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On Diagnostic Procedures in Pulmonary Embolism

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original papers which are referred to by their Roman numerals.

I. Nilsson T, Söderberg M, Lundqvist G, Cederlund K, Larsen F, Rasmussen E, Svane B, Brohult J, Johnsson H.
A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as gold standard.
Scandinavian Cardiovascular Journal 2002; 36: 373-7.

II. Söderberg M, Hedström U, Sjunnesson M, Lärfars G, Jorup-Rönström C. Initial symptoms in pulmonary embolism differ from those in pneumonia: a retrospective study during seven years.
European Journal of Emergency Medicine 2006; 13: 225-9.

III. Ljungqvist M, Söderberg M, Ahlgren A, Moritz P, Lärfars G.
Evaluation of Wells score and repeated D-dimer in diagnosing venous thromboembolism.
European Journal of Internal Medicine 2008; 19: 285-8.

IV. Söderberg M, Brohult J, Jorfeldt L, Lärfars G.
The use of D-dimer testing and Wells score in patients with high probability for acute pulmonary embolism.
Journal of Evaluation in Clinical Practice, accepted Dec 2007.
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V. Söderberg M, Schulman S, Lärfars G.
Expression of von Willebrand factor antigen in pulmonary embolism and deep venous thrombosis.
Submitted 2008

ABSTRACT

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are two entities of venous thromboembolism (VTE). PE is a common cause of mortality and morbidity. The symptoms and signs of PE are difficult to interpret, and the diagnosis is difficult to establish. Other diseases can have a similar clinical presentation as PE, increasing the risk for misdiagnosis and inappropriate treatment. A rapid and prompt diagnosis of PE is crucial and has an impact on the mortality rate.

In **Paper I**, we studied 90 hemodynamically stable patients with suspected PE. Computed tomography of the pulmonary arteries (CTPA), and pulmonary arteriography (PA) were performed, the D-dimer was measured, and the diagnostic accuracy of these tests was compared. The prevalence of PE was 37%. CTPA had a positive predictive value (PPV) of 94% and a negative predictive value (NPV) of 95%. With a cut-off of D-dimer of 0.25 mg/L, the PPV was 63% and the NPV was 92%. We concluded that CTPA has a higher sensitivity than D-dimer for diagnosing PE, and that a cut-off value of 0.25 mg/L is sufficient as a screening method, although CTPA is recommended to exclude false positive cases.

In **Paper II**, we retrospectively examined the symptoms and signs in a group of patients with PE (PE/infection, n=25), who were misdiagnosed initially with pneumonia and compared these with the symptoms and signs of patients with correct diagnoses of PE, (PE/medicine, n=64) and community-acquired pneumonia, (CAP, n=54). Dyspnoea and pleuritic chest pain as initial symptoms contributed to 76% (PE/infection), 81% (PE/medicine) and 9% (CAP). Fever, chills, or cough contributed to 8%, 16%, and 80%, respectively. Body temperature, C-reactive protein (CRP), and the presence of pulmonary infiltrates on chest X-rays were higher in PE/infection and CAP than in PE/medicine. The symptoms did not differ significantly between the two PE groups. Dyspnoea and pleuritic chest pain were the predominant initial symptoms in patients with PE whereas fever and cough were the predominant symptoms in patients with CAP. High levels of CRP and the presence of pulmonary infiltrates did not exclude PE.

In **Paper III**, we studied 151 patients with suspected DVT and PE with a Wells pre-test probability score ≤1.5 points and a D-dimer <0.5 mg/L, to determine whether the score and test safely exclude VTE and whether a follow-up D-dimer test measured 3-7 days after admission adds extra information. The patients were followed for three months. A follow-up D-dimer was available for 67% of the patients and was elevated in 13%. None of these patients had a VTE diagnosed. All patients were contacted after three months, and none had clinical signs of VTE. We concluded that a low Wells score and a normal D-dimer safely exclude VTE in patients at the emergency department (ED) and that a follow-up D-dimer test adds no extra information.

In **Paper IV**, we evaluated the diagnostic accuracy of the Wells score, D-dimer, and PA or CTPA to diagnose 120 patients with an intermediate to high risk of PE. The cut-off D-dimer level of 0.5 mg/L was adequate with an NPV of 92%. The combination of the Wells score and D-dimer gave an NPV of 94%, and a cut-off of Wells score of four points was adequate. We concluded that D-dimer and Wells score are safe methods of ruling out PE in patients with intermediate to high risk of

PE, although the specificity is low. Both CTPA and PA can yield false negative and false positive results, which can be difficult to interpret.

In **Paper V**, we compared (a) the level of von Willebrand factor antigen (vWF) on inclusion and after three months in 46 patients with symptomatic PE without signs of DVT, with (b) the level in 45 patients with symptomatic DVT without signs of PE. The mean level of vWF was 1.87 IU/mL in the PE group and 1.64 IU/mL in the DVT group at inclusion. Patients with proximal DVT had a mean level of 1.88 IU/mL and patients with distal DVT had a mean level of 1.52 IU/mL. After three months, the mean level of vWF was 1.45 IU/mL (PE), 1.41 (all DVT), 1.65 (proximal DVT) and 1.28 (distal DVT), respectively. These findings suggest that the level of vWF differs between PE and DVT. The levels of vWF is similar in patients with PE and proximal DVT, whose vWF level is significantly higher than in patients with distal DVT. This difference may indicate that vWF reflects the extention of a DVT.

Conclusions

These studies show that the diagnostic accuracy of CTPA is high and better than D-dimer in diagnosing PE, and that PA and CTPA can produce different results. The initial symptoms of PE are often typical and can be used to discriminate PE from pneumonia. High levels of CRP and body temperature, and findings of pulmonary infiltrates are common in PE. Wells score and D-dimer have a high NPV and can safely exclude PE in patients with suspected PE and DVT. The cut-off of 0.5 mg/L in D-dimer and four points in the Wells score are ade-quate and can be recommended. A follow up measurement of D-dimer after 3-7 days adds no extra information. The vWF level is higher in patients with PE and proximal DVT than in those with distal DVT, indicating the similarity of PE and proximal DVT. The vWF levels can be used to indicate the extension of the thrombus. The levels of vWF decreases after three months in patients with PE and DVT.

The diagnostic work-up of patients with suspected PE should comprise an eva-luation of symptoms, signs, risk factors, and alternative diagnoses. When the suspicion of PE is high, an evaluation of Wells score is recommended, followed by a D-dimer if the score is low. A low Wells score and a low D-dimer can safely exclude PE. If the Wells score or D-dimer is elevated, a diagnostic test is man-datory. CTPA and PA produce equivalent results, although CTPA is recom-mended because of its availability.

Keywords: CTPA, D-dimer, deep venous thrombosis, pre-test probability score, pulmonary arteriography, pulmonary embolism, venous thromboembolism, von Willebrand factor antigen, Wells score.

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ABBREVIATIONS

Ab	Antibody
ACCP	American College of Chest Physicians
APC-R	Resistance to activated protein C
AUC	Area under the curve
BMI	Body mass index, kg/m^2
BNP	Brain natriuretic peptide
CAP	Community-acquired pneumonia
CI	Confidence interval
CID	Clinic for Infectious Diseases
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTPA	Computed tomography of the pulmonary arteries
CXR	Chest X-ray
DVT	Deep venous thrombosis
ECG	Electrocardiography
ED	Emergency department
ELISA	Enzyme-linked immunosorbent assay
HRT	Hormone replacement therapy
h	Hour(s)
iv	Intravenous
LMH	Low molecular weight heparin
NPh	Nasopharynx (cavity)
NPV	Negative predictive value
OAVK	Oral anti-vitamin K treatment, e.g. warfarin
OC	Oral contraceptives
OR	Odds ratio
PA	Pulmonary arteriography
PAP	Pulmonary artery pressure
PE	Pulmonary embolism
PPV	Positive predictive value
PTS	Postthrombotic syndrome
ROC	Reciever operating characteristics
RV	Right ventricle (in the heart)
s	Second(s)
sc	Subcutaneous
t-PA	Tissue plasminogen activator
V/Q-scan	Ventilation-perfusion lung scintigraphy
VTE	Venous thromboembolism
UFH	Unfractionate heparin
vWF	von Willebrand factor antigen
yr	Year(s)

INTRODUCTION

BACKGROUND

Pulmonary embolism (PE) has traditionally been considered an entity of venous thromboembolism (VTE) along with deep venous thrombosis (DVT).

Venous thromboembolism
DVT and PE share in many aspects the same pathoanatomical changes, risk factors, epidemiology, background and therapeutic recommendations [1,2]. However, the clinical presentation, management, and outcome, and possibly the pathophysiology can differ. DVT is a common finding in patients with PE [3] but the signs of DVT are not found in all patients with PE even when bilateral venography is performed. In patients with symptomatic PE, up to 80% have asymptomatic DVT [4]. More than 50% of patients with proximal DVT have pathological radiological chest examinations, indicating asymptomatic PE. In a study of patients with DVT, 22% had pathological lung scintigraphy without symptoms of PE [5]. The embolic risk of DVT is related to the localization and characteristic of the thrombus and to adequate anticoagulant treatment. The risk of PE from an undiagnosed proximal DVT is 40% which decreases to ~5% in treated. The risk of PE from a distal DVT is much lower, but many distal DVTs extend proximally if left untreated.

Definition of PE
PE is a sudden occurence of a blood clot in a pulmonary artery with obstruction of the blood supply to the lung circulation. Embolization occurs when a venous thrombus is dislodged from the endothelial wall of a vein and passes through to the lung circulation. Depending on its size and length, the embolus may occlude different parts of the arterial branch, from the main pulmonary artery, through the bifurcation (saddle embolus), to the left or right pulmonary artery along to the smaller branching pulmonary arteries. The clots arise to a large extent from thrombi within the large deep veins in the legs, mainly the iliac, femoral, and popliteal veins, and less commonly from more distal veins or veins from other locations, such as the heart.

The consequence of a PE can vary between patients. More than 90% of the patients with a diagnosed PE have a non-massive PE [6], and about 5% have a massive PE requiring thrombolytic therapy. The consequence of a PE depends on concomitant disabling diseases such as chronic obstructive pulmonary disease (COPD), congestive heart failure, or malignancy. As reviewed by Nijkeuter et al, more than 50% of the patients with PE still have radiological defects after six months [7], indicating the severity of PE as a chronic disease, although the clinical symptoms were not evaluated in the studies reviewed. Many patients with VTE have an underlying inherited predisposing risk factor that becomes visible clinically in response to an acquired stressor, such as surgery, trauma, or severe medical illness.

Although the symptoms and signs of acute PE are obvious clinically, it is sometimes difficult for the attending physician at the ED to recognize them and perform the correct diagnostic investigation, thus postponing the correct treatment. To diagnose PE correctly, one must think of the disease as a diagnostic possibility.

Hemodynamics in PE
The hemodynamic changes in PE depend mainly on the size of the emboli, but other factors play a role. An acute PE increases the pulmonary vascular resistance, mainly because of to hypoxic vasoconstriction. The pulmonary artery pressure (PAP) can be increased up to 40 mmHg if there is no underlying cardiovascular disease and up to 80 mmHg if there is. In extreme cases, the PAP can exceed the systemic blood pressure: i.e. >100 mmHg [8]. The increased PAP can cause right ventricular distress with dilatation, hypokinesis, tricuspid regurgitation, and right ventricular failure. If the pathological process proceeds, signs of left ventricular failure with paradoxical motions of the septal wall, which disturbs the left ventricular function, may be evident. As the stress in the ventricles continues, the patient may be at risk of developing cardiac ischemia as the distended right ventricle (RV) compresses the right coronary artery. Often >50% obstruction of the pulmonary vascular bed is needed to induce a significant raise in the PAP, and the effect of the raised PAP can vary between patients.

An acute PE impairs gas exchange in the lungs between oxygen and carbon dioxide (CO_2) causing hypoxemia (low arterial oxygen saturation). Mismatched perfusion and ventilation are the main reasons, but other mechanisms are involved, including redistribution of blood flow with variations of the ventilation/perfusion (V/Q) ratios in different parts of the lung [9]. The hypoxemia causes reflexive increased ventilation, often seen as tachypnoea and hypocapnia (low arterial CO_2 content) in arterial blood gases, albeit normal pCO_2 is the most common finding. Hypercapnia (high arterial CO_2 content) can be seen in massive PE, reflecting an increased dead space. A prompt diagnosis and risk stratification of the patient with PE is mandatory to diminish the risk of mortality and morbidity.

Risk stratification, classification an definitions of PE [6,8]
Risk stratification of patients with PE is important to determine the appropriate management. The tools for risk stratification include clinical findings, especially heart and respiratory rates, peripheral oxygen saturation and blood pressure; signs on electrocardiogram (ECG) of right ventricular failure (T-wave inversions in V_{1-4}, $S_1Q_3T_3$-syndrome, and right bundle branch block); elevated cardiac biomarkers (troponins and brain natriuretic peptide, BNP) and signs of right-sided heart failure on echocardiography and CTPA [10].

Classifications of PE [6,11]
Acute PE: PE developed over a short period of time.
Chronic PE: PE with recurring embolization despite treatment. The disease develops over several years.

Clinical classification of PE:
Idiopathic PE: no known risk factor.
Primary PE: thrombophilia as risk factor
Secondary PE: identifiable risk factor(s) such as pregnancy, cancer, surgery or trauma.

Anatomically massive PE: More than 50% obstruction of the vascular bed or two or more of the lobar arteries.
Clinically massive PE: PE with signs of shock or hypotension (blood pressure <90 mmHg or a pressure drop >40 mmHg for >15 min)
Nonmassive PE: all other PE.
Submassive PE: nonmassive PE with signs of right ventricular dysfunction on echocardiography but without hemodynamic instability.
Massive and submassive PE can be divided into *Type A:* PE with highly mobile emboli, arising from peripheral veins (poorer prognosis), and *Type B:* PE with immobile emboli, originating in the RV (better prognosis).

Stable hemodynamics: PE, regardless of size, with normal blood pressure, arterial saturation, heart and respiratory rates, and ECG.
Unstable hemodynamics: PE with two or more of the following criteria: (i) systolic hypotension (blood pressure <100 mmHg), (ii) elevated troponins, or BNP >500 pg/mL, (iii) RV dysfunction on echocardiography, (iv) peripheral arterial saturation <95%, and (v) two of three of the following: heart rate greater than systolic blood pressure, dyspnoea, and syncope (the “triad of death”).

