter of the vein compared to the artery that accompanies it (if the vein diameter is twofold the arteries')
- Lack of venous diameter modification with Valsalva manoeuvring (gives information about flow interruption)

Diagnostic algorithm

The use of a diagnostic algorithm with an integrated approach is recommended because they are safer, more convenient and cost-effective in the diagnostic of VTE (53).

The first step is to use a validated clinical prediction rules in patients with suspected DVT to determine the pre-test probability. Depending on its result, the second step changes, being recommended to do a VTE-validated D-dimer test in patients with a low probability of VTE to rule out the diagnosis. If the probability of VTE is high, the second step consists in imaging tests. Otherwise, when the DVT probability is moderate both strategies may be used although a highly sensitive D-dimer test is suggested as an initial study above US (grade 2C of recommendation). The choice of the initial test will also depend on its availability and patient features in all cases (59,60).

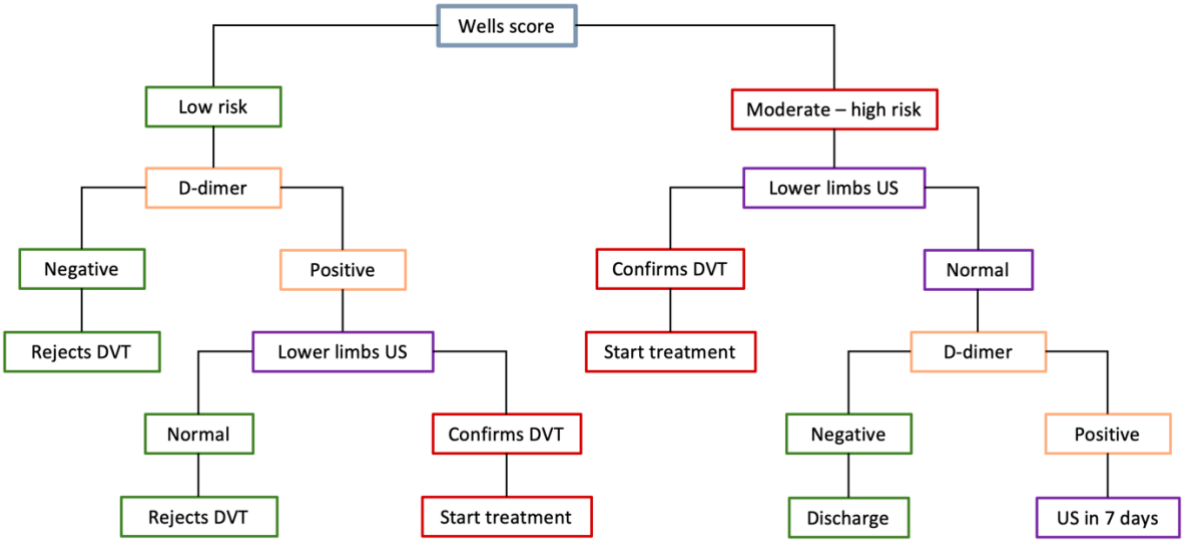

Figure 7. DVT diagnostic algorithm

PE diagnosis

Signs and symptoms

Table 4. PE signs and symptoms

Signs and symptoms
Dyspnoea
Pleuritic pain
Non-pleuritic thoracic pain
Cough
Haemoptysis
Syncope
Tachypnoea
Tachycardia
Fever
Jugular ingurgitation
DVT signs or symptoms
Shock

The clinical presentation of PE is very variable and covers a wide range that goes from asymptomatic to shock. PE is suspected when a patient presents dyspnoea (especially if it has a sudden presentation), chest pain, haemoptysis, hypotension or syncope. A rare but important (due to its consequences) clinical presentation is haemodynamic instability (72,73). Worsening of dyspnoea is often the only symptom in patients with a previous pulmonary disease or heart failure. Chest pain is usually pleuritic but in central PE it can be angina pain because of a right ventricle (RV) dysfunction, making different its differential diagnosis (74). The clinical presentation severity is not always related to the thrombus' size (75).

Clinical prediction rules

It has been shown that the clinical presentation isolated for PE diagnosis has a moderate sensibility (85%) and a low specificity (51%), making necessary to use clinical prediction rules within diagnostic algorithms (76). These diagnostic scales determinate a pre-test probability for patients to have a PE based on a combination of signs, symptoms and risk factors. Most used prediction rules are Wells score and revised Geneva score, although there are others like PERC,

Pisa or Charlotte score (77). The prevalence of PE is different in each category depending on the probability category (78).

Table 5. Wells score for PE. Adapted from: (53)

Clinical variable	Score
DVT signs or symptoms	3
Alternative diagnosis less probable than PE	3
Cardiac rate >100 beats/minute	1,5
Immobilization or surgery during 4 previous weeks	1,5
Previous PE or DVT	1,5
Haemoptysis	1
Active oncologic disease	1

<2p: low risk

2-6p: moderate risk

>6p: high risk

Lab tests

The most used lab method on the diagnosis process for PE is D-dimer *(see D-dimer).* Patients with PE tend to have the following findings (79–82):

- Arterial blood gas analysis: it is frequent to find hypoxaemia (74%), alkalosis and hypocapnia (41%) but it can be normal too (18%).
- Leucocytosis, raise of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST).
- Brain natriuretic peptide (BNP): it has a specificity of around 62% and a sensibility around 60%.
- Troponin: they may be elevated especially among patients with RV dysfunction. It is also a bad prognosis factor.

Electrocardiogram

Electrocardiogram (ECG) changes usually presented in severe cases of PE are:

- Inversion of T waves in V1-V4
- QR pattern in V1
- Incomplete or complete right bundle branch block
- Traditional S1Q3T3 PE pattern (only present in 10%)

Sinus tachycardia may be present as the only ECG sign in patients with PE not so severe (40%). Atrial arrhythmias (frequently atrial fibrillation) can be present in acute PE. Half of the patients with PE have a normal ECG (83).

Imaging tests

Chest X-ray: it usually has abnormal, unspecific findings and can be used to reject other causes of the symptoms. The most frequent finding is cardiomegaly, and other frequent findings are pleural effusion, elevated hemidiaphragm or atelectasis. Hampton's hump or Westermark's sign (focal oligemia) are not frequent but when present, PE has to be a suspicion (84).

Computerized tomographic pulmonary angiography (CTPA): is usually the imaging test of choice to confirm PE diagnosis. According to PIOPED II study (85), its sensibility is around 90% and its specificity around 95% when CTPA is combined with venous phase imaging (with a sensibility of 83% when CTPA is used alone and a similar specificity). The value of the results obtained with CTPA is influenced by pre-test clinical probability. A negative CTPA has a high NPV for PE in patients with low or intermediate pre-test probability (96% and 89% respectively) but a low NPV in patients in high clinical probability group (60%). On the contrary, in patients with an intermediate or high pre-test probability, the positive predictive value (PPV) of a positive CTPA is high (92% and 96% respectively) and in patients with a low clinical probability is low (58%). Therefore, a positive result is useful when a patient has an intermediate/high pre-test probability for PE and a negative CTPA is useful when the pre-test probability is low. Further testing should be considered when there is a discordance between clinical probability and CTPA result and when there is an inconclusive CTPA result. Some advantages of CTPA are that is available in most centres and that CTPA sometimes provides an alternative diagnosis when PE is rejected. However, CTPA also has limitations such as the inability to identify certain subsegmental PE or radiation exposure (85).

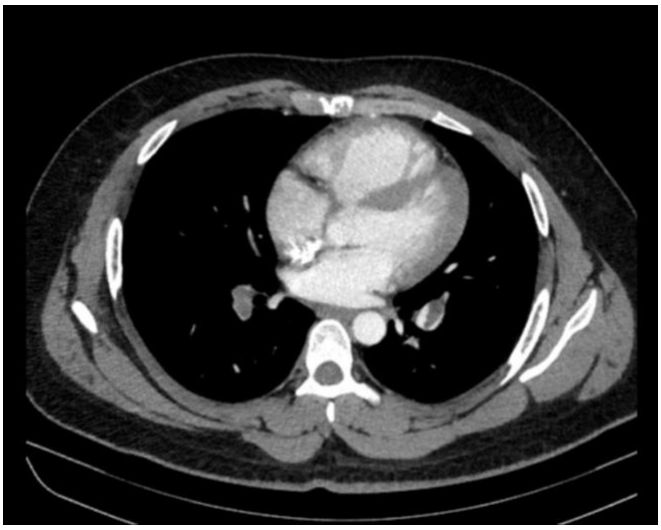

Figure 8. Extensive filling defects involving both main pulmonary arteries extending to the lobar and segmental branches. Case courtesy of Dr Hidayatullah Hamidi, Radiopaedia.org

Ventilation/perfusion (V/Q) lung scintigraphy: this technique combines perfusion scans with ventilation studies. V/Q scintigraphy is recommended in patients in whom CTPA is contraindicated (allergy to the contrast, pregnancy, severe renal failure), the CTPA is negative but the clinical probability is high or with an inconclusive CTPA (86). Planar lung scans are classified in the following categories (87):

- Normal scan: rejects PE diagnosis
- High-probability scan: diagnostic in the majority of patients
- Inconclusive scan

The results must be interpreted in conjunction with pre-test probability. Thus, when clinical probability matches with V/Q scan results confirms or rejects PE diagnosis but when they differ or V/Q scan is inconclusive is recommended to do further testing (88).

