Diploma thesis

Imaging of Venous Thromboembolism: Current Role and Future Perspectives

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Graz, 17. December 2025 Danko Stojanovic, m.p.

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Abstract in German

Pulmonalarterienembolie (PAE) ist die häufigste vermeidbare Todesursache im Krankenhaus. Sie tritt meist als Komplikation einer tiefen Venenthrombose (TVT) auf. Die Anzahl diagnostizierter Lungenembolien nimmt zu, was vermutlich auf eine gesteigerte Zahl an Screenings zurückzuführen ist. Die Computertomographie der Pulmonalarterien (CTPA) gilt in den meisten Fällen als Goldstandard der Diagnostik bei Verdacht auf PAE. Die Anwendung von CTPA ist in den letzten Jahren stark gestiegen (um bis zu 450 % zwischen 2004 und 2016), wobei jedoch nur etwa 5 % der durchgeführten CTPAs tatsächlich positiv auf PAE sind. Dies stellt eine erhebliche ökonomische, Strahlungs- und Arbeitsbelastung dar, wobei die signifikante Verringerung der Mortalitätsrate durch diese Diagnostik fraglich bleibt. Diese Literaturrecherche fokussiert sich auf die Analyse aktueller Leitlinien zur bildgebenden Diagnostik der Lungenembolie sowie auf die zukünftigen Perspektiven der PAE-Diagnostik. Die aktuellen Leitlinien sind sich weitgehend einig, dass in den meisten Fällen eine CTPA, und situativ eine Ventilations-/Perfusionsszintigraphie (V/Q-Scan), als erste bildgebende Untersuchung durchgeführt werden sollte. Ebenfalls stimmen alle Leitlinien überein, dass eine Einschätzung der klinischen Vortestwahrscheinlichkeit sowie bei nicht höherer Wahrscheinlichkeit ein D-Dimer-Test vor der Bildgebung erfolgen sollte. Zur Vermeidung unnötiger Bildgebung sollte zusätzlich der PERC-Score (Pulmonary Embolism Rule-out Criteria) herangezogen werden. Die zukünftigen Entwicklungen in der Diagnostik der PE betreffen vor allem den Einsatz von künstlicher Intelligenz (KI), Photon counting CT (PCCT) sowie Dual energy CT (DECT). KI zeigt vielversprechende Ergebnisse als Zweitleser bei CTPAs, mit einem relativ hohen negativen prädiktiven Wert. Zudem kann KI CTPA-Untersuchungen priorisieren und als dringlich kennzeichnen, um rascher von RadiologInnen befundet zu werden. Ob dies in der klinischen Praxis tatsächlich Vorteile bringt, muss jedoch noch weiter evaluiert werden. DECT und PCCT ermöglichen qualitativ hochwertigere Bilder und eine differenziertere Darstellung thromboembolischer Strukturen, wobei PCCT als vielversprechendere und neuere Technologie gilt. Für die TVT-Bildgebung bestehen zukünftige Perspektiven insbesondere in KI, molekularer Bildgebung und der MRDTI (Magnetresonanz-

Direktthrombusbildgebung). KI wird derzeit dahingehend getestet, ob sie medizinisches Personal ohne Sonografie-Erfahrung bei der Durchführung einer Kompressionssonografie unterstützen kann, um diagnostische Bilder zu erstellen, die anschließend von ÄrztInnen beurteilt werden können. Die molekulare Bildgebung, die bei onkologischen PatientInnen routinemäßig durchgeführt wird, könnte dabei auch Hinweise auf TVT, die ausgewertet werden können, geben. MRDTI erlaubt eine genauere Diagnostik von Rezidivthrombosen im Vergleich zur Kompressionssonografie (CUS) und liefert zusätzliche Informationen zur Therapieentscheidung in unklaren Fällen.