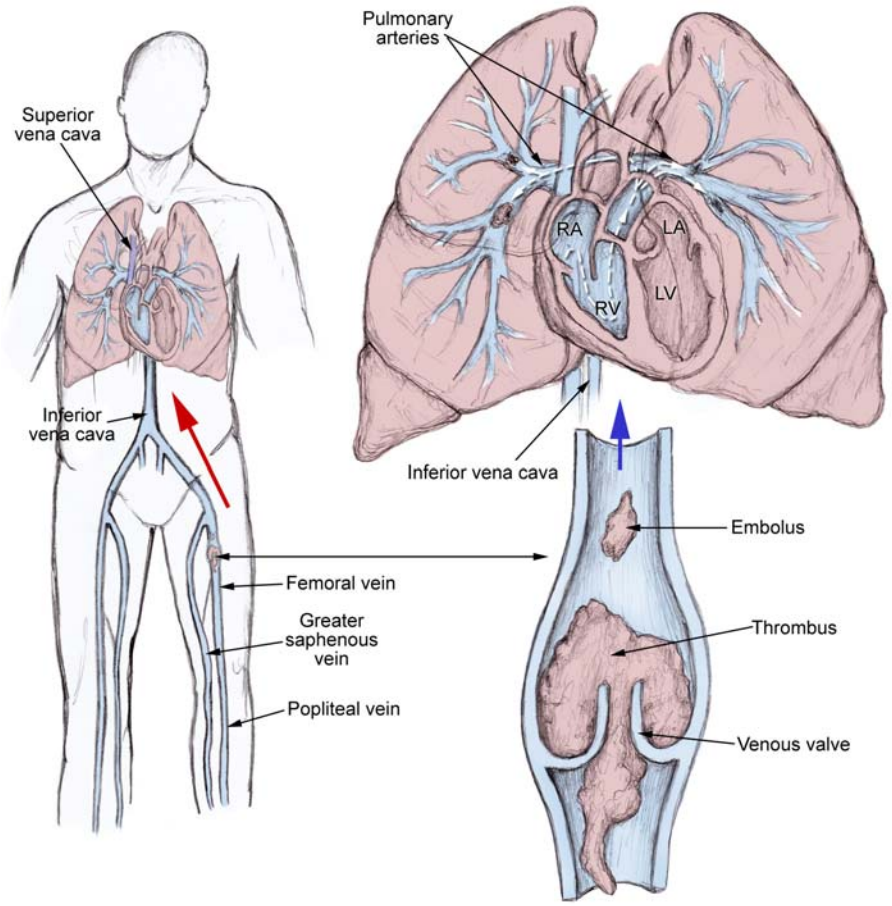

Fig. 1. PE most commonly arises from the deep veins in the leg. The thrombi originate from the venous valves and travel through the right side of the heart to the lung circulation. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle. Figure from www.emedicine.com

Treatment
The tradtional treatment for PE is anticoagulant treatment with iv unfractionate heparin (UFH) or sc injections with low molecular weight heparins (LMH) and concomitant treatment with oral anti-vitamin K (e.g. warfarin) for at least three months [2,12]. According to the 2008 ACCP (American College of Chest Physicians) guidelines, the factor Xa inhibitor fondaparinux is also considered as a firstline option for treatment of VTE [2]. The risk of bleeding associated with UFH is less than 3%, and even lower for treatment with LMH [13]. The risk of complications is higher with older age and increased dosage of heparins.

Other treatment options for PE are thrombolysis with streptokinase or tissue plasminogen activator (t-PA), surgical thrombembolectomy, percutaneous intravascular intervention, catheter extraction, and introduction of a filter in the inferior caval vein to prevent further embolization, but these latter treatments are used only for selected patients in special settings [2].

There are several ongoing studies of new direct- and indirect acting anticoagulants. Anticoagulants can inhibit the initiation or propagation of coagulation or can target thrombin, which attenuates the fibrin formation. Indirect anticoagulants act through naturally occurring plasma cofactors such as antithrombin or heparin cofactor II, e.g. idraparinux and dabigatran (antithrombin mediated) and odiparcil (heparin cofactor II mediated). Direct anticoagulants, such as rivaroxaban and apixaban (direct factor Xa inhibitors) and RB 006 (factor IXa inhibitor) act by inhibiting special coagulation proteins. There are also studies on direct thrombin inhibitors. The main aims of these studies are to investigate the safety profiles, monitoring needs, antidotes, complication rates, and economic factors associated with these drugs. The near future will decide their place in the treatment for venous thromboembolic disease [14].

HISTORICAL REMARKS

The word “thrombosis” was first used by Galenos (130-200 AD) in Greece, but the disease was known by the Chinese several hundred years earlier. The term “pulmonary embolism” was first described by the British surgeon Richard Wiseman in 1676.

The term “venous thromboembolism” was introduced by the German pathologist Rudolf Virchow (1821-1902) in the mid-19th century when he found signs of DVT and PE in the same patient at an autopsy [15]. Virchow also described a principle to explain the pathological mechanisms underlying thrombosis:

1. changes in the blood flow (blood velocity)
2. changes in the vein vessel wall, and
3. changes in the circulating blood (prothrombotic agents)

This principle is known as “**Virchow´s triad**”. Today, most known risk factors and features of VTE can be attributed to one or more of the mechanisms described in the triad.

Since Virchow´s description several scientists and physicians have identified risk factors for VTE and clinical settings where VTE is present. Trauma (Azam 1864),

surgery (von Strauch 1894), cancer (Trosseau 1872), and pregnancy [16] are known risk factors. Inherited coagulation deficiencies such as deficiency in antithrombin, first described by the Norwegian scientist Olav Egeberg (1916-1977) in 1965 [17], and the factor V Leiden mutation (G1691A), resistance to activated protein C (APC-resistance) described in Leiden, Belgium and Lund, Sweden by Dahlbäck et al. 1993 [18] have also been identified as risk factors for VTE, along with other deficiencies [19,20].

The treatment for VTE has changed rapidly and has became more efficient after the characterization and purification of heparin by Erik Jorpes in Stockholm, Sweden, in 1926 [21] and by Charles and Scott in Toronto, Canada, in 1935. Treatment of PE with UFH was shown to be more efficient than no treatment [22]. Anti-vitamin K treatment (K for coagulation) with warfarin was introduced in the 1940s and streptokinase in the 1940-50s [23]. A later landmark in the treatment of VTE was the introduction of low-molecular weight heparins in the 1990s [24] which now allows out-of-hospital care and self-treatment of most patients with DVT [12].

EPIDEMIOLOGY

Although PE is a common disease its true prevalence is unknown. The estimated incidence of PE in the Western world exceeds 1 per 1,000 inhabitants [25], and the annual incidence of VTE in Sweden is 1.5-2 per 1,000 inhabitants. PE is a multi-causal disease it is the most common cardiovascular cause of death after acute myocardial infarction and ischemic stroke. In 2006, about 42% of all deaths in Sweden were caused by cardiovascular diseases (Socialstyrelsen, The Swedish National Board of Health and Welfare [26]), but only 447 of all 91,271 deaths 2006, i.e. <0.5% had PE as the main cause of death, according to the International Classification of Diseases, 10th version (ICD-10, code I26.0 and I26.9), on the death certificate. PE is underdiagnosed, and the real incidence may be 10 times higher than the value derived from clinical diagnosis, hospital records, autopsies, and death certificates. The autopsy frequency in Sweden is low.

The diagnosis is confirmed in only 20-30% of patients with suspected PE that is investigated [27]. This highlights the nonspecific signs and findings in patients with suspected PE and the need for a more accurate diagnostic work-up.

If left untreated, the mortality rate of PE is 30-35% [28], and the overall mortality during the first three months is 7.7-17% [25,29,30]. Seventy percent of patients who die from PE, die within the first four hours [31] and about 10% of patients with PE die within the first hour [32]. Laporte et al showed that patients with symptomatic PE at presentation have a more than fivefold higher risk for fatal PE compared with patients with initial DVT without symptomatic PE. Independent risk factors associated with fatal PE are age >75 yr, cancer, and immobilization due to neurological disease [33]. The risk for recurrent VTE is higher in patients with a first PE than in patients with DVT [34]. PE is sometimes seen as the final killer in patients with severe chronic disease (a ”coup de grace”). Sudden unexplained deaths where the autopsy shows PE, is not uncommon in surgery, oncology, and geriatrics departments, and in pregnant women [35]. Introduction of preoperative thromboprophylaxis with LMH in immobilized orthopaedic patients [36,37] and before cancer surgery has reduced the mortality in PE and prevalence of VTE, but VTE is still the second most common cause of death in patients with cancer. Almost 75% of all deaths from PE arise from hospital-acquired VTE. Thus, PE is important

because it is common, has a high mortality if left untreated, is often misdiagnosed or asymptomatic and death can be prevented with appropriate prophylaxis [38].

COAGULATION AND HEMOSTASIS

Venous thromboembolism is a multicausal condition, and many factors can contribute to shift the fine balance from normal coagulation towards a hyper-coagulable state. It is difficult to predict which individual will develop a VTE. Coagulation is defined as the process that occurs when the blood coagulates inside or outside the blood vessels. The procoagulants are balanced by an anticoagulant system. Hemostasis is defined as the normal pathways that balance bleeding and thrombosis, or the process that maintains the integrity of the circulatory system after vascular damage [39].

Normal coagulation

Normal coagulation has been described traditionally as a pathway of enzymatic reactions that triggers a sequnce in a distinct order or cascade. This cascade model comprises two pathways that converge to a final endpoint- the generation of thrombin, which stabilizes the fibrin clot. The procoagulant pathway is balanced by the anticoagulant pathway which is activated simultaneously to avoid intravascular pathological coagulation. In the **primary hemostatic** process, the platelets are activated and, together with circulating procoagulant factors and the vessel endothelium, form an unstable thrombocytic clot. The **secondary hemostatic** process then starts to form the more stable fibrin clot. Procoagulants, calcium, and inhibitors of activated procoagulants together with factor V, VIII, IX, and X, form a stable clot. There are three pathways of natural inhibition of the coagulation: tissue factor pathway inhibitor system, the heparin-antithrombin system and the protein C system. They are activated to avoid exaggerated coagulation [39,40,41].

Thirteen circulating coagulation factors that regulate the coagulation pathways have been identified in the blood. These are normally inactive. The coagulation factors are synthesized in the liver, except for factor V (which is synthesized in the thrombocytes) and factor VIII (which is synthesized in the endothelium). Factor II, VII, IX and X are vitamin K dependent and fibrinogen, factor V, VIII, XI and XIII are thrombin dependent. When trauma to a vessel occurs, the coagulation process starts immediately to produce a clot to stop the bleeding and heal the wound. The process of coagulation can be triggered by other mechanisms, such as micro-organisms and tumor cells, which initiate a pathological intravascular coagulation process, resulting in thrombus formation. Hoffman and Monroe described a cell-based *in vivo* model of the coagulation process with three overlapping steps- initiation, amplification, and propagation of the coagulation- which emphasizes the interaction between cellular and plasma factors [42]. A recent review by Furie and Furie [39] also discusses this new model.

The hypercoagulable state

Fibrinogen is the precursor of fibrin, the end product of secondary hemostasis. Fibrinogen comprises dimers of three subunits that are encoded by three genes on chromosome 4. The levels of fibrinogen are defined genetically and environmentally. The soluble fibrinogen is cleaved by thrombin to form a fibrin monomer that polymerizes to form an insoluble fibrin clot. Factor XIII links the fibrin chains to stabilize the fibrin network. High levels of fibrinogen have been described in patients with VTE [43] although other studies, have shown no elevated fibrinogen levels [44].

Many conditions, such as inflammation, infection, and malignancy, can induce a hypercoagulable state, but the thrombotic mechanisms differ between these predisposing conditions. When the regulatory mechanisms are overwhelmed, consumption of coagulation proteins and platelets can cause disseminated intravascular coagulation (DIC) with thrombosis and bleeding, a life-threatening condition.

DIAGNOSIS OF PULMONARY EMBOLISM

Until the 1960s, the diagnosis of PE was clinical or based on nonspecific findings or autopsy. Pulmonary arteriography was introduced by Sasahara and Williams in 1963 [45]. Perfusion lung scintigraphy was described in 1964, and ventilation scanning was developed a few years later [46]. Unfortunately, both PA and V/Q-scan had major disadvantages. The complication rate of PA, being an invasive technique, was initially high, but has decreased below 2% [47]. The high rate of nonconclusive lung scan (40-60%) and the problems interpreting the results are described in the large PIOPED study (Prospective Investigation Study of Pulmonary Embolism Diagnosis) [27] and subsequent studies [48,49]. From the 1970s to the early 1990s the diagnostic procedures included performance of a V/Q scan or PA in selected patients. The search for a more accurate and validated investigational tool continued, and helical CT, later named CTPA, was first described in 1992 by Remy-Jardin et al [50]. CTPA has advantages over lung scan and PA [51]. The CTPA can visualize a thrombus in the pulmonary artery directly as an intraluminal filling defect, the investigation is fast (less than 30 s), many alternative diagnoses can be revealed, and the interobserver agreement of the interpretations is high [52]. The accuracy of the diagnosis of PE with CTPA is debated. With the modern technique of multidetector-row CT (MDCT), the specificity and sensitivity are high [53], but misinterpretations can occur [54].

To diagnose PE, the physician must think of the possibility of PE and diagnosing PE is challenging. Clinical suspicion is often raised when a patient seeks medical care with a sudden onset of dyspnoea without another obvious explanation. The presentation is largely variable and heterogeneous. A small PE may cause few or no symptoms in a healthy young adult, but may present with significantly life-threatening symptoms in an older person with cardiopulmonary disease. The findings are nonspecific and many conditions can mimic PE. The clinical work-up of patients with suspected PE is divided into the evaluation of:

1. Symptoms and signs
2. Alternative diagnoses
3. Risk factors
4. Pre-test probability score
5. D-dimer
6. Diagnostic investigations

Symptoms and signs of PE

PE is a disease with different clinical expressions in different patients. The presentation can vary from a clinically silent disease to an acute life-threatening condition requiring intensive care treatment with thrombolysis. PE is potentially fatal. The clinical accuracy and recognition of signs of PE are often inaccurate, and objective diagnostic tests are mandatory in patients with clinical suspicion of PE. Concomitant medical conditions, especially cardiovascular and pulmonary disease, as well as malignancy, along with findings of ongoing medication, hereditary anamnesis, body constitution, and time from onset of the first symptom (patient's delay), can significantly affect the attending physician's ability to diagnose PE. The degree and extent of the vessel occlusion also influences the presentation. Both symptoms and signs of suspected PE can be found in patients with other diseases when PE is excluded [55,56].

Overt and easily recognizable symptoms of PE occur when the compensatory mechanisms in the body are unable to maintain hemodynamic stability; hence, the symptoms can arise from several different organ systems. Prodromal symptoms in PE are most often respiratory or cardiovascular, but can also present as neuro-logical (fainting, seizures, confusion), psychological (apprehension, anxiety), or gastrointestinal (nausea, vomiting) symptoms.

The most common clinical findings in PE are acute onset of dyspnoea at rest or on exertion, and tachypnoea (respiratory rate ≥20 min^{-1}). In a study by Stein et al [57], 90% of patients with PE presented with these symptoms. Other common findings are pleuritic chest pain, shortness of breath, and tachycardia. Less frequent are fainting, anxiety, hemoptysis, nonspecific chest pain, swollen legs (concomitant DVT), cough, or unexplained fatigue or worsening of known chronic disease such as chronic heart failure COPD [58]. PE can present as supra-ventricular arrhythmia such as atrial fibrillation or can mimic pneumonia with productive cough, fever, and dyspnoea. Stein et al also showed that 98% of patients with PE have one or more of the following findings: dyspnoea, tachypnoea, pleuritic chest pain, atelectasis on chest X-ray (CXR), or parenchymal abnormality on CXR. The most common symptoms and signs of PE are listed in **Table 1.**

Table 1.

Common symptoms and signs in patients with PE, frequencies in % [56,57,58]

Symptoms	**%**	**Signs**	**%**
Dyspnoea	73-80	CXR abnormalities	84
dyspnoea at rest	60	Tachypnoea, ≥20 min^{-1}	51-70
dyspnoea at exertion	13-18	Lung examination (any)	32-45
Orthopnoea	31-39	rales (crackles)	26-51
Cough	37-44	wheezes	3-4
Wheezing	25-33	rhonchi	4-6
Pleuritic chest pain	33-66	decreased sounds	29
Swollen leg	28-46	Tachycardia, >100 min^{-1}	21-30
Unspecific chest pain	13-26	Signs of DVT	11
Hemoptysis	13	Hypotension, <100mmHg	8
Syncope	10	Fever, >38.5ºC	0-7
Palpitations	10	Cyanosis	1

The clinical presentation combined with a history and physical examination can help in the diagnostic work-up in patients with suspected PE. Arterial blood gases, ECG, and CXR can help identify alternative diagnoses, and echocardiography can help assess the severity of PE. These investigations are nonspecific and patients with PE can have pathological findings, although normal findings do not exclude PE [59].

The most classical findings on **arterial blood gases** in patients with PE are hypoxemia and hypocapnia. However, the blood gases are normal in >50% of patients with suspected PE [60], and in 15% of patients with proven PE [61].