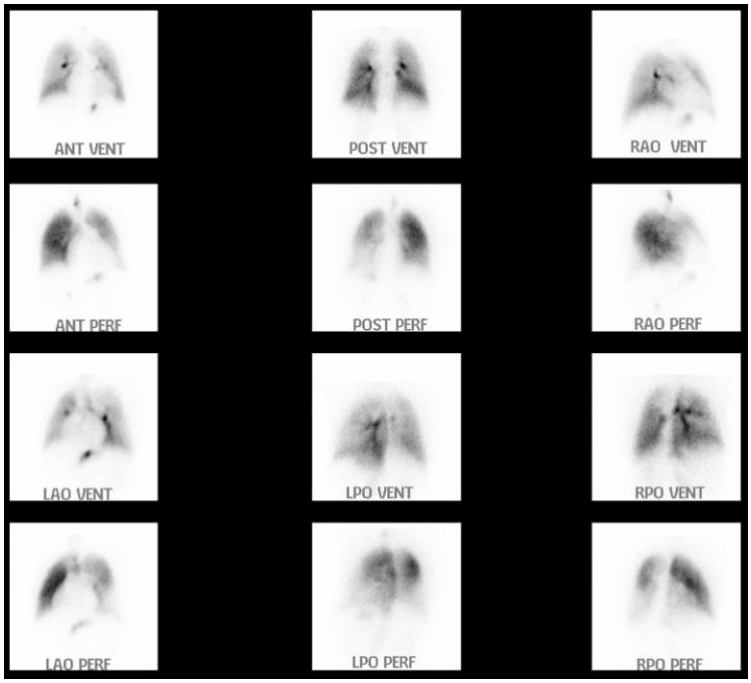

Figure 9. V/Q lung scan. Bilateral major mismatch defect is consistent, with high probability pulmonary embolism. Case courtesy of Dr Hani Salam, Radiopaedia.org

Pulmonary angiography: this technique was the historical gold standard but it has been replaced for CTPA and V/Q scintigraphy. Nowadays is used in patients that CTPA and V/Q scintigraphy are inconclusive and need other complementary studies and in patients in whom interventionism is expected (85).

Transthoracic echocardiography (TTE): a RV pressure overload and dysfunction may be provoked by acute PE and it can be detected by TTE. However, signs of RV pressure overload and

dysfunction may also be found in patients without PE but with another cardiac or respiratory disease and a negative result does not exclude PE (89,90). It can be useful in haemodynamically stable patients for the differential diagnosis of dyspnoea but it is not systematically included in the diagnostic process of PE. In hemodynamically unstable patients, on the contrary, the absence of RV overload or dysfunction practically excludes PE as its cause and may help in the differential diagnosis (90,91). When TTE demonstrates RV overload or dysfunction signs in a hemodynamically unstable patient with PE suspicion justify emergency reperfusion treatment for PE in a patient with high pre-test probability and the absence of other causes. TTE can detect a mobile right-heart thrombus and confirms PE diagnosis of bad prognosis (especially if there is a RV dysfunction) (92).

Lower limbs venous US: many patients with acute PE present a concomitant DVT (30-50%) but only half of them are symptomatic. Venous US can be useful when CTPA and V/Q scan are contraindicated (58).

There are other imaging tests, like magnetic resonance angiography or single-photon emission computed tomography (SPECT) but they are not widely used because their indications are still being studied (77,93).

Diagnostic algorithms

Diagnostic algorithms are combinations of clinical probability (taken from clinical prediction rules), lab tests result and imaging tests. There are different algorithms depending on the hemodynamic stability of the patient.

Hemodynamically stable patients: the major part of the patients is in this group. There are two different strategies depending on whether CTPA or V/Q scan is used as an imaging test. In both is used D-dimer as an initial test (after using Wells or Geneva score) in patients with low or intermediate pre-test probability. In patients with high pre-test probability is not used and the following step is to do an imaging test.

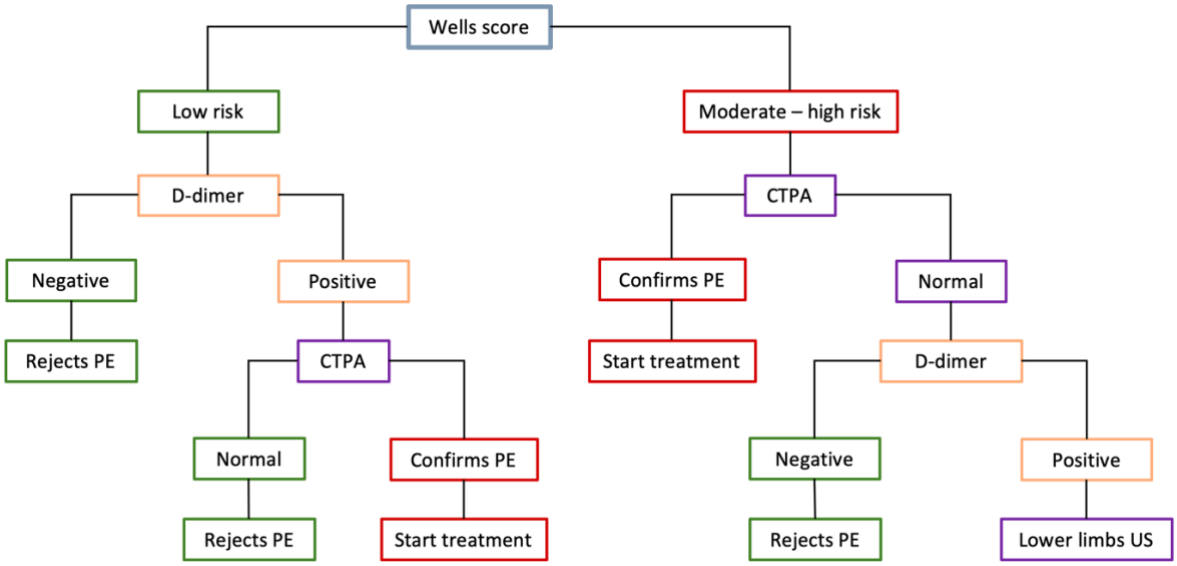

Figure 10. PE diagnostic algorithm for stable patients

Hemodynamically unstable patients: in patients that show up to ED in shock status is essential to perform the basic life support measures as needed initially as well as restore perfusion (fluid therapy and vasoactive drugs). If hemodynamic stability is restored is recommended to do a CTPA. If the patient is still hemodynamically unstable and PE is suspected, is recommended to do a bedside TTE as the initial test if available and if it determines RV dysfunction is allowed to establish immediate reperfusion without further testing. Nevertheless, as soon as the patient is stabilized, a CTPA should be performed to achieve a final confirmation of the diagnosis (77).