Abstract in English

The pulmonary embolism (PE) is the number one most common cause of preventable in-hospital death. It usually occurs as a complication of deep vein thrombosis. The number of diagnosed pulmonary embolisms is rising, but this is probably due to increased testing. The gold standard diagnostic tool for PE is computed tomography pulmonary angiography (CTPA). The use of CTPA for PE has increased recently (up to 450% from 2004 to 2016), while PE positive scan results are present in only 5% of CTPAs performed. This produces high economic, radiation, and workload burden, where a significant mortality reduction after this performed examination is questionable. The main focus of this thesis is the review of the current guidelines for diagnostic imaging of PE, and the evaluation of the future perspectives of diagnostic imaging for pulmonary embolism. The current guidelines mostly agree that in most cases, CTPA and situationally ventilation/perfusion (V/Q) scan should be performed as an initial diagnostic imaging for PE. Most guidelines agree that a workup of clinical pretest probability tests and D-dimer in case of non-high pretest probability clinical test should be performed prior to performing diagnostic imaging. Pulmonary Embolism Rule-out Criteria (PERC) should also be performed to reduce the number of abundantly performed diagnostic imaging tests. The future perspectives for PE diagnostic imaging consist mainly of methods such as artificial intelligence (AI), photon counting computed tomography (PCCT), and dual energy computed tomography

(DECT). The AI is promising in that it can provide a safety net as a second reader on CTPA, where it has a relatively high negative predictive value. AI can also categorize the CTPA studies and flag them as priority cases to be reviewed by Radiologists, but this remains to be further evaluated if it shows benefit in real-world scenarios. DECT and PCCT offer higher quality images and are able to differentiate thromboembolic structures, where PCCT is an upcoming and more promising technology. The future perspectives of deep vein thrombosis (DVT) imaging consist mainly of AI, molecular imaging, and magnetic resonance direct thrombus imaging (MRDTI). In case of DVT, the AI is currently being tested to guide the non-compression-ultrasonography-trained personnel to perform the acquisition of images for them to be later reviewed by a trained physician. Molecular imaging is routinely performed in patients with cancer, and here, the DVT presence could also be assessed. MRDTI is able to more accurately diagnose recurrent venous thrombosis than CUS and give further information needed for decisions about therapy in unclear cases.

Table of Contents

ACKNOWLEDGMENTS 2

ABSTRACT IN GERMAN 3

ABSTRACT IN ENGLISH 4

TABLE OF CONTENTS 6

GLOSSARY AND ABBREVIATIONS 9

LIST OF TABLES 11

LIST OF FIGURES 11

1 METHODS AND MATERIALS 12

1.1 LITERATURE 12
1.2 INCLUSION CRITERIA 12
1.3 ETHICAL APPROVAL 12

2 INTRODUCTION 13

2.1 DEFINITION AND EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM 13
2.2 DEFINITION AND EPIDEMIOLOGY OF DEEP VEIN THROMBOSIS 14
2.3 DEFINITION AND EPIDEMIOLOGY OF PULMONARY EMBOLISM 15
2.4 AETIOLOGY AND RISK FACTORS FOR VENOUS THROMBOEMBOLISM (VTE) 15
2.5 PATHOPHYSIOLOGY OF VENOUS THROMBOEMBOLISM 16
2.5.1 Blood flow stasis 16
2.5.2 Endothelial factors 17
2.5.3 Hypercoagulability 17
2.6 PATHOPHYSIOLOGY OF PULMONARY EMBOLISM (PE) 19
2.7 CLINICAL DIAGNOSIS OF DVT AND PRETEST PROBABILITY SCORE 20
2.8 CLINICAL DIAGNOSIS OF PULMONARY EMBOLISM AND PRETEST PROBABILITY SCORE 21
2.8.1 Wells score in patients with suspected pulmonary embolism 23
2.8.2 Revised Geneva Score for ruling out pulmonary embolism 25
2.9 DIAGNOSTIC IMAGING FOR DEEP VEIN THROMBOSIS 26
2.10 COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY 27
2.11 D-DIMER 29
2.12 TUMOR-ASSOCIATED THROMBOSIS 30
2.13 RECURRENT VENOUS THROMBOEMBOLISM 30
2.14 POSTTHROMBOTIC SYNDROME 31
2.15 CHRONIC PULMONARY HYPERTENSION AS A COMPLICATION OF PULMONARY EMBOLISM 32