The **ECG** can show sinus tachycardia, atrial fibrillation and signs of right-ventricular strain with $S_1Q_3T_3$-syndrome (**Fig. 2**), right bundle-branch block, and T-wave inversion in lead V_{1-3}. These signs are nonspecific and the most common finding in PE is normal ECG, although patients with massive PE often show dramatic changes in ECG [62].

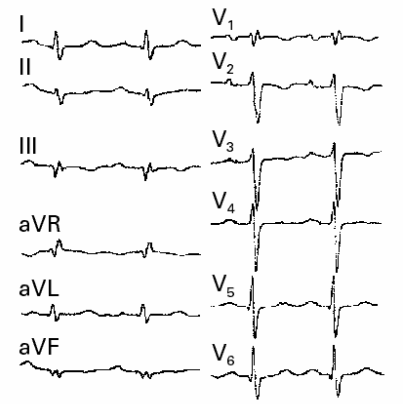

Fig. 2
The $S_1Q_3T_3$ syndrome on ECG in a patient with acute PE and RV dysfunction.

The **chest X-ray** is often abnormal in PE [27,56], and a variety of findings has been described, such as atelectasis, parenchymal consolidations (infiltrates), pulmonary oedema, elevated hemidiaphragm, focal oligemia (an area with diminished blood supply; Westermark's sign), enlarged right pulmonary artery (Palla's sign), pleuritic fluid, and a wedged-shaped density indicating an early lung infarction (Hampton's hump) etc. All of these changes are common but nonspecific and only suggestive of PE. The main value of CXR is to find an alternative diagnosis.

The use of **echocardiography** is well studied in PE [63,64]. Echocardiography is of value at the time of diagnosis and in the follow-up of patients with PE. Signs of right-sided systolic dysfunction are associated with increased mortality and echocardiography is mandatory in the work-up of patients with signs of massive PE requiring thrombolytic therapy [2,65]. More than 50% of patients with PE have a normal echocardiographic pattern.

Alternative diagnoses in PE

The clinician should consider various conditions when a patient seeks medical care with symptoms and signs suggestive of PE. The most common alternative diagnoses are probably congestive heart failure (CHD), COPD, and pneumonia. An alternative diagnosis, especially anxiety, asthma or COPD, viral syndromes, and musculoskeletal pain can cause the physician to diagnose PE infrequently at the ED [66]. Conditions with dyspnoea, chest pain, tachycardia, and tachypnoea are

common, and PE should always be considered as a possible diagnosis when a patient presents with these findings. Common alternative diagnoses to PE are shown in **Table 2.**

Table 2.

Common alternative diagnoses in PE [67]	
Anxiety, panic disorder	Lung tumour
Aortic aneurysm	Perimyocarditis
Asthma	Pneumonia, bronchitis, pleuritis
COPD	Pneumothorax
Chronic pulmonary hypertension	Rib fracture
CHD, pulmonary oedema	Tachy-arrhythmias, atrial fibrillation
Myocardial infarction	Viral infections

Risk factors

Numerous risk factors for VTE have been described, and the most common are shown in **Table 3.** Genetic, acquired, and mixed risk factors of uncertain origin or significance have been described. Some risk factors are probably markers for VTE or just found in patients with VTE. The risk factors are additive and can have different effects on the risk of developing a VTE. Some conditions and factors are more common, as described in **Table 4**, and the Odds ratios for the different factors are described in **Table 5.** The term thrombophilia includes any genetic or acquired risk factor associated with an increased tendency for VTE [20].

Table 3 .

Risk factors for venous thromboembolism [6,32,68]

Primary, genetic, or mixed risk factors [19,69,70,71]	
Deficiency in antithrombin [17]	Hyperhomocysteinemia [72]
Dysfibrinogenemia [73]	Hyperviscosity syndromes [74]
Factor V Leiden, G1691A, APC-R [18,75]	Some platelets abnormalities [74]
High level of factor VII [43]	Prothrombin gene polymorphism [76]
High level of factor VIII [77]	Protein C deficiency [78]
High levels of factor IX [79] and XI [80]	Protein S deficiency [81]
Elevated lipoprotein (a) [82]	High level of thrombin activated fibrinolysis inhibitor (TAFI) [83,84]

Secondary, acquired, or mixed risk factors	
Age >40 yr [85]	Long distance airplane travel [86]
Antiphospholipid syndrome:	Obesity, high BMI [87,88]
Lupus anticoagulans, cardiolipin Ab [89]	Hormone replacement therapy [91]
Systemic lupus erythematosus [90]	Oral contraceptives [92]
Cancer, cancer treatment [93,94]	Pregnancy and puerperium [95]
Fractures, plaster casts [96]	Prior VTE [97], postthrombotic
Surgery and trauma [96]	syndrome [98], varicose veins [99]
Central venous devices [100]	Spinal cord injury [96]
Chronic renal failure [101]	Stroke with paresis or paralysis [102]
Congestive heart failure [103]	Treatment with antipsychotics [104]
COPD [105], smoking [106]	Immobilization [96]
Inflammatory bowel disease [107]	Infectious diseases [107]

Table 4.

Risk factors observed in patients treated for VTE [68]			
Risk factor	**%**	**Risk factor**	**%**
Age ≥40 yr	88.5	Varicose veins	5.8
Obesity	37.8	Fracture (hip or leg)	3.7
Prior VTE	26.0	HRT	2.0
Cancer	22.3	Stroke	1.8
Bed rest ≥ 5 days	12.0	Multiple trauma	1.1
Major surgery	11.2	Childbirth	1.1
Congestive heart failure	8.2	Myocardial infarction	0.7

Table 5.

Odds ratios (OR) for different risk factors [68]	
Strong risk factors (OR >10)	**Moderate risk factors (OR 2–9)**
Fracture (hip or leg)	Arthroscopic knee surgery
Hip or knee replacement	Central venous lines
Major surgery, major trauma	Heart or respiratory failure
Spinal cord injury	HRT and oral contraceptive therapy
Weak risk factors (OR <2)	Malignancy, chemotherapy
Immobility due to sitting or bed rest	Pregnancy, postpartum
Increasing age, obesity	Previous VTE
Laparoscopic surgery	Stroke with paralysis
Pregnancy, antepartum	Thrombophilia
Varicose veins	

Pre-test probability score

Accurate diagnosis of PE is facilitated by a clinical evaluation to assess the probability of the disease. Because the symptoms and signs of PE are non-specific a simple diagnostic algorithm is needed. Several authors have addressed this problem and the need for a simple diagnostic algorithm [48]. Assessment of the clinical probability, especially if it is combined with a D-dimer test, can reduce the need for additional investigational test with 30% [29].

Wells score

The most widely used clinical decision rule, or pre-test probability score, for VTE, is the score designed by Wells et al. It was first described in patients with DVT, **Table 6** [108]. The score was later developed for patients with PE (**Table 7**) [109] and further evaluated also with D-dimer [110,111]. The Wells score for PE was derived from univariate and multivariate analyses from a large cohort of patients with PE. Seven of 40 predictors were found to be independently associated with PE, and these seven predictors are used to devise the score, which has a maximum of 12 points. Cut-off points were created to classify patients as having a low, moderate, or high pre-test probability for PE. The prevalence of PE was 3%, 28% and 78%, respectively, in each subclass. A subset of 1,239 patients with suspected PE underwent scoring according to the Wells score, and 437 (35%) had a low clinical probability for PE and a normal D-dimer. Only 1/437 (0.2%) had recurrent VTE within three months [109]. The Wells score for PE has been validated in several studies. A problem with the score is the item “an alternative diagnosis is less likely than PE”, which is highly subjective and can cause problems at the ED [112].

Table 6.

Wells score for DVT [108,111]	Score
Active cancer (ongoing treatment or within 6 mo or palliative)	1.0
Paralysis, paresis or plaster cast immobilization of a leg	1.0
Recent bedridden >3 days or major surgery within 4 weeks	1.0
Localized tenderness along the distribution of the veins	1.0
Entire leg swollen	1.0
Calf swelling >3 cm (measured 10 cm below tibial tuberosity)	1.0
Pitting oedema	1.0
Collateral superficial veins (nonvaricose)	1.0
Alternative diagnosis as likely or greater than of DVT	-2.0

mo, months

The clinical probability for DVT is determined as follows.

- ≥3 points high probability
- 1-2 points moderate probability
- ≤0 points low probability for DVT

Later revisions have simplified the probability of DVT into two categories.
High probability (score ≥2 points), and low probability for DVT (score <2 points).

Table 7.

Wells score for PE [109,110]	Score
An alternative diagnosis is less likely than PE	3.0
Clinical signs and symptoms of DVT[a]	3.0
Heart rate >100min^{-1}	1.5
Previous VTE	1.5
Immobilization or surgery within 4 weeks	1.5
Hemoptysis	1.0
Malignancy[b]	1.0

[a] Clinical signs and symptoms of DVT: minimum of leg swelling and pain with palpation of the deep leg veins
[b] Malignancy on treatment, treated the last six months or palliative (as for the score for DVT)

The clinical probability of PE is determined as follows.

- ≥6 points high probability
- 2-6 points intermediate probability
- <2 points low probability for PE

Later revisions have simplified the score into two categories, PE likely and PE unlikely with a cut-off of four points. The rates of PE are shown in **Table 8**.

In the validation set, 2/118 patients with a score ≤4 and a normal D-dimer had a PE. Using post hoc analysis, Wells et al showed that PE could be confidently ruled out in another 20% of patients using this cut-off [110]. This has been validated in the Dutch "Christopher" study in 2006 [113], which showed a 0.5% risk (95% CI 0.2-1.1%) of VTE after three months in patients with a normal score and a D-dimer <0.5 mg/L. The revised score has been recommended by the Swedish National Board of Health and Welfare (Socialstyrelsen, 2004) [114] and The Swedish Council

on Technology Assessment in Health Care (SBU, 2002) [32]. A study by Gibson et al showed that the score can be simplified further to one point for each variable without diminishing the validatity [115].

Table 8.

PE rates in the dichotomized PE likely/unlikely validation set of Wells score [110]
Values are shown as % and (95% CI)

Points	PE and D-dimer <0.5 mg/L	PE and D-dimer ≥0.5 mg/L	PE rate overall
>4	10.3 (2.2-27.4)	60.0 (43.3-75.1)	39.1 (27.6-51.6)
≤4	1.7 (0.2-6.0)	11.7 (4.8-22.6)	5.1 (2.3-9.4)

Geneva score

Assessing the same diagnostic problem of patients with suspected PE, other authors have developed their own algorithms, the best known is the Geneva score, published by Wicki et al 2001 [116]. The Geneva score was developed from a database of patients with suspected PE, and logistic regression analysis identified seven variables that were independently associated with PE. The original Geneva score gave points for: recent surgery within four weeks (3p), previous VTE (2 pt), age ≥80 yr (2 pt), age 60-79 yr (1 pt), heart rate >100/min (1 pt), arterial blood gas with pCO_2 <4.8 kPa (2 pt), pCO_2 4.8-5.19 kPa (1 pt), arterial pO_2 <6.5 kPa (4 pt), pO_2 6.5-7.99 kPa (3 pt), pO_2 8.0-9.49 kPa (2 pt), pO_2 9.5-10.99 kPa (1 pt), and also atelectasis (1 pt) or elevated hemidiaphragm (1 pt) on CXR. Each variable was given a score between 1 and 4, with a maximum score of 16 points, and the total score was used to calculate the probability of PE. The score requires blood gases and CXR and classifies risk into three categories: low (score ≤4), moderate (score 5-8) and high (score ≥9) probability of PE. The probability of PE is 10% (95% CI 8-13%) in the low-probability group, 38% (95% CI 34-43%) in the moderate-probability group, and 81% (95% CI 69-90%) in the high-probability group. The Geneva score was revised to omit arterial blood gases and CXR [117]. This revised score includes points for age >65 years (1 pt), previous VTE (3 pt), surgery or fracture previous month (2 pt), active cancer (2 pt), unilateral leg pain (3 pt), hemoptysis (2 pt), heart rate 75-94/min (3 pt), heart rate >95/min (5 pt), and unilateral leg oedema and pain with palpation (4 pt). The interpretation is a low probability of PE if the score is 0-3 points, intermediate probability with a score of 4-10 points, and high probability if the score is 11 or higher. The Geneva score is equivalent to the Wells score [118] but is not used often as the Wells score and is not considered further in this thesis.

D-dimer and other biochemical markers

The use of D-dimer and other biochemical markers of coagulation or thrombotic burden, as well as markers of inflammation or endothelial activation, such as CRP, and von Willebrand factor, have been used more in the diagnostic work-up of patients with PE since the 1990s. Markers for right ventricular strain in the heart muscle, troponins [119], and natriuretic peptides, especially BNP [120,121] are used widely, especially for risk stratification of PE.

D-dimer

D-dimer tests are used in the diagnostic work-up in patients with VTE mainly to limit the need for additional objective investigations. D-dimers are degradation products of cross-linked fibrin that are released in the blood when a thrombus is degraded. In the fibrinolytic system, the main protein plasminogen which forms plasmin, dissolves fibrin to produce degradation products of varying sizes. The smallest fragments are called fragment D and crosslinked D-fragments, D-dimers, are established markers of fibrinolytic activity [122]. Measurement of D-dimer has become more widely spread with the development of monoclonal antibodies that bind to D-dimer fragments, and the resulting complexes are detected by latex agglutination tests, or enzyme-linked immunosorbent assays (ELISA). The D-dimer level is measured in mg/L or fibrinogen equivalent units (FEU). Marlar et al proposed that two mg/L FEU has an immunoreactivity equivalent to 1 mg/L of purified D-dimer [123]. The cut-off of 0.5 mg/L has been used in most studies, but other cut-offs, such as 0.25 mg/L have also been used.

The D-dimer level is elevated in VTE, and in other conditions, as shown in **Table 9** [124]. The D-dimer is typically elevated up to ten days after a thrombotic event, but it can also be found later with a lower specificity.

Table 9.

Conditions with elevated concentration of D-dimer [124,125]	
Cancer	Pregnancy
DIC	Renal failure
Infectious diseases	Surgery, postoperative state
Age > 70 yr	Trauma, fractures
Myocardial infarction	VTE

With a cut-off of 0.5 mg/L, the sensitivity of an elevated D-dimer, for diagnosing VTE is 97-100% [126]. The specificity is lower and varies between 35% and 45% for different D-dimer tests [124], see **Table 10**.

Table 10.

Performance of different D-dimer tests for suspected PE [124]

Test	n / PE%	Sensitivity (95% CI)	Specificity (95% CI)
Classic ELISA	1,579 / 34	98% (96-99)	43% (40-46)
Rapid ELISA	635 / 24	100% (98-100)	44% (39-48)
Classical latex tests	364 / 46	92% (88-96)	68% (61-74)
Microlatex (Liatest)	887 / 33	100% (98-100)	40% (36-44)
Whole blood latex SimpliRED®	1,317 / 18	87% (82-91)	65% (62-68)

CI, confidence interval

A normal D-dimer in combination with a low pre-test probability score can obviate the need for additional diagnostic investigations by 15% [127].

There are different commercially available D-dimer tests, which have been compared in several studies. van der Graaf et al [128] compared 13 D-dimer tests in outpatients with VTE. The prevalence of DVT was 50%. Of the quantitative D-dimer tests, Tinaquant® and VIDAS® have a sensitivity of 100% and a specificity of 40%. The same methods have a sensitivity of 82% (Tinaquant®) and 88% (VIDAS®) for PE, with a specificity of 61% and 52%, respectively [129].