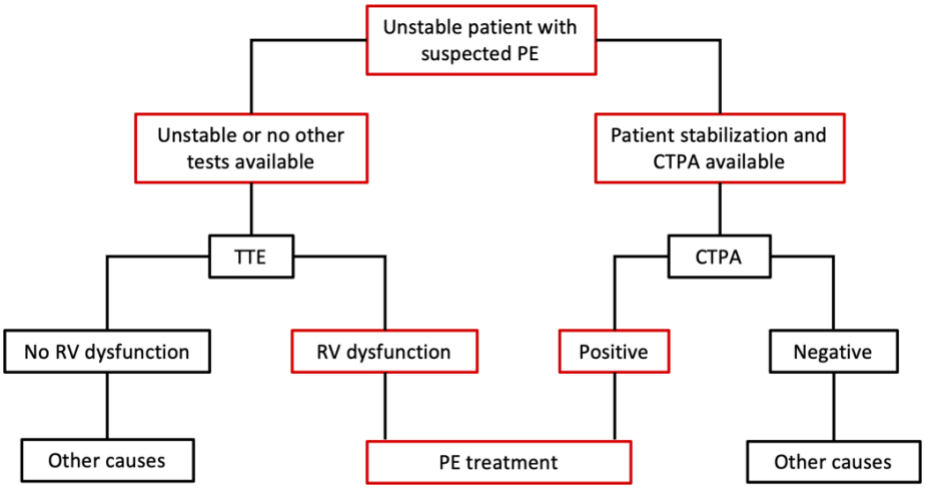

Figure 11. PE diagnostic algorithm for unstable patients

3.6.Treatment

VTE treatment aims to avoid the extension of the thrombus, avoid VTE complications and to favour fibrinolysis. Patients with VTE must receive anticoagulant treatment as soon as possible if there isn't any contraindication and a bleeding risk assessment has to be done before. To do the bleeding risk assessment, there are different scores but none of them is validated enough (94,95) *(See annex 16.5: Haemorrhagic risk).*

DVT treatment

In proximal DVT, the initial therapeutic measure will be pharmacological anticoagulation generally. If the suspicion for DVT is high, the treatment can be started immediately. For anticoagulation, there are different options: a direct oral anticoagulant (DOAC) or a vitamin K antagonist (VKA). Some of the DOAC, need a previous treatment with low-molecular-weight heparin (LMWH) during five days before starting DOAC treatment. In VKA treatment, LMWH or unfractionated heparin (UFH) must be combined with VKA at least for five days and until an international normalized ratio (INR) level of 2,0-3,0 is reached for two consecutive days. Is recommended that treatment with anticoagulants lasts three months in general. Other treatments can be used in combination with pharmacological anticoagulation in acute DVT:

- Thrombolysis: is an endovascular procedure that consists of thrombus fragmentation and local fibrinolysis. Is used in patients with an extensive proximal DVT with a high risk for developing a PTS.
- Vena cava filters: they are used when in a proximal DVT the anticoagulation is contraindicated and until the contraindication disappears.

Patients with distal DVT have different management. Is recommended to do serial imaging tests in patients without severe symptoms and extension risk and initial anticoagulation (as in proximal DVT) in patients with important symptoms or extension risk factors. If US serial testing is done, patients will start anticoagulation when there is an increase of thrombus size o when it is extended to the proximal territory (94).

PE treatment

First of all, it is important to perform basic life support measures or support treatment as needed. About the specific PE treatment, as seen in DVT, if the clinical probability is high the treatment is started immediately. For the initial management of patients with PE is important to do a prognostic assessment. Patients can be stratified in the following different groups (95):

- High-risk PE: presence of hemodynamical instability (arterial hypotension or shock). Thrombolytic treatment is recommended in this group.
- Low-risk PE: is recommended to use prognostic clinical scores to identify this group of patients. Pulmonary embolism severity index (PESI) and simplified PESI (PESIs) have been validated as excellent tools to identify low-risk patients (96,97) *(See annex 16.3 PESI score).*
- Intermediate-risk PE: a combination of several diagnostic tests is recommended to identify intermediate-risk patients. Diagnostic tests used to identify this kind of patients are TTE, CTPA (previously done to confirm the diagnosis), troponin elevation, BNP and venous US (concomitant DVP).

In the majority of patients, the goals of the treatment are achieved using pharmacological anticoagulation, but in some patients is necessary to perform other types of treatments (especially in patients hemodynamically unstable).

Pharmacological anticoagulation is used as in patients with DVT with few differences such as the preference of UFH rather than LMWH in high-risk PE or high bleeding risk. About the duration of the treatment, it depends on an individual assessment based on a balance between the risk of recurrence and risk of bleeding, being necessary at least keep it during a minimum of 3 months.

Fibrinolysis is used in high-risk PE without high bleeding risk and can be considered in patients with an intermediate risk PE with low bleeding risk, especially in those under 75 y.o. In case of fibrinolysis failure or contraindication, an embolectomy can be considered. Vena cava filters are used in the same scenarios as DVT.

Early mobilization in patients with low-risk PE is recommended, unlike intermediate-risk PE which resting during the first days is recommended (95).

3.7.Complications

DVT complications

Acute complications: most typical signs in a patient after a DVT episode are oedema and pain. Nevertheless, the most important acute complication for DVT is PE due to its severe possible consequences. Other acute complications are phlegmasia alba dolens (acute total occlusion of deep venous system but respecting superficial system) and phlegmasia cerulea dolens (total occlusion of deep and superficial venous system). The last one can lead to tissue ischemia, even to gangrene with limb loss, PE or death (6).

Chronic complications: the main chronic complication of DVT is PTS. PTS is developed after lower limbs DVT in 20-50% of the patients. This syndrome is provoked by persistent obstruction of the DVT zone or the presence of valvular failure (although it also can be a consequence of the combination of both). Some symptoms of this syndrome can be heaviness and tension of the limb, oedema or dermatological manifestations (such as hyperpigmentation, pruritus or eczema) (9,98).

PE complications

Early complications (under 3 months): some of the early complications are mortality (more incidence in patients with hemodynamically instability), shock (is the first cause of immediate and short-term death) and recurrences (6).

Late complications (over 3 months): one of the late complications is CTEPH. It is a vascular disease of major pulmonary arteries as a result of chronic obstruction. This process leads to a fibrotic pulmonary artery occlusion, an increase of pulmonary vascular resistance (provoking pulmonary hypertension) and at the end, RV failure. Some other late complications are mortality, recurrence or auricular fibrillation (6,9,99).

4. Justification

As we previously mentioned, VTE is a usual cause of morbidity and mortality over the world and is considered the third cause of CVD behind myocardial infraction and ictus (5). The majority of the deaths caused by VTE occur in a sudden way or during the first 2 hours after the event, so a diagnosis and treatment in the shortest possible time are of vital importance (6).

VTE is hard to diagnose and this is the reason why clinical prediction rules and diagnostic algorithms exist.

It has been shown that these scores and algorithms are barely used and followed in daily practice. This fact could lead to inappropriate use of diagnostic tools and increase its adverse effects (decreasing diagnostic safety) as well as a failure on VTE diagnosis and, therefore, a major incidence on its complications. An accurate diagnosis of VTE is needed because untreated VTE can be fatal. Plus, VTE treatment with anticoagulation therapy can produce significant complications like bleeding, so is also important to discriminate patients in whom VTE diagnosis should be ruled out (100–102).

Besides, VTE has an important amount of expenditures, adding importance to the need of an accurate VTE management to reduce the number of complementary studies and the time spent in ED and, consequently, the expenditures. It is estimated up to €76 million in Spain annual expenditures, which 80% are of hospital expenses. The European Union annual costs for VTE are estimated at €3.000 million (7,103).

One of the main reasons for the lack of use of clinical prediction rules may be the deficiency of awareness and training regarding pre-test probability assessment. This study proposes to implement a formation program to physicians who work in ED to ensure their correct training and acknowledgement of the importance of these scores. We think that this formation will improve VTE diagnosis and will help to reduce the time until diagnosis as well as to decrease the number of complementary studies' requests. To make sure that pre-test scores are used in the diagnostic process after the implementation of formation, the radiology department would not accept a CTPA or US without the result of Wells score.

No studies comparing patients' time spent until VTE diagnosis on the ED with and without using the clinical prediction rules in the VTE diagnostic process could be found in the literature. For this reason, and due to the importance of time in the VTE diagnostic process, the purpose of this study is to assess whether the use of clinical prediction rules decreases time spent in ED until

diagnosis. The reason for which we decided to determine the time until the diagnosis instead of the whole amount of time spent on the ED is to avoid external factors that can enlarge patients' stay in ED such as the extra time until a patient is hospitalized (if that is the case).

5. Hypothesis of the study

5.1. Main hypothesis

The application of clinical prediction rules in patients with a suspected VTE reduces the time until VTE is diagnosed.

5.2. Secondary hypothesis

The application of clinical prediction rules in patients with a suspected VTE reduces the number of complementary studies done.

6. Study objectives

6.1. Main Objective

The principal purpose of this study is to assess whether the application of clinical prediction rules on patients with VTE suspicion reduces the time until VTE diagnosis is established.

6.2. Secondary Objective

The secondary objective of this study is to assess whether the application of clinical prediction rules in patients with suspected VTE reduces the number of requests for complementary studies.