2.16 TREATMENT OF VTE 32
2.16.1 *Treatment of pulmonary embolism* 33
2.17 PROGNOSIS OF PULMONARY EMBOLISM 34
3 CURRENT DIAGNOSTIC IMAGING FOR PULMONARY EMBOLISM AND GUIDELINES 35
3.1 DIAGNOSTIC IMAGING FOR PULMONARY EMBOLISM 35
3.2 COMPARISON BETWEEN CURRENT GUIDELINES CONSIDERING DIAGNOSTIC IMAGING AND TREATMENT OF PE 36
3.3 ESC/ERS GUIDELINES ON DIAGNOSIS AND MANAGEMENT OF PULMONARY EMBOLISM 38
3.3.1 *Predisposition factors for developing or having VTE* 38
3.3.2 *ESC/ERS on PE clinical diagnostic and D-dimer* 38
3.3.3 *ESC/ERS on high-risk 30-day mortality PE cases* 39
3.3.4 *ESC/ERS guidelines on diagnostic imaging in PE* 39
3.4 PREFERRED DIAGNOSTIC TESTS FOR SUSPECTED PULMONARY EMBOLISM BY THE AMERICAN COLLEGE OF RADIOLOGY (ACR) 43
3.5 COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY (CTPA) 44
3.6 VENTILATION/PERFUSION LUNG SCAN (V/Q SCAN) AND VENTILATION/PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) 45
3.7 MAGNETIC RESONANCE ANGIOGRAPHY (MRA) 46
3.8 RADIOGRAPHIC SIGNS OF PULMONARY EMBOLISM 47
3.9 ECHOCARDIOGRAPHY 48
3.10 STRATIFICATION OF PULMONARY EMBOLISM MORTALITY RISK 48
3.10.1 *Pulmonary Embolism Severity Index (PESI) and simplified (sPESI) scores* 50
3.11 FOLLOW-UP IMAGING AFTER PULMONARY EMBOLISM 50
4 FUTURE PERSPECTIVES OF PULMONARY EMBOLISM DIAGNOSTIC IMAGING 51
4.1 DYNAMIC CHEST RADIOGRAPHY (DCR) 51
4.1.1 *Magnetic resonance direct thrombus imaging (MRDTI) in PE patients* 53
4.2 ARTIFICIAL INTELLIGENCE (AI) IN DIAGNOSING PULMONARY EMBOLISM 54
4.2.1 *Effect of AI in the reduction of turnaround, read, and wait times* 56
4.2.2 *AI pulmonary embolism diagnosis and differentiation of embolus location* 57
4.2.3 *Artificial intelligence in incidental pulmonary embolism detection* 58
4.3 PCCT COMPARED TO EID CT IN DIAGNOSING PULMONARY EMBOLISM 59
4.4 DUAL ENERGY COMPUTED TOMOGRAPHY (DECT) AND ITS USE IN DIAGNOSING PULMONARY EMBOLISM 60
4.4.1 *Computer-aided detection of pulmonary embolism when using DECT* 62
5 FUTURE PERSPECTIVES OF DVT DIAGNOSTIC IMAGING 63

5.1 MAGNETIC RESONANCE DIRECT THROMBUS IMAGING (MRDTI) OF DEEP VEIN THROMBOSIS...63
5.2 AI IN DVT DIAGNOSTIC IMAGING...63
5.2.1 AI-guided DVT imaging acquisition with ultrasound by non-expert operators...63
5.2.2 AI in analysing ultrasonography DVT images...64
5.3 FLUORODEOXYGLUCOSE- POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (FDG-PET/CT) MOLECULAR IMAGING FOR DIAGNOSING DVT IN CANCER PATIENTS...64
6 CLINICAL CASES...65
6.1 CASE 1...65
6.2 CASE 2...67
6.3 CASE 3...68
6.4 CASE 4...69
6.5 CASE 5...70
7 DISCUSSION...71
8 REFERENCES...73