Studies have shown that the agglutination D-dimer test is not sensitive enough to exclude VTE and should be used in combination with a clinical score. The ELISA D-dimer test is considered the gold standard because a of its high sensitivity and an NPV of 99-100%. A normal D-dimer result can be used to exclude PE, but not to verify the diagnosis [130].

von Willebrand factor (vWF)
The von Willebrand factor is a multimeric carrier protein of factor VIII (fVIII) and an important determinant of the concentration of fVIII in plasma. vWF antigen is synthesized in the vascular endothelium, and its level correlates with the concentration of fVIII but not with that of other cell-derived coagulation proteins [131]. The von Willebrand factor plays an important role in primary hemostasis, and fVIII plays a role mainly in secondary hemostasis. vWF is elevated after venous occlusion [132], and the level of vWF is high in patients with acute inflammatory conditions such as infections, trauma, and thrombosis [133] and high levels are seen in patients with arterial thrombosis [134]. vWF can be measured by an immunoturbidimetric method, over a measurable range of 0.5-4.0 IU/mL, and the preferred reference range is 0.6-1.6 IU/mL.

Troponins
Troponins I and T, as well as BNP, have been introduced as tools in the risk assessment of patients with PE [135]. Troponins are used traditionally as markers of cardiac ischemia in acute myocardial infarction and unstable angina pectoris. Troponins are released in patients with acute PE by injured cells in the RV because of the abrupt increase in PAP and the acute dilatation and wall stress of the RV [136].

Brain natriuretic peptide (BNP)
BNP is excreted from the cardiac ventricles in response to stretch in the myocytes and is elevated in conditions with increased strain in the heart, such as congestive heart failure and PE. BNP has a low statistical performance for diagnosing or excluding PE. Sohne et al showed that elevated BNP is significantly associated with early fatal recurrent VTE in hemodynamically stable patients with PE [137]. Patients with increased BNP and troponins are at risk for adverse outcome, and patients with high troponin T have a higher in-hospital mortality than patients with normal values [138]. The use of BNP and troponins may be useful in risk stratification of normotensive patients with PE.

C-reactive protein (CRP)
CRP, a marker of inflammation, is significantly elevated in patients with VTE [139,140]. In a large study of 50 potential markers of PE only D-dimer, CRP, and myeloperoxidase showed sufficient diagnostic accuracy to suggest their potential use as biological markers [141]. A study by Steeghs et al showed that a normal CRP (<5 mg/L) has a similar NPV as D-dimer, (99.1% vs. 99.4%), in excluding PE [142]. The use of CRP in the diagnostic work-up of patients with suspected PE is not yet established.

Diagnostic investigations

As discussed above, neither evaluation of of the clinical symptoms nor D-dimer, is sufficient for diagnosing PE. An accurate diagnostic radiological investigation is

mandatory in diagnosing PE [143]. This section describes the use of PA, V/Q-scan and CTPA in diagnosing PE. Newer techniques, such as magnetic resonance angiography (MRA), CT angiography (CTA), tomographic scintigraphy (V/P_{SPECT}) and multidetector row CT (MDCT), are not described further.

Pulmonary arteriography (PA)

PA is considered the most specific test for PE and is used as the reference method in many studies. Although the performances cannot be calculated, studies have shown that it is safe to withhold anticoagulants in patients with a normal PA [47]. PA is an invasive investigation- contrast medium is injected iv directly into the pulmonary arteries through a catheter introduced in the femoral vein. PA has several advantages because it can be used to visualize the emboli, directly and because it provides hemodynamic data and opportunities for direct treatment through the insertion of thrombolytic agents and vena caval filters. PA also has several disadvantages: for example, the high cost, limited availability, invasive technique with risk for bleeding and arrhythmias, and complications related to the contrast media [144]. The use of PA has diminished during the past decade, in favor of CTPA, mainly because of the disadvantages, but there are still clinical conditions when PA should be used, for example in patients with contraindications for or, inconclusive CTPA.

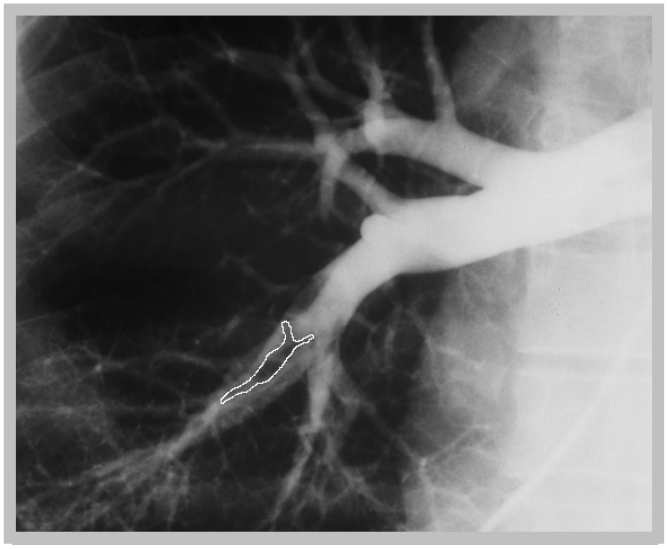

Fig. 3
Filling defect in a pulmonary artery on PA.

Ventilation-perfusion lung scintigraphy (V/Q-scan)

The V/Q-scan was introduced in the 1960s, and there has been many uncertainties in the interpretation of the scans. To address this problem, in 1990, the prospective investigation of pulmonary embolism diagnosis (PIOPED) study, a large prospective randomized multicenter study, was designed to determine the sensitivity and specificity of the V/Q scan in diagnosing PE. PA was used as the gold standard. The study showed that the V/Q scan is inconclusive in 55-65% of the patients, and that a normal lung scintigraphy has an NPV of 98% [27].

Lung scintigraphy comprises two components, ventilation (V) and perfusion (Q)-imaging of the lung circulation. The investigation is noninvasive, and the perfusion part is performed by iv injection of radioactive particles, mainly ^{99m}Technetium

labeled microaggregates of albumin. These particles block the pulmonary capillaries if there is an embolus present. The ventilation part is performed by inhaling of a radioactive isotope. The difference in the distribution of particles in the arterial pulmonary circulation, called mismatch, is then analyzed. The perfusion scan is matched against a ventilation scan. A normal V/Q scan is considered to exclude PE safely [145]. The PIOPED-study classified the interpretation of the scans into low, intermediate, or high suspicion of PE according to the classification, as shown in **Table 11** and **12**.

Table 11.
Interpretation of lung scintigraphy according to the PIOPED study [27]

Probability of PE	Perfusion defects	Prevalence of PE (95% CI)
High	>2 large perfusion defects, >2 moderate large perfusion defects and 1 large defect, or >4 moderate large perfusion defects	75% (55-100%)
Intermediate	Intermediate between low and high	30% (15-65%)
Low	Few moderate mis-match Non-segmental perfusion defects Perfusion defect with large CXR abnormality	8% (5-40%)
Normal	No perfusion defects visible	<5%

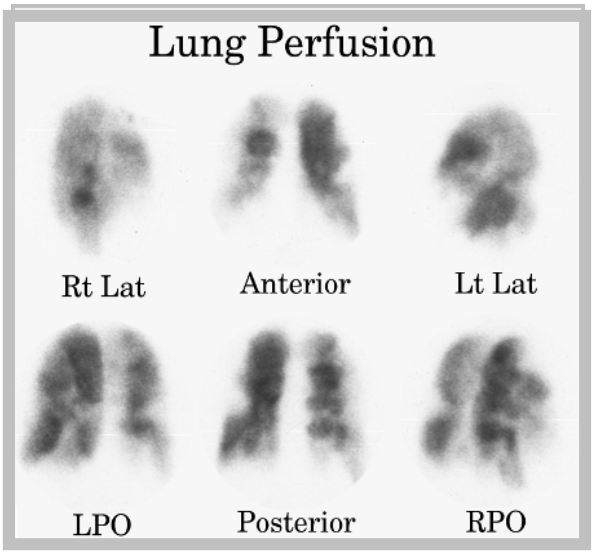

Fig 4. Perfusion scintigraphy with several perfusion defects.
High probability for PE according to the PIOPED criteria.
Rt Lat, right lateral view; Lt Lat, left lateral; LPO, left posterior oblique, RPO, right posterior oblique view.

Table 12.
Clinical assessment and V/Q scan probability in PIOPED [27]

V/Q scan probability for PE	Clinical probability for PE (%)		
	Highly likely (80-100%)	**Uncertain (20-79%)**	**Unlikely (0-19%)**
High	96	88	56
Intermediate	66	28	16
Low	40	16	4

The prospective investigative study of acute pulmonary embolism diagnosis (PISA-PED) study that followed PIOPED, found that a positive perfusion scan had a PPV of 95% and a negative scan had an NPV of 81% [48]. Only 21% of patients had clinical presentation and perfusion scan results that were contradictory. The interpretation criteria and the study populations differed between the two studies. In PISA-PED, 24% of the patients had normal perfusion scans com-pared with 2% in PIOPED. Unfortunately, many conditions other than PE can cause pulmonary hypoperfusion and a false positive perfusion scan. A normal V/Q-scan is considered to rule out PE safely. Hull et al found a 0% (95% CI 0-3.2%) risk of VTE within six months after a normal lungscan [146]. The scinti-graphic technique has been developed further, and other methods are avai-lable, such as the ventilation/perfusion single photon emission tomography (V/P_{SPECT}) which has high NPV and PPV [147], but this method is not widespread.

Computed tomography of the pulmonary arteries (CTPA)
CTPA has become more widely used as a diagnostic tool in PE because of the disadvantages of PA and V/Q scans, and the development of the computed tomography (CT) technique. A CTPA can be used both to exclude and to diagnose PE [148] and it can confirm alternative diagnoses with high sensitivity and specificity [54]. Indirect signs of PE, such as atelectasis, (i.e. pleural-based densities), dilatations of pulmonary arteries and pleural effusions can also be visualized on CTPA [149].

CTPA is available at almost all hospitals and is considered as the firstline investigation in many recommendations [145]. CTPA is fast, and relatively inexpensive, and requires less contrast media than PA. Newer CT techniques with multi-detector row CT (MDCT) and multiple slice CT (MSCT) are thought to increase the diagnostic safety of subsegmental PE. CTPA can safely diagnose PE down to the subsegmental part of the pulmonary arteries, although the investigation is more less specific more distally. Recent studies show that MDCT and conventional single-detector row CT have similar accuracy in detecting subsegmental PE [150].

CTPA has lower overall specificity than PA. van Beek et al showed that the risk of a fatal PE is 0.3% (95% CI 0.02-0.7%) three months after a normal PA [151], and the risk of a fatal PE is 0.5% (95% CI 0.2-1.0%) three months after a normal CTPA [152]. CTPA has other disadvantages. It requires iv contrast medium to visualize the pulmonary arteries, and there is a risk of contrast medium-induced nephropathy and allergic reaction. The radiation exposure is higher in CTPA than in V/Q scan but lower than in PA.

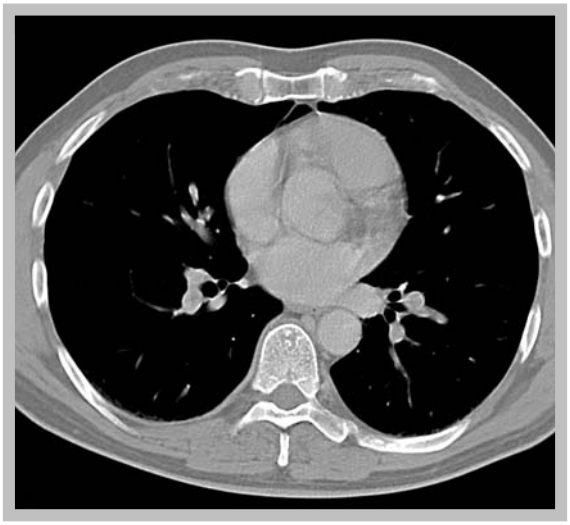

Fig 5. A CTPA that shows PE with filling defects in the pulmonary arteries

AIMS OF THE THESIS

The general aim of this thesis was to investigate the diagnostic procedures in patients with PE. The specific aims were:

- To compare the diagnostic accuracy of CTPA and D-dimer in patients with suspected PE with pulmonary arteriography as reference method. (*Paper I)*

- To investigate whether the initial symptoms and clinical signs in patients with PE and community-acquired pneumonia differ. (*Paper II)*

- To evaluate the sensitivity and specificity of the Wells score and repeated measurement of D-dimer as diagnostic tools in VTE. (*Paper III)*

- To evaluate the use of the Wells score and D-dimer test in patients with a high probability of PE. (*Paper IV)*

- To evaluate the expression of von Willebrand factor antigen in patients with DVT and PE. (*Paper V)*

PATIENTS AND METHODS

PAPER I

Nilsson T, Söderberg M, Lundqvist G, et al.
A comparison of spiral computed tomography… *Scand Cardiovasc J 2002; 36: 373-7.*

Patients

Ninety hemodynamically stable patients, aged 18-79 yr, with clinically suspected PE were investigated. The patients were recruited from the EDs at Södersjukhuset, Stockholm and Karolinska University Hospital, Solna, Sweden. The patients were screened for eligibility by the physician on call and one of the study investigators. Inclusion criteria were symptoms and signs of PE, the ability to perform the necessary investigations within 24 h, and none of the exclusion criteria. In all, 139 persons were screened in the study. The investigations could not be performed in 32 patients, and there were protocol violations in another 17 patients, giving a final study population of 90 patients. The exclusion criteria for study I (which were also applied for study IV) are listed in **Table 13.**

Table 13.

Exclusion criteria for studies I and IV	
Advanced psychiatric disorder	Adverse reaction to contrast media
Age <18 or >80 yr	S-creatinine >150 µmol/L
Hepatitis	Severe malnutrition or cachexia
HIV infection	Thrombocytes $<70x10^9$/L
Myocardial infarction	Treatment with metformine
Ongoing anticoagulation	Unstable hemodynamics
Pregnancy	≥2 previous DVT or PE

Methods

All 90 patients were investigated with PA and CTPA, D-dimer test, and clinical evaluation within 24 h of admission. All patients were followed up after three months with a clinical evaluation.

Radiology

The first radiological investigation was made within the first 12 h of admission to minimize the risk of misinterpretations.

PA was performed using the standard Seldinger technique applied to the femoral veins at the local radiological laboratory with a Siemens High Cor or Philips Integris digital, single plane instrument at 12.5 or 25 frames/s. A standard dose contrast medium of 40 mL Visipaque (320 mg I/mL) or Iomeron 350 mg I/mL was injected. The PAs were interpreted by two independent radiologists, who where blinded to the other data.

- **The diagnostic criterion for PE on PA** was the finding of an intraluminal filling defect or an occlusion with a concave border indicating a trailing edge of an embolus [153].

CTPA was performed by the local radiological laboratory with a Siemens Somatom Plus scanner (Siemens, Erlangen, Germany) or a GE Advantage scanner (GE Medical Systems, Canada). The investigations were made with a

3 mm collimation and a table speed of 3-5 mm/s. The contrast medium Omnipaque (120-150 mL) was introduced 15-20 s before the scanning. The CTPAs were interpreted by the same two radiologists who interpreted the PAs, with the same blinded condition.

- **The diagnostic criterion for PE on CTPA** was a finding of a low-attenuation area that filled, completely or partially, the lumen of an opacified pulmonary artery [154].

D-dimer assay
Venous blood samples were obtained at the ED and centrifugated immediately, and citrate plasma was stored at -70 °C. A semiquantative rapid latex agglutination D-dimer test (Tinaquant®, Boehringer-Mannheim, Germany) was performed according to the the manufacturer's recommendation. The cut-off was set at 0.5 mg/L, and a second tentative cut-off was set at 0.25 mg/L, to study the diagnostic outcome compared with PA.

Follow-up
All patients were followed up with an out-patient visit at the Department of Internal Medicine at each hospital, which included an evaluation of any recurrences of VTE during the three months.

PAPER II

Söderberg M, Hedström U, Sjunnesson M, Lärfars G, Jorup-Rönström C.
Initial symptoms in pulmonary embolism differ…*Eur J Emer Med* 2006; 13: 225-9.