7. Materials and methods

7.1.Study design

This study is designed to be a quasi-experimental study. It will be a before and after evaluation for an intervention to improve VTE diagnostic process. The intervention will consist in implementing formation sessions about VTE diagnostic process in physicians who work in ED (both attending and resident physicians who are currently working in this department). This study will be conducted in the ED of Hospital Universitari Josep Trueta (HUJT).

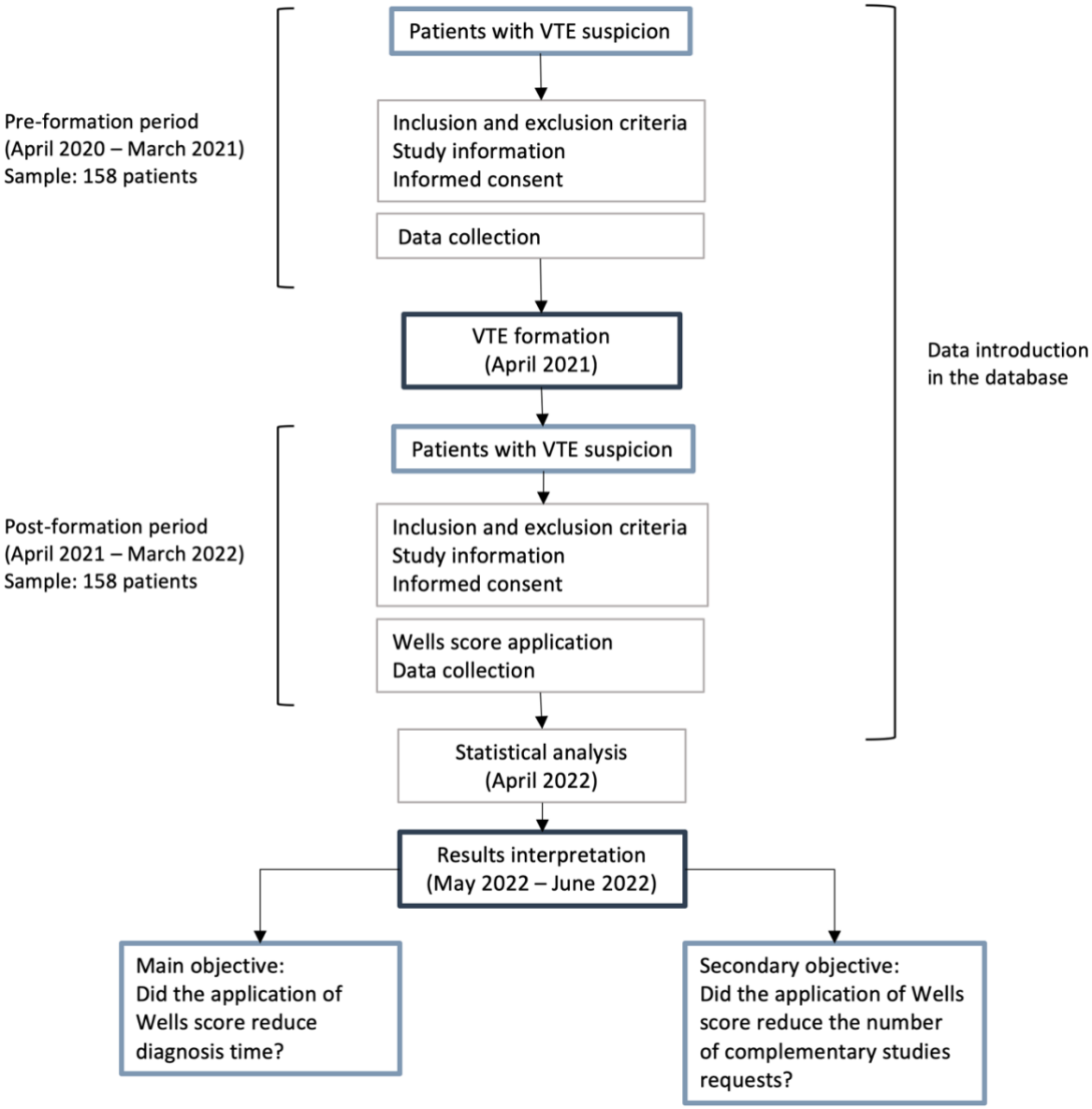

Figure 12. Diagram representing the study

7.2.Study population, inclusion and exclusion criteria

The study population will be composed of all the patients who come to the ED with suspected VTE and confirmed.

We will define DVT suspicion as patients with suspected VTE based on risk factors or suggestive signs and symptoms. For PE, we will define a patient with PE suspicion as a patient with suspected VTE based on risk factors, suggestive signs and symptoms or low diffusing capacity of the lungs for carbon monoxide (DLCO) with normal lung volumes.

Inclusion criteria

- Patients with VTE suspicion
- Patients that are over 18 years old (y.o.)
- Patients that agree to participate in the study and sign the informed consent

Exclusion criteria

- The current episode has already been previously diagnosed
- Patients that reject to participate in the study

7.3.Sample

Sample size

The online free application *Calculadora de Grandària Mostral* (GRANMO) was used to calculate the sample size. As the main dependent variable of the study is time until VTE diagnosis, we need to know which is the mean of time for patients with VTE until they are correctly diagnosed in the ED. As no studies with this data were found in the literature, we asked to technical secretary from HUJT the number of patients presenting in the ED with VTE during last year, a total of 222 patients (86 patients with PE and 136 patients with DVT) as well as their stay time in the ED, a mean around 7h (7h and 31 min for PE and 6h and 37min for DVT).

Accepting an alfa risk of 0,05 and a beta risk of 0,2 in a two-sided test, 158 patients are needed in each group (pre and post-formation period) to recognize as statistically significant a difference greater than or equal to 1h between both groups. Thus, a total of 316 patients' recruitment is needed. It has been anticipated a dropout rate of 10% due to the possibility of data collection sheet misplacing or incomplete collection of the information.

Sample selection

A non-probabilistic consecutive method of recruitment will be used in this study as is the best method for sample selection in acute and non-predictable diseases like VTE. All patients who

come to the ED with VTE suspicion that meet the inclusion criteria will be asked to participate and given the study information document as well as the informed consent (that patient will sign if agrees to participate). Is important that the physician highlight the voluntarily and confidential aspects of their participation. During one year the ED of HUJT diagnosed 222 patients with VTE so is possible to collect the sample of our study from HUJT. Thus, the recruitment process will take place for 24 months (12 months per period) to reach the necessary sample size of 158 patients for each group (a total of 316 patients).

7.4.Variables and methods of measurement

Independent variable

The independent variable is the application of clinical prediction rules (Wells score) when a VTE is suspected.

Dependent variables

The main dependent variable is the time spent until the patient is correctly diagnosed. We will obtain this data from data collection sheets in which physicians will register diagnosis time. This is a discrete quantitative variable.

The dependent variable of the secondary objective is the number of complementary studies requests for a patient with a suspected VTE. Physicians will register which complementary studies did they requested in data collection sheets. This is a discrete quantitative variable.

Covariates

Age (years): is measured as a continuous quantitative variable. It will be collected from the ID card of the patient or another official documentation.

Gender (male/female): is a nominal qualitative variable. It will be collected from the ID card of the patient or another official documentation.

Signs and symptoms presentation (DVT: pain/ inflammation/ Homan's sign/ increase on limb diameter/ superficial veins' dilatation/ increase of limb's temperature/ PE: dyspnoea/ pleuritic pain/ non-pleuritic thoracic pain/ cough/ haemoptysis/ syncope/ tachypnoea/ tachycardia/ fever/ jugular ingurgitation/ DVT signs or symptoms/ shock): is a nominal qualitative variable. Is important to register the presence or absence of symptoms as well as which does the patient have because patients with most common symptoms will be more easily diagnosed than patients

without symptoms or with more uncommon presentations. They will be registered in the data collection sheet.

Risk factors (inherit thrombophilia/ previous thromboembolism/ malignancy/ surgery/ trauma/ pregnancy/ drugs with procoagulant effect/ immobilization/ APS/ renal disease/ haematological procoagulant conditions/ inflammatory bowel disease): is a nominal qualitative variable. Is important to register if patients have risk factors and which are them. The presence of risk factors in the anamnesis process would favour thinking into VTE as a diagnostic possibility rather than its absence. They will be registered in the data collection sheet.