Glossary and Abbreviations

AHA - American Heart Association

AI - Artificial Intelligence

ASH - American Society of Hematology

CHEST - American College of Chest Physicians

CT - Computed Tomography

CTEPH - Chronic Thromboembolic Pulmonary Hypertension

CTPA - CT Pulmonary Angiography

CUS - Compression Ultrasonography

DCR - Dynamic Chest Radiography

DECT- Dual Energy Computed Tomography

DOACs - Direct Oral Anticoagulants

DVT - Deep Vein Thrombosis

ECG - Electrocardiogram

ESC/ERS - European Society of Cardiology / European Respiratory Society

FDG-PET CT - Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography

IVC Filter - Inferior Vena Cava Filter

LMWH - Low Molecular Weight Heparin

MRA - Magnetic Resonance Angiography

MRDTI - Magnetic Resonance Direct Thrombus Imaging

MRI - Magnetic Resonance Imaging

NICE - National Institute for Health and Care Excellence

NOACs - Non-Vitamin K Oral Anticoagulants

NPV - Negative Predictive Value

PCCT- Photon Counting Computed Tomography

PE - Pulmonary Embolism

PERC - Pulmonary Embolism Rule-out Criteria

PERT - Pulmonary Embolism Respiratory Response Team Consortium

PESI - Pulmonary Embolism Severity Index

PET - Positron Emission Tomography

POCUS - Point of Care Compression Ultrasonography

PPV - Positive Predictive Value

PTS - Post-Thrombotic Syndrome

RV/LV Ratio - Right Ventricle to Left Ventricle Ratio

SPECT - Single Photon Emission Computed Tomography

sPESI - Simplified Pulmonary Embolism Severity Index

TTE - Transthoracic Echocardiography

V/Q Scan - Ventilation/Perfusion lung scan (or Scintigraphy)

VKA - Vitamin K Antagonists

VTE - Venous Thromboembolism

WLUS - Whole Leg Ultrasonography

List of tables

Table 1: Wells Score for Deep Vein Thrombosis (DVT) 21
Table 2: Wells Score for PE 24
Table 3: Revised Geneva Score for Pulmonary Embolism Probability 25
Table 4: Original PESI and sPESI Scales 50

List of figures

Figure 1: Case 1: Axial CT with Central and segmental PE, and pulmonary hypertension 66
Figure 2: Case 2: Axial CT with septal bowing, enlarged truncus pulmonalis, and PE 67
Figure 3: Case 3: Axial CT with central and segmental pe, signs of pleural effusion, and pulmonary infarction 68
Figure 4: Case 4: Axial CT of CTPA of COPD patient 69
Figure 5: Case 5: Axial CT with large segmental PE 70

1 Methods and materials

This diploma thesis is a literature review of current guidelines and future perspectives of venous thromboembolism diagnostic imaging. In addition, a few clinical cases are presented where CTPA is performed in patients with pulmonary embolism.

1.1 Literature

The literature used in this diploma thesis stems from scientific articles in PubMed and guidelines from the research field of venous thromboembolism. The terms used in search of such articles include but are not limited to: “Venous thromboembolism”, “deep vein thrombosis”, “pulmonary embolism”, “thrombosis”, “diagnostic imaging”, “artificial intelligence”, “photon counting”, “dual energy”, “computed tomography”, “sonography”, “ultrasound”, “radiology”, “machine learning”, “deep learning”.

1.2 Inclusion criteria

Patients with pulmonary embolism diagnosed in CTPA are included in the case series. The data used in this diploma thesis are images that are obtained at the Division of General Radiology, Department of Radiology, Medical University of Graz in addition to clinical information. Patients included are aged from 18 to 99 years.

1.3 Ethical approval

This case series is approved by the Ethics Committee of the Medical University of Graz.
EK number: 1011/2024.

2 *Introduction*

2.1 Definition and epidemiology of venous thromboembolism

The term venous thromboembolism (VTE) is used to describe the inappropriate formation of blood clots and their dislocation to other body regions (Thromboembolus). Patients with VTE can present with deep vein thrombosis (DVT) and pulmonary embolism (PE) alone or DVT and PE together. Statistically, about two-thirds of patients present only with DVT, and one-third present with PE with or without DVT. (1) (2)
Venous thromboembolism is the most common cause of preventable death in hospitalised patients. Between 59% to 75% of all VTEs are acquired in the hospital, and this occurrence is highly preventable in approximately 18% to 65% of cases. (3) Some groups that are particularly at risk of developing VTE are patients undergoing radio- or chemotherapy, patients in and after pregnancy, patients after operations, surgical debulking, and traumatic injury. (4)
This condition presents, overall, with relatively high morbidity and mortality. VTE plays a particularly big role in patients with cancer, where it affects mortality and morbidity more so than in the general population, because many patients with active malignancy develop VTE in the progression of the malignant disease. (1) (2)
There is a great economic burden of health care costs reaching up to multiple billions of euros yearly in Europe concerning VTE. The incidence of VTE worldwide is estimated to be around 1-2 per 1000 person-years. Death associated with PE is declining, although still reaching up to 20% within 1 year after diagnosis. The incidence of pulmonary embolism is 4 times higher in high-income countries than in low-income countries. However, this data can potentially be attributed to increased screening and diagnostics that are performed in those countries. Incidence varies widely depending on sex, age, and medical conditions that the person has. It is estimated that per year, around 10 million people are afflicted worldwide by venous thromboembolism. (5) (4) The data on VTE epidemiology rely, however, on incomplete data and assumptions, and a population-based