Patients
We found that 25 patients in the Clinic for Infectious diseases (CID) at Södersjukhuset had PE but had been misdiagnosed on admission during the years 1993-1999. The patients were admitted for suspicion of pneumonia or bronchitis, but after reevaluation, they were diagnosed correctly with PE, according to the given criteria, which are shown in **Table 14**. These 25 patients were compared retrospectively with 54 patients with correctly diagnosed community-acquired pneumonia (CAP) with known ethiology at the CID and 64 patients with established diagnosis of PE at the Dept. of Internal Medicine at the same hospital, during the same time period. All patients with CAP with a verified microbiological agent diagnosed in the CID during these years (n=584), and all patients with a PE diagnosed in the Dept. of Internal Medicine (n=729) were eligible for comparison. To diminish the number of comparisons needed we used a retrospective randomization process that randomized about 20% of the eligible patients. The diagnostic criteria for CAP and PE are shown in **Table 14** and the randomization process is shown in **Table 15**.

Table 14.

Diagnostic criteria for CAP [155]	Diagnostic criteria for PE [145]
Acute illness with respiratory symptoms, Infiltrate on CXR not previously known, Microbiological agent proven in blood culture, sputum, pneumococci in NPh or increased serological titer	High-probability V/Q-scan, CTPA, PA, Autopsy, or DVT on phlebography and high clinical probability of PE

Table 15.

Randomization process for CAP	Randomization process for PE
All patients with CAP, n=584	All patients with PE, n=729
Randomized, n=132 (~20%)	Randomized, n=140 (~20%)
Did not fulfill criteria, n=46	Did not fulfill criteria, n=64
Medical records not found, n=32	Medical records not found, n=12
Finally evaluable patients, n=54	Finally evaluable patients, n=64

Methods

The initial symptoms, signs, and clinical findings were compared in the three groups: “PE/infection”, “PE/medicine” and “CAP”. The data from the patients were recorded retrospectively through a systematized review of the medical records, using a special protocol (slightly modified and translated from Swedish) shown in **Table 16**. The three main initial symptoms, mentioned by the patient or interpreted by the attending physician, were recorded along with demographics such as age and sex, as well as clinical parameters, such as blood pressure, heart rate, peripheral saturation, respiratory rate and body temperature. Laboratory test results and findings on chest X-ray (heart and lung investigation) were recorded, along with information on risk factors and treatment.

Table 16.

The special protocol used to categorize patients in study II

Demographics	**Laboratory findings**
Age / sex / smoker (y/n) /	Hemoglobin / leukocytes /
alcohol consumption (specify) /	thrombocytes / CRP /
Clinical findings (specify)	erythrocyte sedimentation rate /
Heart rate / respiratory rate /	arterial blood gases /
body temperature / weight / length	blood culture / sputum culture / NPh /
peripheral saturation / blood pressure	**Anamnestic findings (y/n)**
heart sounds / lung sounds (specify) /	Known coagulopathy / previous VTE /
signs of DVT (y/n) /	hereditary anamnesis for VTE /
Clinical presentation	thrombophlebitis / varicose veins /
Symptoms from charts: 1st, 2nd, 3rd	asthma / COPD / ischemic heart
Symptoms (y/n): shivering / cough /	disease / congestive heart disease /
hemoptysis / sputum / common cold /	malignant disease / cancer treatment /
dyspnoea / pleuritic chest pain /	stroke / transient ischemic attack /
central chest pain / syncope /	recent infectious disease /
dizziness / tachycardia / sweating /	immobilization / plaster / surgery /
other (specify) /	pregnancy / postpartum /
Investigations (specify)	overweight / dehydration /
ECG / chest X-ray: pleuritic fluid /	other (specify) /
infiltrates / atelectasis / other /	**Treatment (specify)**
PE diagnosis: PA / CTPA / VQ-scan	HRT / contraceptive pills /
	antibiotics / anticoagulants / other /

y, yes; n, no

PAPER III

Ljungqvist M, Söderberg M, Ahlgren A, Moritz P, Lärfars G.
Evaluation of Wells score and repeated D-dimer…*Eur J Int Med* 2008; 19: 285-8

Patients and methods

Outpatients with a clinical suspicion of DVT or PE were screened at the ED at Södersjukhuset, Stockholm, for eligibility in the study during one year. The screening process is shown in **Figure 6**. Exclusion criteria were age <18 yr, pregnancy, known genetic thrombophilia, ongoing anticoagulant treatment, short life expectancy, or another reason for radiological investigation than VTE.

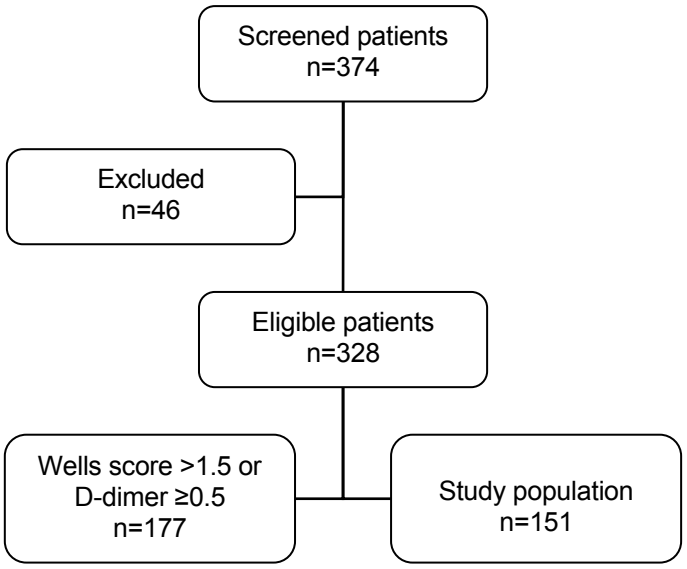

Fig. 6.
Schematic presentation of the screening process in **study III.**

Of the 151 patients, 118 (78%) had a suspected DVT and 33 (22%) had a suspected PE. All patients were evaluated according to the Wells score for DVT and PE, respectively. A latex agglutination D-dimer test (Tinaquant®) was performed for all patients with a Wells score ≤1.5 points, irrespective of the suspicion of DVT or PE. The cut-off of the D-dimer test was set at 0.5 mg/L. If the D-dimer test was normal, i.e. <0.5 mg/L, no further testing was performed and the patient was discharged. A follow-up D-dimer test after 3-7 days was recommended in all patients with an initial low D-dimer and low Wells score. All patients were followed for three months and contacted by the study investigators by telephone.

Patients with a Wells score >1.5 or a D-dimer ≥0.5 mg/L (n=177) were not investigated further in the study but they were evaluated according to the hospital's routine procedures.

PAPER IV

Söderberg M, Brohult J, Jorfeldt L, Lärfars G.
The use of D-dimer testing and Wells score…*J Eval Clin Pract* , accepted 2007

Patients

One hundred twenty patients aged 18-80 yr were investigated in this study. The patients were recruited from the EDs at Karolinska University Hospital, Solna and Södersjukhuset, Stockholm, Sweden. The inclusion criteria were clinical suspicion and symptoms or signs of acute PE, that CTPA or PA could be performed within 24 h of admission and that both investigations were completed within 48 h, and that a D-dimer could be measured. One hundred forty-six patients were screened for eligibility in the study and 26 patients were excluded because investigations could not be done according to the protocol. Ninety of

the investigated 120 patients were also included in study I. The exclusion criteria were the same as in study I, listed in **Table 13**.

Methods
The patients were screened and evaluated at the ED according to a special protocol (not shown), with included questions on medical history and symptoms and signs of PE. CTPA and PA were performed at the local radiology department according to the recommendation as described above for paper I. The investigations were interpreted by two independent chest radiologists, and the diagnosis was set if one investigation fulfilled the criteria for PE, as described in paper I.

The D-dimer was measured with a latex agglutination test (Tinaquant®). Blood samples were obtained on arrival at the ED, and citrate plasma samples were frozen and stored at -70 °C at the local coagulation unit until all patients' samples had been obtained. The attending physician at the ED was not aware of the D-dimer result prior to the radiological investigations. All patients with a high clinical suspicion of PE received initial treatment with tinzaparin (Innohep®, Leo Pharma) 175 U/kg sc, or dalteparin (Fragmin®, Pfizer) 200 U/kg sc, or a standard dose of UFH (5,000 U iv) prior to the investigations. All patients with established diagnosis of PE received continuous treatment with LMH for five days and concomitant therapy with OAVK for at least six months.

A pretest probability score, according to Wells et al [109,110] was set retrospectively. All clinical data needed to perform the score were obtained in the used protocol, but the original Wells score was not established in clinical practice when the study begun. Because one inclusion criterion was "clinical suspicion and signs or symptoms of PE" all patients were considered to comply with the Wells criterion "pulmonary embolism as likely as or more likely than an alternative diagnosis", thus scoring at least three points in this study [109].

PAPER V

Söderberg M, Schulman S, Lärfars G.
Expression of von Willebrand factor antigen in pulmonary.. *Submitted* 2008

Patients
Forty-six patients with previously diagnosed symptomatic PE without symptoms or signs of concomitant DVT were compared with 45 patients with symptomatic DVT without symptoms or signs of PE. Patients with signs of both DVT and PE were not investigated. Exclusion criteria were known malignancy, systemic inflammation, pregnancy, renal failure, thrombophilia, bleeding tendency, or ongoing anticoagulant treatment. The patients were recruited from the ED at Södersjukhuset.

The mean age and sex distribution were equal between the groups. The diagnosis of PE was proven by CTPA (n=20) and by high probability V/Q-scans (n=26). The diagnosis of DVT was confirmed by ultrasound with duplex technique (n=23) or with ascending venography (n=22). Of the patients with DVT, 15 had a proximal DVT (i.e. thrombosis in the popliteal, femoral or iliac veins), and 30 had a distal DVT, that was limited to the calf veins. No patient with PE or DVT were considered hemodynamically unstable or required thrombolytic therapy.

Methods
After informed consent was obtained at the ED, the diagnostic investigations were performed within 24 h. The patients with suspicion of DVT were investigated with ultrasonography or venography of the affected leg according to local practice. The patients with suspected PE were investigated with either CTPA or V/Q-lung scintigraphy, also according to local practice.

Blood samples were collected at the ED at inclusion (day 0) and after three months (day 90) for all patients studied. The samples were immediately centrifuged and anticoagulated. The von Willebrand factor antigen (vWF) was assayed using an immunoturbidimetric assay (Dade Behring, Germany) with a measurable range of 0.5-4.00 IU/ml. The reference level of vWF was set at 0.6-1.6 IU/mL. Routine venous blood samples and samples for the Factor V Leiden mutation (APC-resistance, only DVT-patients) were also obtained at the ED.

Marder score
The volume and degree of the vein occlusion were calculated retrospectively according to the score designed by Marder et al [156]. The score is based on the calculated volume and degree of occlusion of the veins in the calf, knee, thigh and pelvis.

The Marder score concists of points for thrombosis in the iliacal vein (6 pt), common femoral vein (4 pt), superficial femoral vein (10 pt), popliteal vein (4 pt), anterior tibial veins (2 pt each, 4 pt total), posterior tibial veins (2 pt each, 4 pt total), and fibular veins (3 pt each, 6 pt total).

A maximum score of 40 points reflects complete thrombosis of all these veins. The score was established initially for venographic studies of thrombosis and were not validated for DVT diagnosed by ultrasonography. Using the method of Marder, we performed a score even in these patients, thus it is not validated. We assigned a maximum score to a total occlusion or nonfilling of a given vein, and a lesser score to a segmental occlusion or filling defect in proportion to the degree of involvement [156].

ETHICS CONSIDERATIONS

All studies were approved by the local ethics committee at Karolinska Institutet, Stockholm, Sweden. Informed consent was obtained from all patients where appropriate.

The studies were sponsored by unconditional grants from the following organizations, all in Stockholm, Sweden:

- Amersham Health AB
- Karolinska Institutet
- Stockholms läns landsting (Stockholm County Council, Expo -95)
- Swedish Heart and Lung Foundation
- Swedish Medical Research Council (project no. 04139)

RESULTS

PAPER I

Nilsson T, Söderberg M, Lundqvist G, et al.
A comparison of spiral computed tomography… *Scand Cardiovasc J 2002; 36: 373-7*

The prevalence of PE was 33/90 (37%) with PA as the reference method. The patient's characteristics and baseline demographic data, including medical history, in the patients studied are shown in **Table 17**.

Table 17.
Characteristics of the study population.
Values are in mean (SD) or n (%), otherwise noted.

Parameter	PE	No PE
Patients	n=33	n=57
Age, yr (SD)	59.0 (14.2)	49.5 (15)
Male sex, n (%)	19 (58)	23 (40)
Durations of symptoms, h (SD)	114 (136)	137 (196)
Body temperature, ^{o}C (SD)	37.0 (0.7)	37.2 (0,5)
Heart rate, min^{-1} (SD)	85 (25)	85 (15)
Median heart rate, min^{-1}	90.5	86.0
Respiratory rate, min^{-1} (SD)	20.5 (8.0)	18.0 (3,7)
Per. saturation, % (SD)	94.8 (3.0)	96.0 (2,9)
Systolic blood pressure, mmHg	138.4 (17.0)	131.5 (18)
Body weight, kg (SD)	79.3 (12.0)	71.4 (17)
Hemoglobin, g/L (SD)	138 (16.0)	141 (14)
Mean D-dimer, mg/L (SD)	1.9 (2.0)	0.5 (0.3)
Median D-dimer, mg/L	1.02	0.47
Medical history:		
Current smokers, n (%)	5 (15)	14 (26)
Family history of VTE, n (%)	6 (18)	10 (18)
Previous VTE, n (%)	13 (39)	4 (7)
Varicose veins, n (%)	7 (21)	12 (22)
Known thrombophilia, n (%)	0	3 (5)
COPD, n (%)	3 (9)	2 (4)
CHD, n (%)	1	4 (7)
Known cancer, n (%)	4 (12)	3 (5)
Immobilization >2-3 days, n (%)	6 (18)	7 (13)
Stroke or paresis, n (%)	2 (6)	4 (7)
OC use/ HRT (females), n (%)	2 / 5 (25 / 62)	5 / 8 (22 / 35)
BMI >30 kg/m^2, n (%)	4 (12)	4 (8)

Per. saturation, peripheral oxygen arterial saturation.

PE was diagnosed by CTPA in 32 patients and there were two false-positive and three false-negative results (**Table 18**). CTPA had a sensitivity of 91% and a specificity of 96%. The PPV was 94% and the NPV 95%. Three patients had a PE diagnosed by PA but a D-dimer <0.25 mg/L and another four patients had a D-dimer 0.25-0.5 mg/L. Two of these seven patients with positive PA and D-dimer <0.5 mg/L had lobar bilateral PE and 5/7 had unilateral subsegmental PE, see **Table 19** for the comparison of PA and CTPA after consensus reading. With a cut-off of the D-dimer set at 0.5 mg/L there were six false-positive and seven false-negative results, yielding a sensitivity of 79% and a specificity of 88%.

The test performance of PA, D-dimer <0.25 and 0.5 mg/L are shown in **table 20.**

Table 18.
Findings in the five patients with different results on PA and CTPA

Sex / age, yr	PA result	CTPA result	D-dimer, mg/L
M 63	PE	Normal	0.71
M 54	PE	Normal	0.36
M 51	PE	Normal	0.13
F 68	Normal	PE	0.24
F 52	Normal	PE	0.24

M, male; F, female

Table 19.
Comparison of PA and CTPA after consensus reading, n

	PA, PE pos.	PA, PE neg.	Total
CTPA, PE positive	30	2	32
CTPA, PE negative	3	55	58
Total	33	57	90

Table 20.
Test performances, values in %

	PA	D-dimer <0.25 mg/L	D-dimer <0.5 mg/L
Sensitivity	91	91	79
Specificity	96	65	88
NPV	95	92	87
PPV	94	63	81

All patients were followed for three months, and none had a recurrent VTE during this period.

PAPER II

Söderberg M, Hedström U, Sjunnesson M, Lärfars G, Jorup-Rönström C.
Initial symptoms in pulmonary embolism differ…*Eur J Emer Med* 2006; 13: 225-9.