Socioeconomic status (social class I to V): is a polytomic variable. Is important to determine the socioeconomic level because it can affect the diagnostic process. Thus, in patients with lower socio-economical level, risk factors or signs and symptoms can be undetermined because of this fact. Constructed with the education level and occupation according to Domingo et al. (104,105). It will be registered in the data collection sheet.

Table 6. Variables and covariates of the study

Variables/co-variables	Type of data	Categories or values	Measure instrument
Time until VTE diagnosis	Discrete quantitative	Number of hours	This data will be collected by physicians in data collection sheets.
Number of complementary studies	Discrete quantitative	Number of complementary studies requests	This data will be collected by physicians in data collection sheets.
Age	Continuous quantitative	Number of years	Patient's ID card. Registered in data collection sheets.
Gender	Nominal qualitative	Male/female	Patient's ID card. Registered in data collection sheets.
Signs and symptoms	Nominal qualitative	DVT: pain/ inflammation/ Homans' sign/ increase of limb diameter/ superficial veins dilatation/ increase of limb temperature PE: dyspnoea/ pleuritic pain/ non-pleuritic thoracic pain/ cough/ haemoptysis/ syncope/ tachypnoea/ tachycardia/ fever/ jugular ingurgitation/ DVT signs or symptoms/ shock	Anamnesis and physical exploration. Registered in data collection sheets.
Risk factors	Nominal qualitative	Inherit thrombophilia/ previous thromboembolism/ malignancy/ surgery/ trauma/ pregnancy/ drugs with procoagulant effect/ immobilization/ APS/ renal disease/ haematological procoagulant conditions/ inflammatory bowel disease	Anamnesis and patient's clinical history. Registered in data collection sheets.
Socioeconomic status	Ordinal polytomic variable	Class 1 to Class 5 (being Class 1 the most affluent)	Education level and occupation according to Domingo et al. (104,105). Collected by physicians in data collection sheets.

7.5. VTE diagnosis formation

One of the main causes for the lack of use of clinical prediction rules may be the deficiency of awareness and training in VTE diagnostic. For this reason, as our intervention, a formation program will be implemented in HUJT to all the physicians who work in the ED, that considering both attendings and residents make a total of 80. They will be divided into 4 groups of 20 persons each one to make sure all of them can assist to the formation session.

This formation sessions will take place in HUJT and during them, there will be a review of VTE disease and the importance of pre-test probability and of following the diagnostic process will be highlighted. Also, a pocket diagnostic algorithm card will be given to each physician to facilitate finding this information in the case is needed during their daily clinical practice.

Each group will receive a 2h formation session, and as physicians will be divided in a total of 4 groups, a week has been scheduled to carry out the formation. There will be a total of 8h inverted in VTE sessions.

Physicians will collect patients' information in a data collection sheet *(See annex 16.7: Data collection sheet)*. Besides, to ensure the use of the scores in the post-intervention period, the radiology department and the laboratory will ask for Wells score before doing any imaging test or doing a D-dimer test in VTE suspicions.

7.6. Data collection methods

During 24 months of patient recruitment, data collection sheets will be used by physicians to register the variables and covariates. The study will have a pre-formation and a post-formation period in which relevant information for the study will be collected using the same methodology in both periods.

Data collection sheets will be used to register demographic items of patients, the reason for the consult, variables and covariates of the study, means by which patient consult the ED, Wells score punctuation, algorithm applied during the diagnostic process, whether the diagnosis is confirmed and the time of stay in the ED. Physicians will use DVT or PE data collections sheets according to their suspicion.

An information document of the study will be given to each patient before joining it as well as an informed consent that, if the patient agrees to join the study, will voluntarily sign. If a patient is not able to give the consent before data collection due to the severity of the disease and/or the

lack of consciousness, the informed consent will be given to first-degree relatives if present or will be given to the patient afterwards.

Study information document, informed consent and data collection sheets will be available in Catalan, Spanish and English. An example of each Catalan version is available in annexes 16.7, 16.8 and 16.9: *Data collection sheet, Information document of the study and Informed consent.*

8. Statistical analysis

8.1. Descriptive analysis

Both dependent variables (time until VTE diagnosis and number of complementary studies requests) will be summarized pre and post-intervention using the median and the interquartile range (because both are discrete quantitative variables).

All the analysis will be stratified by the covariates. Age will be categorized in quartiles.

In addition, for the dependent variables, we will summarize the covariates pre and post-intervention using the proportions (qualitative variables) and the mean, standard deviation, median, interquartile range (age).

8.2. Bivariate analysis

The difference of the medians of the dependent variables pre and post-intervention will be tested through the Mann-Whitney's U test.

All the analysis will be stratified by the covariates. Age will be categorized in quartiles.

The difference of proportions of the qualitative covariates pre and post-intervention will be tested by the chi-square test (or the exact Fisher's test when the number of expected counts in the cells of the table of contingency was lower than 5). The difference in the means of age pre and post-intervention will be tested by Student's t.

8.3. Multivariate analysis

The effect of the intervention on dependent variables (time until VTE diagnosis and number of complementary studies requests) will be assessed in Poisson regressions controlling for all the covariates. A significant difference between both groups will be considered when p-value <0,05.

9. Ethical considerations

The present study has been designed according to the ethical principles for medical research established by the World Medical Association (WMA) in the *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects* (106) (June 1964), last revised on 2013.

This research will be also conducted under the normative framework according to *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales* (107). All patient personal and clinical information collected in this study will be anonymous and the medical record number will be used instead of patients' personal information to achieve it. All data collected will be only used for research purposes.

Besides, all patients will be informed by ED physicians and will be given an information document about the study. They will also be given an informed consent document to collect their personal information as well as to allow us to enter their clinical history and use its data (only the one which is relevant for the study and with research purposes). The informed consent will be voluntarily signed for the patients before joining the study. The voluntary nature of their participation has to be highlighted. If the patient is unconscious or die, the informed consent will be given to the relatives.

This study protocol will be presented to the Clinical Research Ethics Committee (CEIC, *"Comitè Ètic d'Investigació Clínica"*) of HUJT. The present study will be evaluated by this committee and its approval has to be obtained before starting the project.

Investigators of this study declare that there are no conflicts of interest.

10. Study limitations

The main limitation of this study, as it is designed as a before-and-after study, is that it can demonstrate an association between the dependent and independent variable but it can't determinate if the changes occurred during the intervention are a consequence of it (a causal association). In this type of studies, there is no control group and the possible effect found in the study could be due to differences between both groups of patients (before and after the intervention). For this reason, we have stratified the bivariant analysis and especially, we have adjusted the possible confounding variables in the multivariant analysis. However, it is difficult to control all confounding variables that can affect the diagnostic process.

Another limitation would be the lack of suspicion in patients without signs and symptoms (VTE silent presentation), so they are likely not to be detected even less if they don't have risk factors. These patients won't be benefited from our intervention because there is not any diagnostic tool to identify them in the current diagnostic process.

The formation will be taught by only one professional. That means there will not be interobserver bias but there can be an intraobserver one. Nevertheless, the expected time for the intervention won't be a lot (a week in total). On the other hand, the teacher will be a professional with clinical and formative experience.

As physicians could feel that they are being evaluated, due to the Hawthorne effect, they could be more prone to change their attitude and follow the diagnostic process more methodically.

This study doesn't have a following-up process, that's why dropouts will be minimal. However, due to the assistance pressure in the ED, it may happen that some case won't be collected because of the time involved in filling the data collection sheet as well as in explaining the informed consent. Despite this fact, the benefits like the time reduction in patients' stay in the ED as well as making the diagnostic process safer, may be a motivation for professionals to do as much as possible to include patients in the study.

11. Feasibility

This study will take place in HUJT ED, in which 222 VTE cases have been diagnosed during a year (according to data provided by the technical secretary of HUJT). Therefore, 2 years (one year for each period, pre and post-formation) will be enough to achieve the needed sample size which is 316 in total.

Besides, physicians who work in HUJT ED will be those in charge to collect the necessary data for the study, so no additional staff will be needed except for a statistician, a data manager and a professional to impart VTE sessions. The data manager will create a database and will introduce the registered data. Then, the statistician will analyse the database.

No further diagnostic testing will be needed in this study in addition to tests that will be used in the usual diagnostic process. In fact, the secondary objective of this study is to reduce the number of complementary studies requests so during this study, a reduced need for clinical resources is likely to happen.

For these reasons, the budget of the study and patient recruitment process will not be a problem, so the study is feasible in HUJT ED.

12. Working plan

The working plan for the study will be the following:

Phase 0. Preparation (November 2019 – March 2020)

- **Activity 1.** Bibliographic research and elaboration of the protocol (M3)
- **Activity 2.** Ethical evaluation of the protocol (M4).