surveillance of VTE is needed for this data to be more accurate. A modelling study that researched 6 countries in Europe, totaling a population of 310.4 million, showed an annual incidence of 296,000 cases of pulmonary embolism and 466,000 cases of deep vein thrombosis. (4)
VTE incidence increases with advanced age. One study in the United States describes the incidence of 391 per 100,000 for those aged 60-69, 727 for ages 70-79, and 1134 for those aged 80+. (6) Both sexes have a similar incidence of VTE overall, with women having slightly higher rates in ages under 55 and above 80 years old, explained by the effects of estrogen in the group under 55 years old, and the higher incidence in ages 80+, explained by the longer life expectancy of women. Men have higher incidences in the ages 55-80. (7)

2.2 Definition and epidemiology of deep vein thrombosis

Deep vein thrombosis (DVT) is defined as the formation of a blood clot in a deep vein. DVT occurs most commonly in the deep veins of the lower leg and thighs, but sometimes it can also occur in the deep veins of the upper limbs, visceral veins, or the vena cava. The term “thrombosis” should be differentiated from the term “thromboembolism”, with the latter describing the dislodgement of a blood clot from the site of development to a more distal location, mostly in the lung arteries, causing pulmonary embolism (PE). DVT ranges from being a mild, isolated, and self-limiting disease to being severe, causing large swelling and pain, and being a risk factor for potentially life-threatening pulmonary embolism. Mortality rates for DVT are relatively high when untreated, with 10.6% at 30 days and 23% at 1 year, but with timely prompt diagnosis and proper treatment, the mortality rate decreases dramatically. The ten-year recurrence rate is thought to be around 25%. (8) (9)

2.3 Definition and epidemiology of pulmonary embolism

Pulmonary embolism (PE) is characterised by occlusion of pulmonary arteries by blood clots, typically through a blood clot that travels from the lower limbs. It is an obstruction in the pulmonary arterial tree that prevents further blood flow distal from it. Pulmonary embolism is a life-threatening condition and the third most common cause of cardiovascular death, with high complication and mortality rates. (10) (11)

Obstruction of the pulmonary arteries with a blood clot, tumor, fat, or air can be considered a pulmonary embolism. Most commonly, in practice, pulmonary embolism refers to a blood clot that gets lodged in the pulmonary arteries, and in most cases, the blood clot originates from the deep veins of the legs. The Virchow triad explains the pathophysiology of venous thrombosis: stasis of blood, endothelial damage, and hypercoagulability are the foundation for understanding the pathophysiology of PE. (12)

Pulmonary embolism incidence in Western countries is considered to be around 60-120 per 100,000 people years. The incidence seems to be increasing from 2010 onward, being 60 per 100,000 person-years in 1998 and 120 per 100,000 person-years in 2016, which could also be attributed to the detection of smaller pulmonary embolisms, which are less life-threatening. The incidence also greatly correlates with increased age, being 50 per 100,000 person-years for people under 50 years old and 350 per 100,000 person-years for those aged over 75. Pulmonary embolism has a 14% in-hospital and 20% 90-day mortality rate. (11)

2.4 Aetiology and risk factors for venous thromboembolism (VTE)

The Aetiology of VTE can be broadly categorized into 3 Groups: blood stasis, hypercoagulability of blood, and endothelial injury.