When the medical charts and questionnaires were reviewed it was obvious that four symptoms dominated in most cases, both in PE and pneumonia, and they were often presented in couples: dyspnoea and pleuritic chest pain vs. fever/ shivering (chills) and cough with or without productive sputum. The remaining patients appeared with unspecific symptoms such as fatigue, nausea, muscle pain, palpitations and swollen legs.

The characteristics of the study populations are shown in **table 21.**

Table 21.
The characteristics of the study population.
Values are in mean or n (SD or %), otherwise noted.

Parameter	PE/Infection	PE/Medicine	Pneumonia
Patients	n=25	n=64	n=54
Age, yr (SD)	60.9 (21.7)	68.5 (16.7)	60.8 (17.4)
Women, %	52	69	39
Body temperature, °C (SD)	38.1 (1.0)	37.4 (0.7)	38.5 (0.9)
Heart rate, min^{-1} (SD)	99.8 (15.6)	89.8 (15.7)	101.8 (22.0)
Respiratory rate, min^{-1} (SD)	28.9 (7.7)	24.6 (9.8)	33.2 (8.8)
Per. saturation, % (SD)	90.7 (4.1)	94.1 (3.9)	89.1 (5.4)
SBP, mmHg (SD)	128.5 (18.9)	134.3 (21.5)	130.7 (27.9)
Initial symptoms, n (%)			
Dyspnoea, pleuritic pain	19 (76%)	52 (81%)	5 (10%)
Fever, chills, cough	2 (8%)	10 (16%)	38 (70%)
Other symptoms	4 (16%)	2 (3%)	11 (20%)
CRP, mg/L (SD)	209.6 (81.1)	77.7 (101.0)	260.2 (134.0)
Leukocytes, $x10^9$/L (SD)	10.7 (4.6)	13.0 (5.4)	15.6 (8.8)
CXR with infiltrates, n (%)	15 (60%)	10 (16%)	54 (100%)
pleural fluid, n (%)	14 (56%)	9 (14%)	6 (11%)

SBP, systolic blood pressure; Per. saturation, peripheral arterial oxygen saturation.

The symptoms were similar in both PE groups (p=0.48), although they had been diagnosed initially differently. **Figure 7** shows a histogram of the different symptoms in PE and pneumonia.

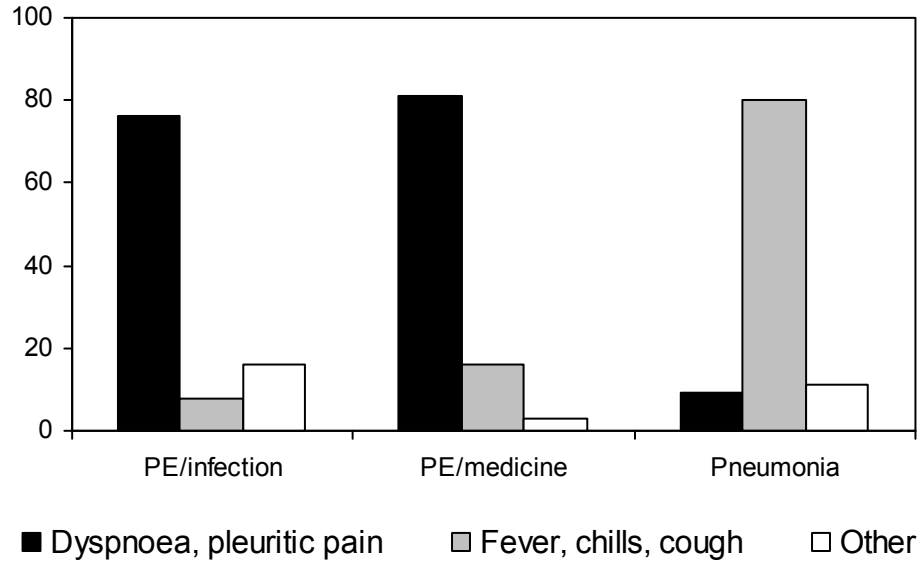

Fig. 7. Initial symptoms in the different groups. Proportions shown as %.

Pulmonary infiltrates with or without pleuritic effusion on CXR were present in 64% (PE/infection), 16% (PE/medicine), and 100% (CAP), respectively as shown in **Figure 8.** CXR pathology of any type was found in 92% of the PE/infection patients. The mean body temperature at admission was 38.1°C (PE/infection) and 37.4°C (PE/medicine),

p<0.005, and 38.5°C in CAP (**Figure 9**). CRP was significantlly higher (p<0.001) in CAP patients than in PE/medicine, although high values did not exclude PE (range 9-490 mg/L). A CRP level <10 was recorded as 9 mg/L (**Figure 10**). All patients with PE received treatment with anticoagulants, and all patients with pneumonia received antibiotics (except in the case of viral ethiology) according to local treatment recommendations.

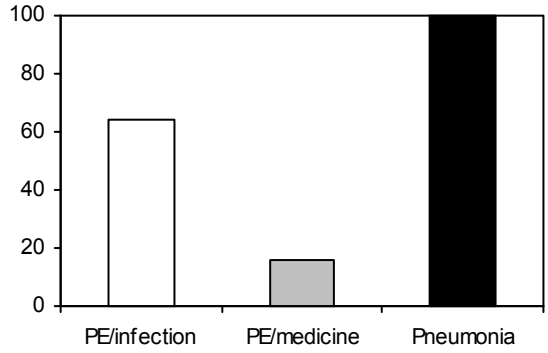

Fig. 8. Infiltrates on chest X-ray in the different groups. Proportions in %

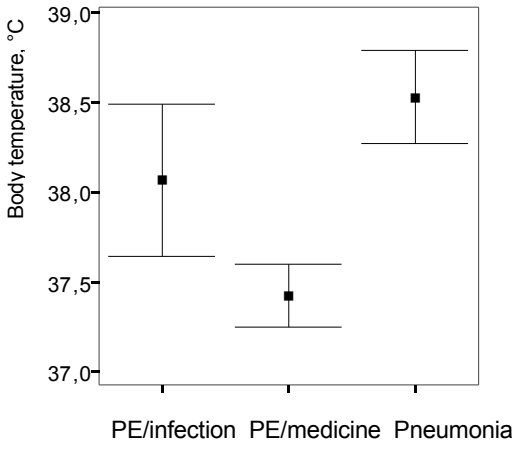

Fig 9.
Mean body temperature in °C with 95% CI in the different groups.

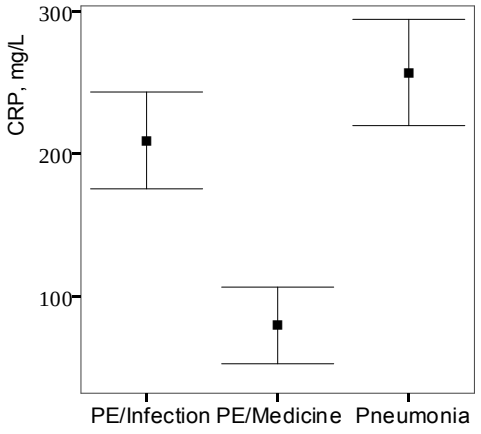

Fig 10.
Mean CRP level (mg/L) with 95% CI in the different groups. A CRP level of <10 mg/L is calculated as 9 mg/L.

During six months in 2007, we conducted a prospective outcome evaluation study at the ED at Södersjukhuset. The aim was to compare our findings in **paper II** with a study of prospectively evaluated patients. Two hundred and fifty-two patients with symptoms or signs of PE or pneumonia, aged 18-80 yr, whose physical examination and interview data were available were investigated. The clinical findings were assessed when the diagnoses were established. The evaluation did not require ethical approval from the ethics committee, though it was considered as a clinical outcome study. The results
of the evaluation are shown in **Table 22.**

Table 22.
Characteristics of the patients.
Values are in mean or n (SD or %), otherwise noted.

Parameter	PE	Pneumonia	p
Patients	n=48	n=204	
Mean age, yr	58.4	57.1	n.s
Sex, male/female, n	30/18	108/96	-
Dyspnoea, pleuritic pain, n (%)	35 (72.9)	45 (22.1)	
Fever, chills, cough, n (%)	4 (8.3)	133 (65.2)	
Other symptoms, n (%)	9 (18.8)	26 (12.7)	
Mean CRP level, mg/L (SD)	61.1 (70.4)	138.1 (106.8)	0.004
Mean body temperature, °C (SD)	37.3 (0.47)	38.0 (1.07)	<0.001
Diagnosis verified by CT, n	46	28	-
V/Q scan, n	2	n.a.	-
CXR, n	n.a.	176	-

n.a, not applicable; n.s, not significant, CT, computed tomography

The findings in this evaluation confirm the findings in the original retrospective study.

PAPER III

Ljungqvist M, Söderberg M, Ahlgren A, Moritz P, Lärfars G.
Evaluation of Wells score and repeated D-dimer…*Eur J Int Med* 2008; 19: 285-8.

During the study period of one year, 374 patients were referred to the ED at Södersjukhuset with suspicion of VTE, and these patients were screened for eligibility in the study. Forty-six patients were excluded because of violations to the protocol, and 177 were not included because of Wells score >1.5 points or D-dimer ≥0.5 mg/L, thus were 151 patients studied. The study included 118/151 (78%) patients with suspected DVT and 33 (22%) with suspected PE (**Table 23**).

Table 23.
Characteristics of the patients in the study

	Included	Not included
Patients	n=151	n=177
Male/female, n (%)	48/103 (32/68)	81/96 (46/54)
Mean age, yr (range)	53 (20-90)	65 (18-95)
Suspected DVT, n (%)	118 (78)	153 (86)
Suspected PE, n (%)	33 (22)	24 (14)

Of the investigated patients, 101/151 (67%) had a follow-up D-dimer test done, and 13 (13%) had elevated D-dimer levels. The mean D-dimer

level was 0.69 mg/L (range 0.5–1.2 mg/L). Six of the 13 patients with elevated follow-up D-dimer had symptoms in the leg and were subjected to objective tests. One patients was evaluated with venography and five with compression ultrasound; none of these subsequent tests showed signs of DVT. The remaining 7/13 had no residual symptoms of VTE, and no further tests were performed. Most of these patients were diagnosed with infection or nonspecific inflammation. Fifty of the 151 (33 %) patients never went to the laboratory for a follow-up D-dimer despite our instruction and a reminder. **Table 24** shows the characteristics of the patients with either a high Wells score or high D-dimer (n=177) and the 46 patients excluded (total n=223).

Table 24.
Characteristics of the patients with either high Wells score or high D-dimer.

Variable	Patients	Patients with VTE
Patients	n=223	n=45
Wells score ≤1.5, and D-dimer ≥0.5 mg/L, n	57	12
Wells score >1.5, n, and	120	33
D-dimer test not done, n	57	20
D-dimer <0.5mg/L, n	25	1
D-dimer ≥0.5mg/L, n	38	12
Excluded for other reasons, n	46	-

After three months, all patients were contacted by the investigators, and none (0/151, 95 % CI 0.0-2.0 %) reported symptoms or were diagnosed with VTE. Seventeen of the 374 (4.5 %) screened patients were not evaluated because they refused consent (n=6), used anticoagulants (5), had known thrombophilia (3), had other reason for radiological examination (2) or were younger than 18 yr (1). There were 29 dropouts from the study, 19 because of protocol violation and 10 were not able to be reached for follow-up. Of the 177 patients with either an elevated D-dimer level or a Wells score >1.5, 153 (86%) had suspected DVT and 24 (14%) had suspected PE. Fifty-seven (32%) were excluded because of D-dimer levels ≥0.5 mg/L but they had a Wells score ≤1.5 points, and 120 (68%) had a Wells score >1.5 points. The NPV of the D-dimer test for all patients, irrespective of their Wells score, was 99.5 % and PPV was 24.2 %. The NPV for a low score (irrespective of the D-dimer) was 93.3% and the PPV was 27.3%. Forty-five of the 177 patients excluded had a VTE diagnosed according to established criteria (**Table 24**).

PAPER IV

Söderberg M, Brohult J, Jorfeldt L, Lärfars G.
The Use of D-dimer testing and Wells score…*J Eval Clin Pract* , accepted 2007

One hundred twenty symptomatic outpatients were evaluated in this study. There were no statistically significant differences between the PE and non-PE-groups concerning age, sex, and main clinical findings. Forty-seven of 120 (39%) patients had a PE confirmed by either PA (n=34) or contrast enhanced CTPA (n=13). Thirty-four patients had both investigations done. In five of these patients, PA and CTPA showed different results, and, for safety reasons, these five patients were

diagnosed with PE and were given treatment. Eight of 47 of the PE patients had a Wells score of ≤4 and 39/47 had a score >4. In the non-PE group, 35/73 had a score ≤4 and 38/73 had a score >4. Fifty of the 120 patients (42 %) had a low D-dimer (<0.5 mg/L), and only one patient had PE diagnosed with a Wells score ≤4 and D-dimer <0.5 mg/L. The characteristics of the patients are shown in **Table 25.**

Table 25.
Characteristics of the study population.

Variable	PE	No PE
Patients	n=47	n=73
Median age, yr (range)	57 (27-80)	57 (20-80)
Female, n (%)	25 (53)	47 (64)
PE diagnosed with PA, n (%)	34 (72)	54 (74)
PE diagnosed with CTPA, n (%)	13 (28)	19 (26)
Known malignant disease, n (%)	5 (10)	6 (8)
Known coagulopathy, n	0	2
Previous VTE, n (%)	14 (29)	12 (16)
Heart rate, min^{-1} , mean (SD)	91 (19)	87 (16)
Per. saturation[a], %, mean (SD)	94 (4)	96 (3)
Resp. rate[a], min^{-1}, mean (SD)	22 (8)	17 (3)

[a] some values are missing. Per. saturation., peripheral arterial oxygen saturation; Resp. rate, respiratory rate

The regression coefficient, calculated by a multiple logistic regression model, was statistically significant for D-dimer (p<0.01) and Wells score (p<0.01). The interaction term Wells score by D-dimer was significant (p=0.013). The logistic regression analysis was combined with calculations of receiver operating characteristics (ROC) curves (**Fig. 11** and **Fig. 12**), showing an area under the curves (AUC) of 70.5% ± 4.9% (SE) for the Wells score and 86.7% ± 3.5% (SE) for D-dimer. We used the Wells score as the *a priori* probability method and D-dimer as the *post priori* test for estimating the risk of PE. Using the regression coefficients, the probability for PE with a Wells score of 4 and a D-dimer of 0.5 mg/L was 0.18 compared with 0.25 with a D-dimer of 1.0 mg/L at the same Wells score. This indicates a 40% relative increase in the risk of disease. With an increased Wells score, the significance of a normal D-dimer level decreased. The NPV of the combination of the Wells score and D-dimer was 94%. The different scores and D-dimers of the study population are shown in **Table 26,** and the number of PE-patients with different Wells score at different D-dimer levels are shown in **Table 27**. The test performances are presented in **Table 28.**

Table 26.
Wells score and D-dimer in patients with PE and without PE.
Values in n.

	Wells score n=120		**D-dimer (mg/L)** n=120		**DD < 0.5 mg/L** n=50	
	WS ≤4 n= 43	WS >4 n=77	DD <0.5 n=50	DD ≥0.5 n=70	WS ≤4 n=26	WS >4 n=24
PE	8	39	4	43	1	3
No PE	35	38	46	27	25	21

WS, Wells score; DD, D-dimer

Table 27.
Patients with PE at different Wells score and D-dimer levels.
Values in n.

D-dimer level	Wells score =3	Wells score ≤4	Well score ≤6
<0.5 mg/L	1	1	2
≤0.67 mg/L	1	1	7
≤1 mg/L	3	3	11

Table 28.
Diagnostic performances of Wells score and D-dimer.