The protocol will be presented to the CEIC from HUJT.

- **Activity 3.** Presentation of a study request to the Emergency Department and the hospital's management (M4).

An authorisation will be asked to the ED and the hospital's management.

- **Activity 4.** Meeting with Emergency Department staff to inform them about the study and train them on how to do the data collection process (M5).
- **Activity 5.** Database creation (M5)

Phase 1. Data collection and study intervention (April 2020 – April 2022)

- **Activity 6.** Pre-formation period patients' recruitment and data collection (M6-M17)
- **Activity 7.** Venous thromboembolism diagnosis formation (M18)
- **Activity 8.** Post-formation period patient's recruitment and data collection (M18-29)
- **Activity 9.** Data introduction in the database (M7-M30).

Phase 2. Data analysis, interpretation and publication (April 2022 – November 2023)

- **Activity 10.** Statistical analysis (M30)
- **Activity 11.** Interpretation of the results (M31-M32)
- **Activity 12.** Paper elaboration and revision (M33-M34)
- **Activity 13.** Results publication and dissemination (M35-37)

Activities	2019		2020												2021												2022										Staff
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	
Phase 0: Preparation																																						
1. Bibliographic research and protocol elaboration																																						IT
2. Ethical evaluation of the protocol																																						CEIC
3. ED and hospital management authorization																																						ED head, hospital manager, IT
4. ED meeting and training on data collection sheet																																						IT, ED physicians
5. Database creation																																						Data manager
Phase 1: Data collection and study intervention																																						
6. Pre-formation data collection																																						ED physicians
7. VTE formation																																						Formation professional
8. Post-formation data collection																																						ED physicians
9. Data introduction in the database																																						Data manager
Phase 2: Data analysis, interpretation and publication																																						
10. Statistical analysis																																						Statistician
11. Interpretation of the results																																						IT
12. Paper elaboration and revision																																						IT
13. Results publication and dissemination																																						IT

Figure 13. Chronogram of the study

IT: investigation team (Anna Taberner and M. Àngels Gispert).

13. Budget of the study

The following table summarizes the budget of the study:

Table 7. Budget of the study

Type of cost	Unit cost	Hours/units	Total
Staff			
VTE formation professional	56€/h	2h x 4 sessions	448€
Data manager	40€/h	10h database creation.	400€
		2h/day x 1day/month x 24 months.	1.920€
Statistician	50€/h	4h/day x 3day/week x 4 weeks	2.400€
Subtotal			**5.168€**
Printings			
Pocket VTE card[1]	1,00€	80	80€
Study information document	0,03€	316	9,48€
Informed consent	0,03€	316	9,48€
Data collection sheets	0,03€	316	9,48€
Subtotal			**108,44€**
Publication and diffusion costs			
Attending to conferences[2]	1.500€/person	2	3.000€
Linguistic correction			150€
Article publication			1.500€
Subtotal			**4.650€**
TOTAL			9.926,44€

The budget includes all the extra stuff hired for the study that consists of a VTE formation professional, a data manager and a statistician. It also includes all the necessary materials (that consist of printings) and the publication and diffusion costs.

Some non-included costs are:

[1] Includes printing the cards in colour, double-page and the plasticization.

[2] Includes a national and an international conferences' inscriptions, diet, accommodation and transport.

- Physicians: they have not been included in the study budget because they are the habitual staff from the ED.
- Diagnostic tests: they are not included in the study budget because, as mentioned before, there will not be further testing other than the usual ones.

14. Impact of the study in the national health system

Clinical prediction rules have shown to be effective and safe when combined with diagnostic algorithms in the VTE diagnostic process. Its use has proven to decrease complications' risk. However, many studies have shown a lack of adherence to current recommendations of using integrated approaches in VTE diagnosis leading to high variability of attitudes towards the diagnosis of these patients. Also, overuse of imaging tests has also been found because of not adhering to VTE diagnostic recommendations. The appropriate and timely diagnosis of VTE could decrease mortality and morbidity rates from undiagnosed or delayed diagnosis of VTE (100,102,108).

Therefore, if our study shows a decrease in time of diagnosis when clinical prediction rules are used in the ED, we could recommend implementing formation programs to other hospitals ED to ensure a correct diagnostic approach for VTE. Besides, if a decrease in the number of complementary studies is shown, this intervention could save the patient from getting unnecessary tests (which have secondary effects). Sanitary system costs will also be reduced because of a decreased number of diagnostic tests done.

In the other hand, if our study fails to demonstrate that applying VTE clinical prediction rules decreases diagnostic time, a review of this study will be done to determine which other possible causes for lack of adherence could be considered and which other possible interventions could be implemented to achieve it.

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16. Annexes

16.1. Figures index

16.2. Tables index

16.3. PESI score

Table 8. Simplified PESI score. Adapted from: (97)

Simplified PESI	Score
Age >80 y.o.	1
Oncologic history	1
Cardiac dysfunction or chronic obstructive pulmonary disease history	1
Cardiac rate ≥110 beats/minute	1
Systolic blood pressure >100mmHg	1
Oxygen saturation <90%	1

Low risk: 0p

Non-low risk: ≥1p

16.4. Anticoagulant drugs

Table 9. Pharmacological anticoagulation and posology. Adapted from: (6)

Heparins and derivates	
UFH	18 U/kg/h before the administration of an 80 U/kg bolus. Used in patients with high risk PE or high risk of bleeding.
Bemiparin	115 U/kg/day (adjust dose in patients with renal dysfunction).
Oral anticoagulants	
Acenocoumarol	INR 2,0-3,0 (5 days with heparin administration).
Rivaroxaban	15mg/12h during 3 weeks. Later, 20mg/day.
Apixaban	10mg/12h during a week. Later, 5mg/12h.

16.5. Haemorrhagic risk

Table 10. American College of Chest Physicians haemorrhagic risk score in patients in anticoagulation treatment during over 3 months due to VTE

Variables	
Age >65 y.o.	Diabetes
Age >75 y.o.	Anaemia
Previous haemorrhage	Antiaggregant use
Oncologic disease	Deficient anticoagulation control
Oncologic disease with metastasis	Comorbidity or reduced functional situation
Renal dysfunction	Recent surgery
Hepatic dysfunction	Frequent falls
Thrombocytopenia <50.000 platelets	Alcohol abuse
Previous ictus	