Blood stasis is usually caused by Immobilisation, prolonged bed rest, heart failure, and post-thrombotic syndrome. Blood hypercoagulability is caused by thrombophilia, paraneoplasia in tumor diseases, cell proliferation as in

polycythemia vera, hormone imbalance in pregnancy and contraception.
Endothelial injury usually develops in trauma and surgery (13)
Common Risk factors include old age, family history of VTE, immobilisation, trauma, surgery, malignancies, puerperium, and exogenous female hormones. Other relatively common causes of VTE that induce thrombus creation are extrinsic venous compression and local infection or intravenous devices. There are also genetic risk factors that promote thrombus creation, and they include deficiencies of natural anticoagulants, antithrombin, protein C, and protein S. Additional biochemical factors that increase the chance of thrombotic events are factor V Leiden, prothrombin G20210A, high levels of VIII, IX, and XI, homocysteine, and fibrinogen. Smoking is thought not to be directly associated with a higher risk of having PE. Cancer patients have the highest correlation and risk of having VTE, so patients who have an unprovoked PE should be screened for occult Cancer or for having a hypercoagulable blood state. (11) (14)

2.5 Pathophysiology of venous thromboembolism

Virchow's triad has been used historically to describe the pathophysiology of venous thromboembolisms, and it still holds true today. It describes the formation of blood clots by the already mentioned 3 factors: hypercoagulability, blood flow stasis, and endothelial dysfunction and injury. (15)

2.5.1 Blood flow stasis

Reduced blood flow and stasis allow the accumulation of prothrombotic factors such as thrombin, which could overcome the anticoagulant factors and result in thrombosis formation. In humans, venous blood clots form most often at valve pockets and sinuses because of their vortical blood flow and low oxygen tension. It is thought that first, small blood clots are formed in these valve pocket sinuses, and then grow over time, lining the inside of the vessel wall, possibly eventually leading to occlusion of the vein. (16)

Venous blood flow stasis and endothelial damage are predispositions to developing VTE, which means that patients who already had pulmonary embolism or deep vein thrombosis are more susceptible to developing VTE again. (17)

2.5.2 Endothelial factors

Under normal circumstances, the endothelial lining is not prothrombotic and expresses factors that inhibit platelet aggregation, such as thrombomodulin, endothelial protein C, tissue factor pathway inhibitor, heparin-like proteoglycans, and others. Also, endothelial cells increase the metabolism of platelet agonist ADP by expressing the ectonucleotidase CD39/NTPDase1, and lastly, they release platelet inhibitors such as nitric oxide and prostacyclin. Endothelial injury leads to the expression of prothrombotic factors such as tissue factor, P selectin, E selectin, and von Willebrand factor that trap leukocytes and platelets, and to the downregulation of anticoagulant factors. (16) Attached leukocytes then become activated and also express tissue factor (TF), which activates the coagulation cascade. (18)

2.5.3 Hypercoagulability

Thrombophilia is a term used to describe the increased tendency of blood to clot. It can be caused by increased presence of procoagulant proteins, a decrease of anticoagulant proteins, and a decrease of fibrinolytic factors. There are genetic factors that affect the state of coagulability, which include deficiencies in anticoagulants like antithrombin, protein C, and protein S, and these are considered to be strong risk factors. Moderate genetic factors would include factor V (FV) Leiden, prothrombin G20210A mutation, fibrinogen C10034T mutation, and non–type O blood. Additionally, increased age, surgery, hormonal contraceptives, obesity, prolonged bed rest, pregnancy, and cancer all increase susceptibility. In normal pregnancy, there is a hormone-induced state of blood hypercoagulability that is thought to be present to protect women from bleeding out during childbirth or miscarriage. In this state, FVII, FVIII, FX, vWF, fibrinogen, and PAI-1 are all increased and stay increased up to 8 weeks after pregnancy. Similarly, various

combinations of increased levels of the mentioned procoagulant agents can be measured in obese individuals, individuals after surgery, and individuals who use hormone replacement. (16)

The blood clot consists of platelets, fibrin, and sometimes red blood cells. Arterial and venous blood clots are different in that arterial clots mostly consist of platelets. They are often associated with endothelial damage and are thought of as “white clots”. Differently, venous blood clots are not often associated with vessel wall damage, are fibrin-rich and contain red blood cells, therefore sometimes called “red blood clots”. The coagulation cascade has 3 activation pathways. The extrinsic pathway with tissue factor (TF) and factor VIIa (FVIIa), the intrinsic with factor XIIa (FXIIa) and XIa (FXIa), and the common pathway with factor Xa (FXa) and thrombin. When pathological conditions are present, the tissue factor is expressed on circulating leukocytes and possibly also on activated endothelial cells, as well as on microvesicles. These sources of intravascular tissue factor could trigger the formation of a venous clot. Extracellular RNA and polyphosphates could activate factor XII, which activates the intrinsic pathway and could lead to the formation of a venous clot. (16)