	Wells score ≤4 p	D-dimer <0.5 mg/L
Sensitivity, %	83.0	91.5
Specificity, %	47.9	63.0
NPV, %	81.4	92.0
PPV, %	50.6	61.4

Table 29.
Logistic regression analysis. Wells score and D-dimer denotes the interaction between the two variables.

Variable	OR	B	SE	p
Wells score	1.75	0.56	0.17	0.001
D-dimer	5.01	1.61	0.56	0.004
Wells score and D-dimer	0.82	-0.19	0.08	0.013
Constant	-	-4.20	0.96	-

OR, Odds Ratio; B, regression coefficient; SE, standard error

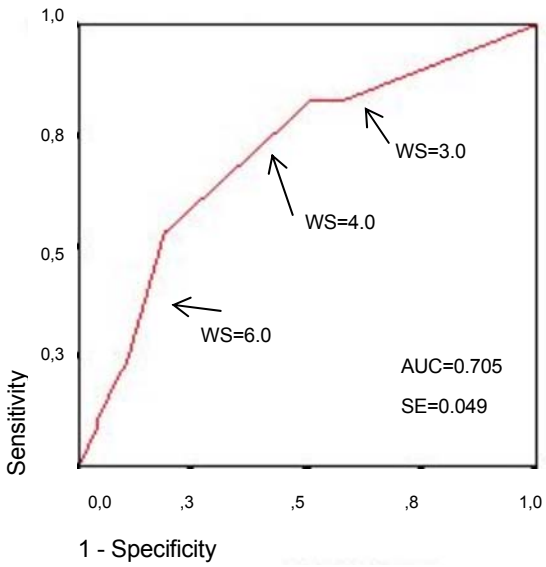

Fig. 11. ROC curve for Wells score with different cut-off levels.
WS, Wells score; AUC, area under the curve, SE, standard error.

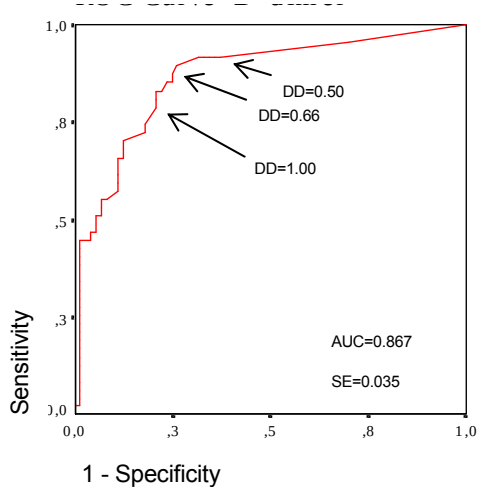

Fig. 12. ROC curve for D-dimer. Abbreviations are the same as in fig 11.

PAPER V

Söderberg M, Schulman S, Lärfars G.
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Ninety-one patients were evaluated in this study, 45 patients with symptomatic DVT and 46 with symptomatic PE. The mean age was 55.6 yr in the DVT group,and 57.2 yr in the PE group. Age and sex did not differ significantly between the groups. The diagnosis of DVT was confirmed by compression ultrasound in 23 patients and by venography in 22 patients. Fifteen of the 45 DVT patients (33%) had a proximal DVT (i.e. the popliteal and more proximal veins), and 30 (67%) had a distal thrombosis limited to the calf veins. Twenty-five (56%) of the DVT patients had an identified risk factor such as bed rest, immobilization, or prior trauma with or without a fracture. Seven patients (16%) had had a previous episode of VTE, and 13 (29%) had no obvious risk factor and were considered as having idiopathic thrombosis. The difference in venographic extension according to the Marder score and other characteristics of the patients with DVT are summarized in **Table 30.** The diagnosis of PE was confirmed by CTPA (n=20) and by lung scintigraphy (n=26) according to local recommendations and availability. There was no statistically significant difference in the presence of Factor V Leiden mutation between the two DVT groups. Material for analysis of the mutation was not available in the PE group.

No patient had massive thrombosis or embolism requiring thrombolytic therapy in the study. After the diagnostic procedure, all patients received anticoagulant therapy with sc injections of dalteparin (Fragmin®, Pfizer) at a dose of 200 IU/kg (maximum 18,000 IU) daily for five consecutive days overlapping and followed by oral warfarin (Waran®, Nycomed, Stockholm, Sweden) with a targeted International normalized ratio (INR) of 2-3 for at least three months.

Table 30.
Characteristics of the patients.

Variable	Proximal DVT	Distal DVT
Patients	n=15	n=30
Median age, yr (range)	62 (19-74)	55 (25-75)
Sex, M/F, n	9/6	21/9
Location of DVT, R/L, n	5/10	12/18
Mean initial Marder score, pt (SD)	7.07 (2.7)	4.33 (1.6)
Mean CRP[a], mg/L, day 0 (SD)	34.80 (35.0)	24.97 (44.9)
Mean CRP[a], mg/L, day 90 (SD)	9 (0.6)	9 (0)
Factor V Leiden, n	2[b]	4[c]

M, male; F, female; R, right; L, left; pt, pontis; a, A value of CRP <10 mg/L is calculated as 9;
b, 2 heterozygous; c, 3 heterozygous, 1 homozygous

The mean level of vWF on day 0 was 1.87 ± 0.41 IU/mL in the PE group (n=46), and 1.64 ± 0.34 IU/mL in the DVT group (n=45), p=0.003. Sub-group analysis showed a mean level of vWFof 1.88 ± 0.34 IU/ml in patients with proximal DVT (n=15) and 1.52 ± 0.20 IU/mL in patients with distal DVT (n=30), p<0.001. The difference in the vWF levels between proximal DVT and PE was not significant. After three months (day 90), the level of vWF was 1.45 ± 0.31 IU/ml in the PE group and 1.41 ± 0.37 IU/mL in the all-DVT group, p=0.33. The level at day 90 was 1.65 ± 0.28 IU/ml for proximal DVT and 1.28 ± 0.35 IU/mL, for distal DVT, p=0.001. There was a significant difference between the two DVT groups on day 90. The levels of vWF on day 0 and on day 90 in the different groups are shown in **Figure 13.** The reduction of the vWF level from day 0 to day 90 was significant in all subsets, p<0.05. The difference between baseline and 3 months was greater for patients with PE than DVT, p<0.05.

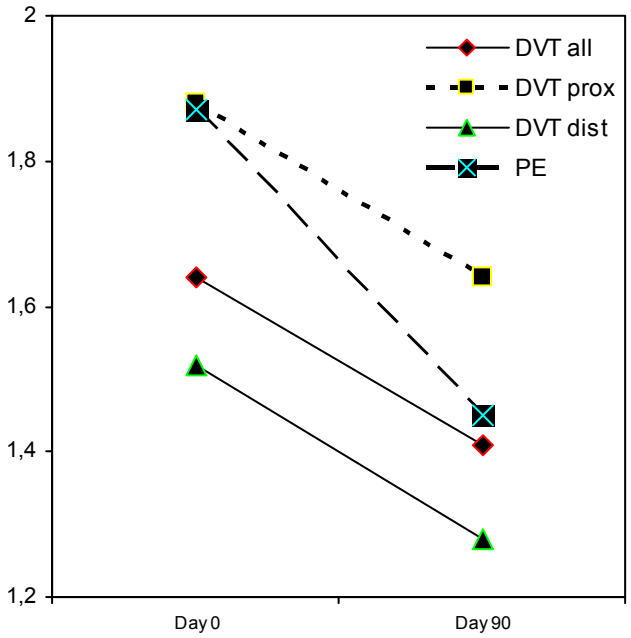

Fig. 13. Mean values of von Willebrand factor antigen i n the different study groups on day 0 and day 90. Values are shown in IU/mL.
DVT prox, proximal deep vein thrombosis; DVT dist, distal DVT; PE, pulmonary embolism.

STATISTICS

In **paper I, III, IV,** and **V,** standard descriptive diagnostic tests for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated. Sensitivity is defined as the proportion of positives (here PE) that are correctly identified by the test (PA, CTPA, D-dimer or Wells score). Specificity is the proportion of negatives that are correctly identified by the test. To assess the usefulness of the results in clinical practice, we performed predictive values as follows. NPV is the proportion of patients with negative test results who are correctly diagnosed, and PPV is the proportion of patients with positive test who are correctly diagnosed. The predictive values depend on the prevalence of the disease.

Table 31.
The general representation of the diagnostic tests.

		Disease status		
		Positive	**Negative**	Total
Test result	**Positive**	*a*	*b*	*a + b*
	Negative	*c*	*d*	*c + d*
	Total	*a + c*	*b + d*	*n*

Test, PA, CTPA, D-dimer or Wells score; disease, PE

In this analysis, *(a)* is the true positive, *(b)* the false positive, *(c)* the false negative and *(d)* the true negative results. The prevalence is calculated as *(a + c / n).* The diagnostic performance values are calculated as:

$$\text{Sensitivity} = a / (a + c)$$
$$\text{Specificity} = d / (b + d)$$
$$\text{NPV} = d / (c + d)$$
$$\text{PPV} = a / (a + b)$$

The chi square (χ^2) -test or Fisher's exact test were used to analyze categorical data. Comparisons between groups were calculated using the Student's *t*-test for continuing data. A p-value <0.05 was considered significant in all studies.

In **paper II**, the population of patients with PE identified at the CID was compared with two randomized samples, using one-sample analysis. Two-sample analysis was used to compare the two randomized samples. The p-values were adjusted using the Bonferroni correction bcause of repeated tests of every variable.

In **paper IV** the data were analyzed using the t-test, Wilcoxon rank sum test, or logistic regression where appropriate. The AUC was calculated using the ROC curves to assess the best diagnostic cut-offs of D-dimer and Wells score.

For the analyses we used the SPSS software package (SPSS, Chicago, IL, USA). All statistical analyses were performed by the study investigators.

DISCUSSION

The diagnosis of PE is a challenge. The symptoms, signs, and clinical appearance of patients with PE can be nonspecific and nondiagnostic. Most patients with PE have symptoms, but these symptoms are sometimes difficult to interpret. There are also many alternative diagnoses with similar findings. PE has numerous risk factors and is often misdiagnosed. The diagnostic work-up for patients with suspected PE comprises an evaluation of all clinical findings, assessment of hemodynamics, evaluation of the Wells pre-test probability score, D-dimer and radiological investigations. The big challenge is to find the right patient to the right investigation and to avoid unnecessary investigations in patients with low clinical probability for the disease. A correct diagnosis of PE can have implications on the mortality and morbidity since an untreated PE has a relatively high mortality and many patients suffer from postthrombotic complications [98].

In the retrospective study of patients with PE diagnosed at the Clinic for Infectious Diseases and at the Dept. of Internal Medicine (**paper II**), we showed that the initial symptoms of PE were mainly dyspnoea and pleuritic chest pain. The symptoms did not differ between patients diagnosed at the CID and the Medical Dept. ($p=0.48$). Review of the medical charts showed that all patients had classical symptoms. The patients with pneumonia exhibited mainly fever, chills and cough with or without productive sputum, although some had dyspnoea. The difference between the initial symptoms presenting with PE and pneumonia was significant, $p<0.001$. Some patients with PE diagnosed at the CID had signs of inflammation with high body temperature, high CRP, and infiltrates on chest X-rays. The frequency of these findings was significantly higher than in the patients diagnosed with PE at the Medical Dept. We had no suspicion that the PE/infection patients suffered from secondary pneumonia as they improved during anticoagulant treatment, and the deceased patients showed no signs of pneumonia at autopsy. Why certain patients with PE exert more inflammatory changes is unclear. The signs of inflammation in these patients were probably the reason for a first false diagnosis. Many patients with PE also had infiltrates and other pathological changes on chest X-ray [25], sometimes misleading the attending physician. We emphasize that the initial symptoms in PE are often typical, with sudden onset of dyspnoea and pleuritic chest pain, but other symptoms occur frequently [56].

When the suspicion of PE is established, a pre-test probability score as described by Wells et al should be performed [110] (**paper III** and **IV**). A clinical algorithm that includes both Wells score and D-dimer test is recommended in order to minimize the number of radiological investigations needed for patients with a low probability of PE [32]. Wells score is the most validated clinical decision rule for VTE and, combined with a negative D-dimer, can safely rule out clinically important PE. Wells score and D-dimer can be elevated in diseases other than PE. We found that

the algorithm is adequate and that the cut-off values of 4 (Wells score) and 0.5 mg/L (D-dimer) provides significant results. The predictive strength of the combination of a low Wells score and a normal D-dimer level is illustrated by the observation that 21% of the patients with a low Wells score but an elevated D-dimer had VTE but only one (<0.01%) patient with a normal D-dimer and a high score had a VTE during the study period. In the Christopher study from 2006, 1,057 of 3,306 patients with suspected PE (32%) had a low Wells score and a normal D-dimer. Only five of these patients, (0.5%, 95 % CI 0.2-1.1%) had a VTE during the three months follow-up, showing the safety of the algorithm [152]. Probably some patients with small emboli were left untreated without any increased risk for a fatal PE.

There are some limitations to discuss. PA and CTPA occasionally give different results, although both are considered accurate and safe. We found conflicting results in five of 34 patients who had PA and CTPA done (**paper IV**), indicating that the diagnosis of PE might be difficult to establish in some patients. These contradictory interpretations concerned only small subsegmental emboli. Both Wells score and D-dimer can be elevated in patients with nonthromboembolic diseases. Kruip et al [113] showed that a high Wells score in hospitalized patients with other diseases is nondiagnostic. One difficulty with the Wells score is that it forces the physician to make a subjective decision in deciding whether a PE is likely or not. Both Well et al [110] and other authors [66] have shown that the most likely diagnosis before confirmatory tests influences the probability. D-dimer testing at the ED increases the number of clinical investigations of patients with suspected PE but does not increase the diagnosis of PE, indicating a need to follow established algorithms.

The Wells score can be used in patients with intermediate to high suspicion of PE. The probability that a patient with a low score and normal D-dimer level has VTE is low. In **paper III**, we showed that none of the 151 patients investigated developed symptomatic PE or DVT within three months, although the cut-off in this study was set at 1.5 points. In this study, we also performed a follow-up D-dimer test after 3-7 days with the objective to reduce the number of incorrect diagnoses caused by an initial false negative D-dimer. None of the patients with an elevated D-dimer after 3-7 days had a VTE. Most patients with an elevated D-dimer had an inflammatory or infectious disease. D-dimer was measured in only for 53% of patientys with high clinical probability of VTE. This could explain why the NPV of the D-dimer test was high regardless of the Wells score result. Whether the D-dimer test can be used without a Wells score to identify low-risk patients requires further studies. New, sensitive D-dimer tests have improved its usefulness as a negative predictive index of VTE [157,158].

The use of Wells score and D-dimer test in the ED increases the effectiveness of patient triage and reduces the costs and inconvenience for patients and providers of medical services.

In **paper V**, we compared the expression of von Willebrand factor antigen (vWF) in patients with symptomatic PE and symptomatic DVT at inclusion

and after 90 days. A higher level of vWF in the acute stage of the disease could indicate a larger thrombotic burden, and we know that large thrombi are more likely to embolize than small thrombi. A high level of vWF may indicate a more endothelial activation, and other markers of inflammation, such as CRP, are shown to be elevated in patients with VTE [139], although the significance and use of these markers in clinical practice is unknown.

Earlier studies have shown that about 60% of patients with PE have a proximal DVT, and 20% have a distal DVT that limited to calf veins [3]. The risk of recurrent VTE, albeit initially higher in patients with PE than in those with proximal DVT, becomes similar in the long-term follow-up and is higher than in distal DVT [159].

We showed that the initial level of vWF was higher in patients with PE and proximal DVT than in patients with distal DVT. Patients with proximal DVT had the same levels of vWF as patients with PE. This could indicate that these two conditions differ from distal DVT in terms of the underlying disease mechanisms. All patients, regardless of whether they had PE or DVT, had lower levels of vWFthree months after admission. The vWF decreased faster for patients with PE than for patients with DVT, indicating a faster resolution of the thrombotic material in PE.