Low risk: 0 risk factors

Moderate risk: 1 risk factor

High risk: ≥2 risk factors

16.6. Pocket VTE cards

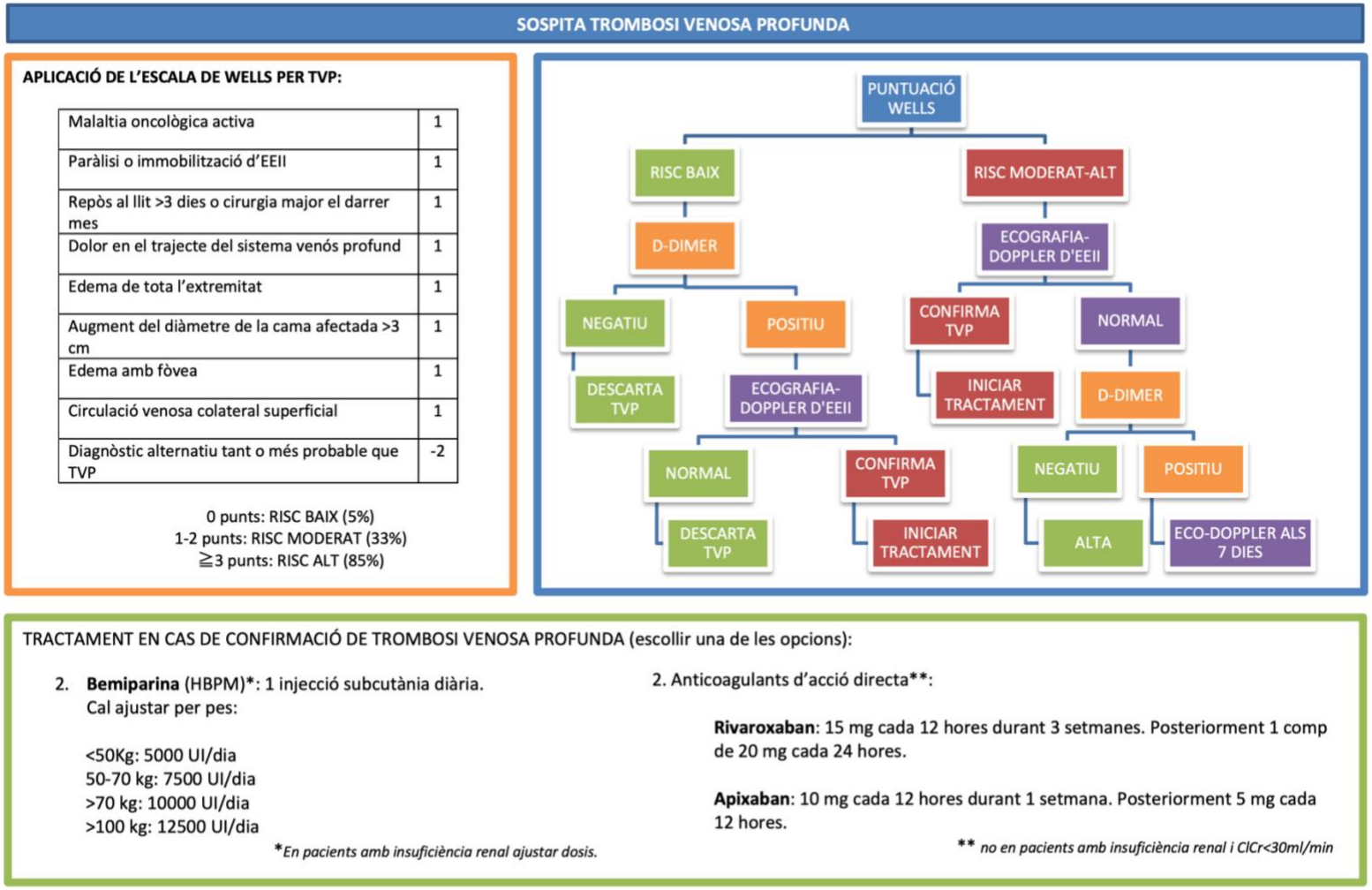

Figure 14. DVT pocket card

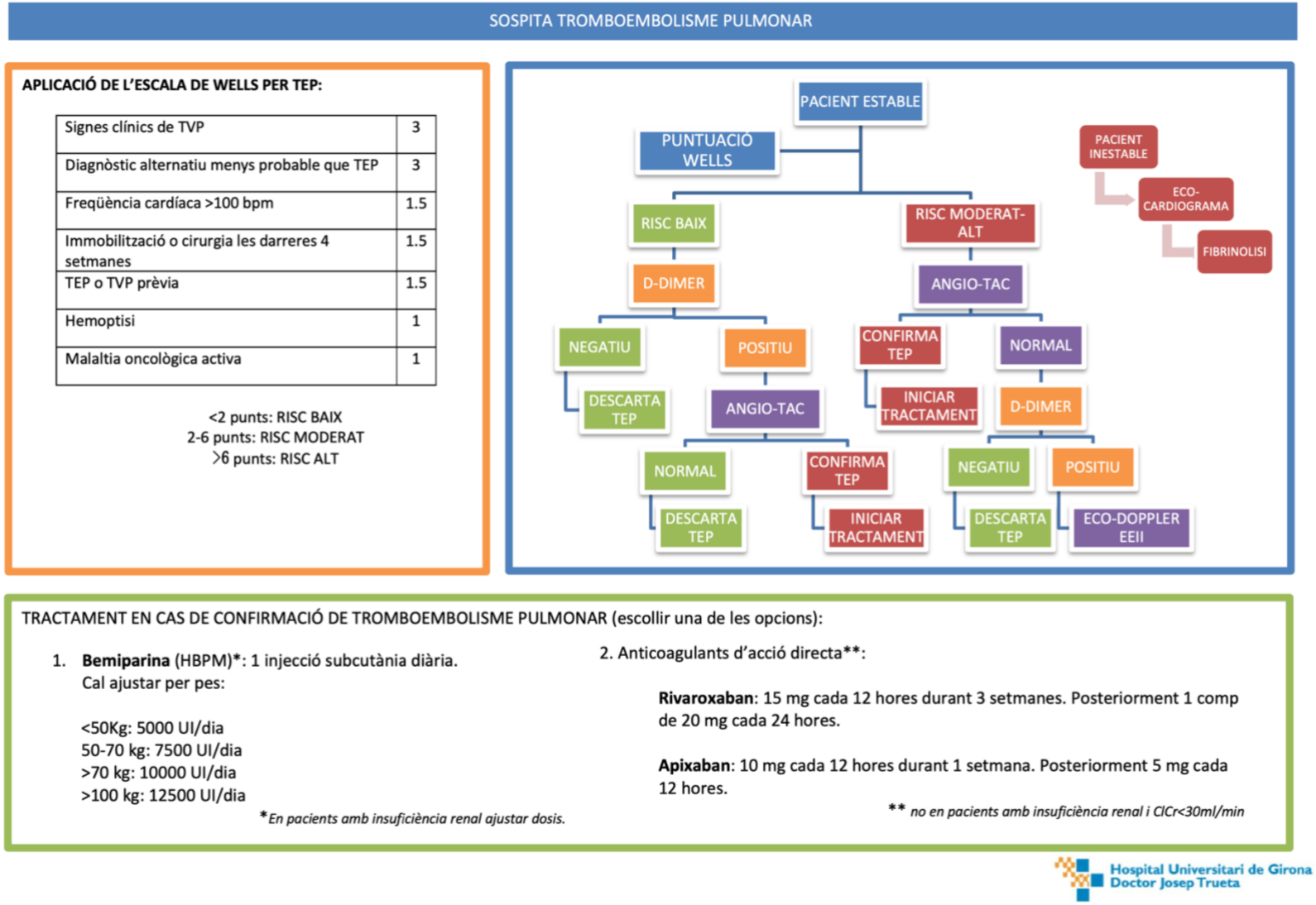

Figure 15. PE pocket card

16.7. Data collection sheet

FULL DE RECOLLIDA DE DADES PER SOSPITA TVP

ESTUDI: Efficacy evaluation of clinical prediction rules to reduce diagnostic time of venous thromboembolism in the emergency department.

Informació referent al pacient

Nº Història clínica: .....

Edat: ..... **Gènere**: ☐ Home. ☐ Dona. ☐ Desconegut.

Motiu de consulta a urgències:
☐ Dolor a nivell d'EEII
☐ Augment de diàmetre EEII
☐ Edema EEII
☐ Dispnea
☐ Dolor toràcic no pleurític
☐ Altres: .....

Símptomes i signes:
☐ Dolor a nivell d'EEII
☐ Dolor toràcic pleurític
☐ Augment de diàmetre EEII
☐ Edema EEII
☐ Dispnea
☐ Altres: .....

Factors de risc
☐ Trombofília
☐ Malaltia tromboembòlica prèvia
☐ Malaltia oncològica activa
☐ Cirurgia
☐ Immobilització
☐ Traumatisme
☐ Embaràs/ puerperi
☐ Altres: .....

Mitjà pel que ha consultat a urgències:
☐ Mitjans propis
☐ Derivació pel metge de família
☐ Derivació des d'un altre centre hospitalari
☐Trasllat mitjançant SEM

Nivell socioeconòmic:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

SOSPITA TROMBOSI VENOSA PROFUNDA

Sospita TVP: PUNTUACIÓ ESCALA DE WELLS..... RISC: ☐ Baix ☐ Mitjà ☐ Alta

Malaltia oncològica activa	1
Paràlisi o immobilització d'EEII	1
Repòs al llit >3 dies o cirurgia major el darrer mes	1
Dolor en el trajecte del sistema venós profund	1
Edema de tota l'extremitat	1
Augment del diàmetre de la cama afectada >3cm	1
Edema amb fòvea	1
Circulació venosa colateral superficial	1
Diagnòstic alternatiu tant o més probable que TVP	-2

Algoritme diagnòstic aplicat:

☐ **D-dímer** Resultat: ☐ negatiu ☐ positiu → ☐ **Eco-doppler EEII** Resultat: ☐ negatiu ☐ positiu

☐ **Eco-doppler EEII** Resultat: ☐ negatiu ☐ positiu

☐ **Altres** .....

Es confirma TVP: ☐ SI ☐ NO

Temps estada a urgències:

Hora entrada a urgències: --:--

Hora sortida d'urgències: --:--

FULL DE RECOLLIDA DE DADES PER SOSPITA TEP

ESTUDI: Efficacy evaluation of clinical prediction rules to reduce diagnostic time of venous thromboembolism in the emergency department.