Antiphospholipid syndrome is a rare condition where the patient has antiphospholipid antibodies, together with recurrent venous or arterial thrombosis, obstetric morbidity, or various other non-thrombotic associated complications. Antiphospholipid syndrome often comes in conjunction with other autoimmune diseases, especially lupus erythematosus. (19)

Heparin-induced thrombocytopenia is a rare complication of heparin therapy. Paradoxically, it is a prothrombotic blood state. It is caused by antibodies targeting complexes of heparin and platelet factor 4. VTE is the most common complication of this condition, but arterial thrombosis can also occur. (20)

2.6 Pathophysiology of pulmonary embolism (PE)

Most commonly, PE occurs when the dislodged blood clot from deep vein thrombosis gets stuck in the pulmonary arteries, but sometimes the obstruction can also be caused by fat, air, or a tumor. Even though pulmonary gas exchange is affected by PE, and it can come to a state of hypoxemia, the most important prognostic factor for the outcome of PE is the response of the right ventricle of the heart to this condition, and generally, the hemodynamic response of the body. The right ventricle becomes dilated and bowed into the left ventricle, which then causes limited left ventricle filling and obstructive shock. The result of vessel occlusion and its associated vasoconstriction, and the increased pulmonary vascular resistance, increases right ventricular afterload and reduces left ventricular preload, resulting in reduced cardiac output. (11) (2)

Pulmonary embolisms consist of red blood cells and fibrin, and they usually originate from the deep veins of the leg or pelvic veins (in 80% of cases), but it is possible for them to originate from the subclavian, axillary, or arm regions rarely (in 6% of cases). (11) Thrombi go through the venous system and get to the pulmonary arteries, where they get stuck. Big thrombi can get stuck at the bifurcation of pulmonary arteries, but it is more common for thrombi to get stuck in smaller, more distal vessels. (17)

There are a lot of potential pathophysiological effects that can result from pulmonary embolism. Increased pulmonary vascular resistance results from obstruction of vessels, neurohumoral agents, or baroreceptors. Limited gas exchange results from increased alveolar dead space from vascular obstruction. Bigger airway resistance happens due to bronchoconstriction. Lastly, decreased lung compliance is caused by lung edema, hemorrhage, and loss of surfactant. (17)

2.7 Clinical diagnosis of DVT and pretest probability score

Clinical features of DVT include calf pain, calf swelling, history of DVT, malignant disease, recent immobilization, recent surgery, obesity, difference in calf circumference bigger than 3cm (measured 10cm below tibial tuberosity), Homan's sign (pain in the calf with dorsiflexion), Payr's sign (pain with pressure application on medial foot sole), tenderness, warmth, erythema, and edema. (21)
The most severe form of DVT with total vein occlusion (and secondary arterial compression) is Phlegmasia Cerulea Dolens. It presents with severe swelling, edema, cyanosis, and absence of pulse. Phlegmasia Alba Dolens is the less severe form with only partial vessel occlusion and less severe symptoms. (22)
The clinical assessment of patients for risk factors, symptoms, and signs of venous thromboembolism is required to estimate the likelihood of having DVT before doing any further tests or treatment. The first step that should be done clinically in case of DVT is to estimate the pretest probability of having DVT, and it is usually done with gestalt or preferably by using standardised scores. (5) For deep vein thrombosis, the most widely used test is the Wells score, which classifies the probability of having deep vein thrombosis as likely or unlikely. It has 9 points where each gives +1 point: cancer, paralysis or recent plaster cast, bed rest longer than 3 days or surgery within 4 weeks, pain on palpation of deep veins, swelling of the entire leg, circumference difference on affected leg bigger than 3 cm (10 cm below tibia tuberosity), pitting oedema, dilated superficial veins and has one -2 points criterion of an alternative diagnosis being just as or more likely. Having less than two points on the Wells score categorises the risk as being low, while having 2 or more points would classify it as intermediate/high risk. This scoring system is the simplified version, where the other original version classifies the risk between low risk (0 points), intermediate (1-2), and high risk (3 or more points). (23) (8)