There are some limitations to discuss. First, the sample size was small. Second, we did not exclude concomitant PE in the DVT patients and vice versa. Third, we did not investigate other markers such as CRP, D-dimer, and FVIII or blood group genotype. The factor V Leiden mutation was not investigated in the PE patients.

We conclude that distal DVT can be regarded as a low risk for PE, and that vWF is probably a reactant responding to the endothelial activation induced by the thrombus in relation to its size, and not a marker or a risk factor for VTE.

In **paper I**, we established that CTPA has a high sensitivity and a high diagnostic specificity, similar to PA, in hemodynamically stable patients with PE. The specificity, PPV, and NPV were higher for CTPA than for D-dimer, irrespective of the chosen cut-off level. When the probability of PE is set, a radiological investigation is mandatory to diagnose or exclude the disease.

The improved CT technique has now made CTPA the recommended first-line imaging modality in most hospitals [145]. This strategy has been challenged by some authors [54,160] because the evidence is based on a number of small studies, with sensitivities and specificities between 53-100% and 81-100% respectively. Our study showed both high sensitivity and specificity, and this favorable outcome of interpretation in our study compared with others may reflect that the images were read in consensus and that the patients selected were hemodynamically stable. Several studies have investigated the frequency of PE three months after a negative CTPA and reported a low frequency of PE (0-

1.5%) [29,113,152,161]. We conclude that with a normal CTPA, PE can safely be ruled out.

Compared with PA, CTPA yielded both false-negative and false-positive results. The differences concerned only minor emboli. PA is still the gold standard in diagnosing PE, although PA produces false-positive and false-negative findings [162]. The mean interobserver agreement for lobar and segmental vessels is 90-100%, but the conformity is lower in subsegmental vessels. The shortcoming of diagnosing subsegmental emboli was the same using PA as CTPA in an experimental study [163]. This might partly explain the low sensitivity of CTPA in some studies, which was also reflected by the five discordant investigations in our study.

Different D-dimer assays are available. Latex agglutination D-dimer assays have sensitivities and specificities ranging of 70-90%, whole blood assays perform slightly better, and enzyme-linked immunosorbent assays (ELISA) have the highest sensitivity (90-100%) but have relatively low specificity (30-40%) [122,164].

The specificity of all D-dimer assays is low because these degradation products are produced whenever there is an active fibrin formation and fibrinolysis. This often occurs in elderly patients with confounding conditions. If D-dimer assays are to be used in the workup of acute PE, the diagnostic level must be determined and compared with a gold standard, which still is PA. However, most studies have used different noninvasive diagnostic algorithms and different D-dimer assays, and have seldom used the same test to compare D-dimer in the same patient. We chose to compare two cut-off levels for D-dimer (0.25 and 0.5 mg/L) in our study. The lower one had the same sensitivity as CTPA, but a low specificity. The higher cut-off value had lower sensitivity, but had higher specificity and a similar NPV as the lower cut-off.

Sijens et al [165] showed that a negative D-dimer safely excludes massive and segmental PE, but the test has poor NPV in subsegmental emboli. We could confirm this finding only partly, of seven patients with normal D-dimer, two had bilateral, lobar PE.

In our study, the clinical suspicion for acute PE was high, although no patient was hemodynamically unstable. The NPV was 95% for CTPA and 92% for D-dimer, using 0.25 mg/L as cut-off level and 87% using 0.5 mg/L as cut-off level. These results suggest that the latex D-dimer agglutination method is a valuable screening method for ruling out significant PE in stable patients at the ED.

CONCLUSIONS

From the findings in **paper I-V** the following conclusions may be drawn:

- In hemodynamically stable patients suspected of having acute PE, there is good agreement between PA and CTPA.
- CTPA has high sensitivity, similar to that of PA. A negative CTPA should safely rule out clinically important PE.
- A negative latex agglutination D-dimer test would rule out clinically significant PE with almost the same certainty as CTPA in out-patients with moderate to high clinical probability for PE.

- A detailed patient history is mandatory to decide the preliminary diagnosis of PE.
- Dyspnoea and pleuritic chest pain are dominating initial symptoms in patients with PE, and fever, shivering and cough are rare initial symptoms
- High values of CRP and presence of pulmonary infiltrates do not exclude PE.

- A low Wells score in combination with a low D-dimer safely excludes venous thromboembolism at the ED.
- A follow up D-dimer after 3-7 days adds no further information.

- The combination of Wells score and D-dimer testing is superior to the sole use of the score to exclude PE, and a D-dimer test is in this purpose superior to the Wells score.
- Wells score has a higher specificity than D-dimer in selecting patients with a higher risk of PE, whereas the sensitivity for D-dimer is higher.
- A cut-off level in the dichotomized Wells score of 4 is accurate and the cut off level of D-dimer of 0.5 mg/L is accurate and should be used.
- CTPA is sufficient for most patients, but some false cases, both positive and negative might occur.

- Patients with symptomatic PE without signs of DVT express von Willebrand factor antigen (vWF) at the same level as patients with proximal DVT.
- Patients with distal DVT express vWF at a lower level than patients with PE and proximal DVT.

Suggestion of an algorithm for the work-up on patients with suspected PE.

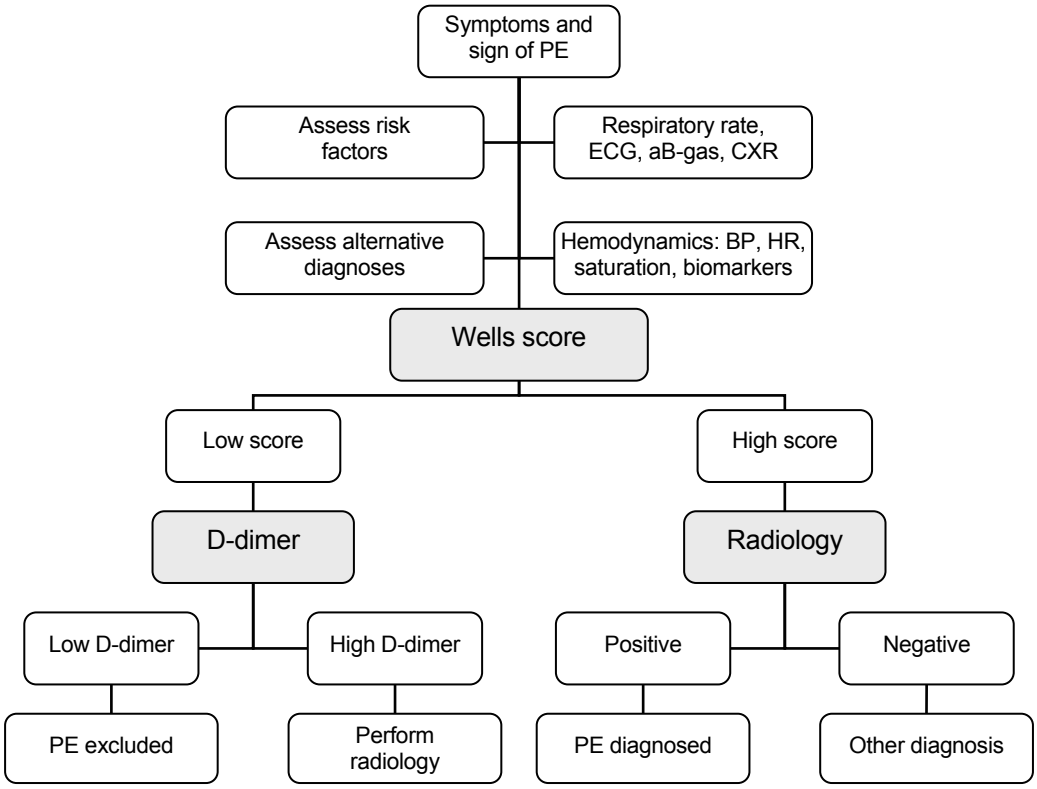

Fig. 14. Algorithm for the diagnostic work-up of patients with suspected PE. Assessment of risk factors, alternative diagnoses, hemodynamics and clinical signs are optional and do not exclude the use of Wells score, or other clinical decision rules.
aB-gas, arterial blood gas; CXR, chest X-ray; BP, blood pressure; HR, heart rate.

Suggestions for future research

The diagnostic work-up for patients with suspected PE is still a challenge for every physician. Despite modern technology using advanced methods with high capacity and diagnostic performances, PE must still be suspected by the attending physician at the ED in order to diagnose or exclude the disease. With the ageing population, the incidence of PE and DVT will probably not diminish in the future as more patients survive cancer, stroke, and other disabling conditions with a high incidence of VTE. There is a need for further studies in the area of diagnostic procedures in PE and other VTEs. Some suggestions for further studies are as follows:

- Better definitions and more disseminated use of the diagnostic algorithms in order to improve the diagnostic performances for clinical decision rules.

- Definitions of the use of combinations of biomarkers, such as CRP, BNP and troponins as well as new, not yet well defined markers, in the diagnostic work-up.

- Further studies of the use of different cut-off values of D-dimer in different clinical settings, age, etc. is warranted. The use of D-dimer as a diagnostic and prognostic tool is still not fully understood or established.

- Definitions of the use of the different available diagnostic investigations such as CTPA, MRA, MDCT, MSCT, V/P_{SPECT} etc. and also PA in different clinical settings and in different patients in order to optimize the use and the health economics.

SAMMANFATTNING PÅ SVENSKA

Lungemboli (LE) är en allvarlig och ofta svårdiagnosticerad sjukdom. Djup ventrombos (DVT) och LE sammanfattas i begreppet venös tromboembolism (VTE). Grundstenarna i diagnostiken av LE bygger på en bedömning av symtom, kliniska fynd och riskfaktorer följt av bedömning av blodprovsanalyser, bl. a D-dimer, och av radiologiska undersökningar.

I **arbete 1** undersöktes 90 hemodynamiskt stabila patienter med akut LE med D-dimer, datortomografi av lungartärer (DTLA) och pulmonalisangiografi (PA) som referensmetod. Hypotesen var att DTLA har högre sensitivitet än D-dimer i diagnostiken av LE. Fem av 90 patienter hade olika resultat på PA och DTLA. Sensitiviteten för DTLA var 91% och specificiteten 96%. Låg D-dimer utesluter LE med en sensitivitet på 79%, specificitet var 88%. Slutsatsen är att DTLA har högre sensitivitet och specificitet än D-dimer i diagnostiken av LE.

Arbete 2 var en retrospektiv journalstudie av patienter med LE, initialt felaktigt bedömda som lunginflammation, som vårdats på infektionsklinik (LE/inf, n=25). Dessa jämfördes med en grupp LE-patienter korrekt diagnosticerade och vårdade på medicinklinik (LE/med, n=64) och en grupp av patienter med säkerställd lunginflammation (pne, n=54). Debutsymtom, röntgen- och laboratoriefynd jämfördes för patienter i dessa grupper. Andnöd eller pleuritsmärta var debutsymtom hos 76% av LE/inf, 81% av LE/med och 10% av pne. Feber/frossa/hosta var debutsymtom hos 8% (LE/inf), 16% (LE/med) och 80% (pne), $p<0.001$. CRP (mg/L, medelvärde) var 209 (LE/inf), 79 (LE/med) respektive 257 (pne). Medeltemperatur (^{o}C) var 38,1 (LE/inf), 37,4 (LE/med) respekttive 38,5 (pne). Förekomst av lunginfiltrat på röntgen var 64% (LE/inf), 16% (LE/Med) och 100% (pne). Debutsymtomen var samma i LE/inf- och LE/med-grupperna och tydligt annorlunda än de i pneumonigruppen. Debutsymtomen vid lungemboli skiljer sig tydligt från debutsymtomen vid lunginflammation, medan lab- och röntgenfynd kan vara likartade.

I **arbete 3** undersöktes 151 akutpatienter med misstänkt DVT och/eller LE men med låg klinisk misstanke enligt Wells score (≤1.5 poäng) och negativt D-dimer (<0.5 mg/L). 177 patienter exkluderades pga. hög klinisk misstanke på VTE (Wells score >1.5 p) eller D-dimer ≥0.5 mg/L. En uppföljande D-dimer kunde tas på 67% av studiens patienter efter 3-7 dagar. Av de 151 undersökta patienterna med lågt score och låg D-dimer hade ingen kliniska tecken på VTE efter 3 mån uppföljning, 13% hade ett förhöjt D-dimer efter 3-7 dagar, ingen av dessa hade kliniska tecken på VTE. Av de exkluderade hade 25% VTE. Endast en av totalt 176 patienter (<0.01%) med normal D-dimer hade VTE. En normal Wells score och ett normalt D-dimer utesluter med stor sannolikhet VTE på akutmottagningen. Ett nytt D-dimer efter 3-7 dagar ger ingen ytterligare information.

I **arbete 4** undersöktes 120 hemodynamiskt stabila patienter (18-80 år) med misstänkt akut LE på akutmottagning med Wells score, D-dimer, pulmonalisangiografi eller DTLA. Kliniskt score sattes retrospektivt. Fyrtiosju av 120 (39%) patienter hade LE, 21/47 (45%) av dessa hade Wells score >6. Sjuttiotre av 120 (61%) hade inte LE, av dessa hade 12 (16%) Wells score >6. D-dimer var förhöjt, ≥0.25 mg/L, hos 43/47 (91%) av LE-patienter och hos 18/73 (11%) hos de utan LE-diagnos. Sensitiviteten för en kombination av normalt D-dimer och normalt Wells score (<6) i diagnostiken av LE blev 94%. Slutsatsen blir att ett lågt Wells score och normalt D-dimer utesluter med stor sannolikhet lungemboli och kan användas i den kliniska beslutsprocessen.

I **arbete 5** jämfördes 46 patienter med verifierad LE utan samtidig klinisk DVT med 45 patienter med DVT utan LE. Prov för von Willebrand faktorantigen (vWF) togs i akutskedet inom 24 h och efter 3 månader. I akutskedet var vWF (mätt i IU/mL) 1,87±0,41 hos patienter med LE och 1,64±0,34 hos DVT patienter, p=0,003. Hos de med proximal DVT var vWF 1,88±34 och de med distal DVT hade 1,52±0,20, p<0.001. Efter 3 månader var nivåerna: 1,45±0,31 (LE), 1,41±0,37 (alla DVT), p=0,33, samt 1,65±0,28 (proximala DVT) och 1,28±0,35 (distala DVT), p=0,001. Uttrycket av vWF skiljer sig statistiskt signifikant mellan patienter med LE och DVT i akutskedet samt mellan proximala och distala DVT:er, men inte mellan proximala DVT:er och LE. Samtliga patienter hade lägre nivåer av vWF efter 3 månader. vWF kan vara en markör för utbredningen av DVT.

Sammanfattning:

- Datortomografi av lungartärer (DTLA) utesluter lungemboli (LE) bättre än D-dimer. DTLA är ett säker diagnosmetod för diagnos av LE. Osäkra fall bör undersökas med pulmonalisangiografi.

- Initialsymtomen vid LE är oftast dyspne eller pleuritsmärta. Feber, frossa eller hosta är ovanliga som initialsymtom vid LE. Patienter med LE kan ha stegring av kroppstemperatur och CRP och ofta infiltrat på lungröntgen. En noggrann bedömning av symtom och fynd är nödvändig vid utredning av misstänkt lungemboli.

- Wells diagnostikstöd i kombination med D-dimer kan säkert användas för att utesluta LE och djup ventrombos (DVT), även hos patienter med intermediär till hög risk för sjukdomen. Uppföljande D-dimer efter 3-7 dagar ger ingen extra information.

- Uttrycket av von Willebrand faktorantigen är högre hos patienter med LE än DVT, men de med proximal DVT har samma nivå som LE och högre än de med distal DVT. Samtliga undersökta hade lägre nivå av vWF efter 3 mån. LE och proximal DVT är mer lika i uttrycket av vWF än proximala och distala DVT.

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APPENDIX

PAPER I-V