Informació referent al pacient

Nº Història clínica: .....

Edat: ..... **Gènere**: ☐ Home. ☐ Dona. ☐ Desconegut.

Motiu de consulta
☐ Dolor toràcic pleurític
☐ Dispnea
☐ Edema EEII
☐ Altres: .....

Símptomes i signes:
☐ Dolor toràcic pleurític
☐ Dolor toràcic no pleurític
☐ Dispnea
☐ Edema EEII
☐ Tos
☐ Hemoptisi
☐ Altres: .....

Factors de risc
☐ Trombofília
☐ Malaltia tromboembòlica prèvia
☐ Malaltia oncològica activa
☐ Cirurgia
☐ Immobilització
☐ Traumatisme
☐ Embaràs/ puerperi
☐ Altres: .....

Mitjà pel que ha consultat a urgències:
☐ Mitjans propis
☐ Derivació pel metge de família
☐ Derivació des d'un altre centre hospitalari
☐Trasllat mitjançant SEM

Nivell socioeconòmic:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

SOSPITA TROMBOEMBOLISME PULMONAR

Sospita TEP: PUNTUACIÓ ESCALA DE WELLS..... RISC: ☐ Baix ☐ Mitjà ☐ Alta

Signes clínics de TVP	3
Diagnòstic alternatiu menys probable que TEP	3
Freqüència cardíaca >100bpm	1.5
Immobilització o cirurgia les darreres 4 setmanes	1.5
TEP o TVP prèvia	1.5
Hemoptisi	1
Malaltia oncològica activa	1

Algoritme diagnòstic aplicat:

☐ **D-dímer** Resultat: ☐ negatiu ☐ positiu → ☐ **Angio-TAC** Resultat: ☐ negatiu ☐ positiu

☐ **Angio-TAC** Resultat: ☐ negatiu ☐ positiu

☐ **Altres** .....

Es confirma TEP: ☐ SI ☐ NO

Temps estada a urgències:

Hora entrada a urgències: --:--

Hora sortida d'urgències: --:--

16.8. Information document of the study

FULL D'INFORMACIÓ PEL PACIENT

Benvolgut / da Sr / a. Vostè/el seu familiar presenta la sospita d'una malaltia tromboembòlica. La malaltia tromboembòlica és la tercera causa de morbiditat i mortalitat deguda a patologies vasculars, per darrere de la cardiopatia isquèmica i dels ICTUS. Un ràpid diagnòstic i tractament d'aquestes patologies millora la supervivència i disminueix les complicacions derivades d'aquesta malaltia. Existeixen unes escales i uns algoritmes que ens ajuden a diagnosticar de forma més objectiva questes patologies, i sembla també que de forma més ràpida. És per això que el convidem a participar en aquest estudi: *Efficacy evaluation of clinical prediction rules to reduce diagnostic time of venous thromboembolism in the emergency department.*

Aquest estudi el durà a terme l'investigador / a: Anna Taberner i M. Àngels Gispert.

Abans de confirmar la seva participació en l'estudi de recerca, és important que entengui en què consisteix. Llegiu detingudament aquest document i faci totes les preguntes que li puguin sorgir.

Objectiu de l'estudi:

Aquest estudi pretén analitzar si l'aplicació d'escales diagnòstiques disminueix el temps des de la sospita fins a la confirmació diagnòstica en el cas de la malaltia tromboembòlica.

Participació voluntària:

Vostè és completament lliure de triar participar o no en l'estudi. La seva decisió no influirà en la seva atenció mèdica.

Nombre de pacients i durada estimada de la participació dels pacients:

En aquest estudi es preveu la participació d'un total de 316 pacients atesos al servei d'urgències de l'Hospital Universitari de Girona Doctor Josep Trueta amb motiu de consulta de sospita de malaltia tromboembòlica. Es preveu una durada total de l'estudi de 3 anys.

Procediments de l'estudi

En el seu cas, i depenent de la sospita diagnòstica, s'aplicarà l'escala de Wells. Aquesta és una escala que ens prediu la possibilitat que vostè pateixi aquesta malaltia, i ens classifica als pacients en tres grups de risc: baix, mitjà i alt.

Segons el resultat d'aquesta escala s'aplicarà l'algoritme diagnòstic més adequat basat en l'evidència científica actual, per confirmar o descartar la patologia tromboembòlica.

Beneficis i riscos esperats

Vostè no corre cap risc esperat derivat de la participació en l'estudi. Esperem que es beneficiï d'un diagnòstic més ràpid i un inici del tractament amb més premura.

Confidencialitat

D'acord amb la Llei Orgànica 15/1999, de 13 de desembre, de protecció de dades de caràcter personal (LOPD) i Reial Decret 1720/2007, les dades personals i de salut (ja constin en la seva

història clínica ja els hagi proporcionat com conseqüència de la seva participació en aquest estudi) que es recullin amb motiu d'aquest estudi són els necessaris per cobrir els objectius d'aquest. Aquestes dades seran identificats per mitjà d'un codi per garantir la confidencialitat de la seva identitat i únicament el metge tindrà accés a aquesta informació.

Tanmateix, els representants autoritzats del promotor poden necessitar accedir a la seva història clínica que conté dades personals (no codificats) per tal de garantir que l'estudi s'estigui duent a terme de forma adequada i que les dades documentats són correctes. També podran accedir a aquestes dades les autoritats sanitàries i el Comitè Ètic d'Investigació Clínica. Tots ells mantindran en tot moment la confidencialitat d'aquesta informació.

Les dades que es recullin amb motiu d'aquest estudi, entre els quals es trobaran dades personals i de salut (ja constin en la seva història clínica ja els hagi proporcionat com a conseqüència de la seva participació en aquest estudi) seran processats i analitzats pels investigadors amb la finalitat d'avaluar-les científicament. Si vostè decideix participar en aquest estudi estarà consentint expressament en el tractament de les seves dades personals i de salut pel promotor. Tot això de conformitat amb la LOPD i amb la normativa que la desenvolupa.

Vostè podrà exercitar en qualsevol moment els seus drets d'accés, rectificació, cancel·lació i oposició dirigint-se al metge que l'atén en aquest estudi el qual ho ha de posar en coneixement del promotor.

Així mateix, els resultats de l'estudi poden ser comunicades a les autoritats sanitàries i eventualment a la comunitat científica a través de congressos i publicacions sense que la seva identitat sigui revelada en cap moment.

Preguntes / Informació:

Per fer alguna pregunta o aclarir algun tema relacionat amb l'estudi, o si necessita ajuda per qualsevol problema de salut relacionat amb aquest estudi, si us plau, no dubti en posar-se en contacte amb:

Dr: .....

Telèfon: .....

L'investigador li agraeix la seva inestimable col·laboració.

16.9. Informed consent

CONSENTIMENT INFORMAT PER A LA REALITZACIÓ DE L'ESTUDI

(Gener 2020, versió català)

TÍTOL DE L'ESTUDI: *Efficacy evaluation of clinical prediction rules to reduce diagnostic time of venous thromboembolism in the emergency department.*

CODI DEL PROMOTOR: .....

PROMOTOR: .....

INVESTIGADORS PRINCIPALS: *Anna Taberner, M. Àngels Gispert*

CENTRE: *Hospital Univeristari Josep Trueta*

☐ He llegit el full d'informació de l'estudi i rebut la informació suficient.

☐ Entenc que l'estudi inclou l'aplicació d'escales i algoritmes diagnòstics per facilitar la correcta diagnosi del meu problema de salut.

☐ Comprenc que la meva participació és voluntària.

☐ Comprenc que puc retirar-me de la participació en l'estudi:

- Quan vulgui.
- Sense haver de donar explicacions.

☐ Comprenc que tinc els drets d'accés, rectificació, supressió, oposició, limitació del tractament de dades i, fins i tot, a traslladar les meves dades a un tercer autoritzat (portabilitat), d'acord amb el que disposa el nou Reglament de Protecció de Dades (UE) 2016/679 del Parlament Europeu i del Consell, de 27 d'abril de 2016, relatiu a la protecció de les persones físiques en referència al tractament de dades personals i a la lliure circulació d'aquestes dades, i en el seu defecte, la Llei orgànica 3/2018, de 5 de desembre, de protecció de dades de caràcter personal, i el Reglament que la desplega.

☐ Presto lliurement la meva conformitat per participar en l'estudi.

[Rúbrica del pacient] [Rúbrica de l'investigador]

Nom: ..... Nom: .....

Data: ..... / ..... / .....