TABLE 1: WELLS SCORE FOR DEEP VEIN THROMBOSIS (DVT)

Clinical Feature	Points
Active cancer (on treatment, treated in the last 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower limb	1
Recently bedridden for ≥ 3 days or major surgery within the previous 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling ≥ 3 cm larger than asymptomatic leg	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previous documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Clinical probability simplified score: DVT likely: 2 points or more; DVT unlikely: 1 point or less *Clinical probability non-simplified score: low risk:0 points; intermediate: 1-2 points; high risk: 3 or more points*	

Adapted from: Olaf M, Cooney R. Deep Venous Thrombosis. Emerg Med Clin North Am. 2017 Nov; 35(4): 743-770

2.8 Clinical diagnosis of pulmonary embolism and pretest probability score

Pulmonary embolism, relatively often, remains unrecognized before the event of death. Despite the increase of ante mortem diagnosis of PE, less than half of autopsy-detected PEs are diagnosed before the event of death. (24)

Clinical symptoms of pulmonary embolism are very nonspecific, and only 10% of patients who are evaluated for PE are later actually diagnosed with PE, making it hard to clinically diagnose. The clinical assessment should start with clinically classifying the risk of having PE as low, moderate, or high. This translates to about 15% of risk in patients in low, 15-40% in patients in moderate, and over 40% in patients in the high-risk group. (11)

Pulmonary embolism is usually hard to diagnose. The most common symptoms are dyspnea and tachypnea. The chest pain is then often caused by distal emboli, causing pulmonary infarction or alveolar hemorrhage. Other common symptoms include increased heart rate (over 100/min) and other signs of DVT. Specific signs and symptoms that present more often in severe cases are syncope, signs of shock, arterial hypotension, distended jugular veins, and hemoptysis. However, something to be cautious about: 2 prospective studies showed that patients with isolated syncope (without other PE symptoms or syncope explained by other conditions) have a 30-day incidence of PE of 0.6% and 2.2.%. (25)

Electrocardiogram (ECG) changes remain controversial in their ability to diagnose pulmonary embolism. The most common sign is sinus tachycardia, present in 28% of patients with acute PE. Other, more specific PE signs like S1Q3T3, P pulmonale, and right axis deviation are infrequent, with 3.7%, 0.5% and 4.2% occurrence in acute PE patients, respectively, while signs like right bundle branch block, atrial dysrhythmias, and clockwise rotation were also frequent in control groups. One Study by Thomson et al. suggests that signs of right ventricular (RV) strain in patients who have breathlessness are most suggestive of present acute PE. RV strain could be recognized on ECG by T wave inversion in the inferior II, III, and avF and in right precordial leads V1 to V4. (26)

It is important to evaluate the clinical probability of having pulmonary embolism, similarly to DVT. Here, clinicians usually use their Gestalt or clinical pretest scores to evaluate said probability. There are multiple clinical pretest scores that are used to evaluate the clinical probability of having PE and to exclude further testing. (23)

In practice today, the most widely used clinical pretest scores are Wells (27), YEARS (28), PERC (29), and Revised Geneva Score (30), which are used to determine if patients are likely or unlikely to have pulmonary embolism and to help reduce unnecessary further evaluation. These help us with decision making, which next test should be used, for example, D-Dimer, or if this step should be skipped

and proceed straight to diagnostic imaging. However, some studies suggest that even though these scores are helpful, the clinical gestalt does not perform worse than clinical pretest probability scores. It is also suggested that about half of clinicians in emergency departments choose not to use these scores, possibly because of the high pressure of work in emergency departments. It should be noted that the Wells Score already has a subjective criterion of “alternate diagnosis less likely than PE”, and also the YEARS score includes the subjective criterion “PE most likely diagnosis”. (31)
Patients who have a low clinical probability of having PE (under 15%) and fulfill all 8 of the PERC rule characteristics require no further testing. These PERC rule characteristics are: age under 50, heart rate under 100, oxygen saturation more than 94%, no prior trauma surgery, no prior VTE history, no estrogen use, no hemoptysis, and no unilateral leg swelling. Patients who have intermediate clinical probability and a D-dimer level less than 500ng/mL are associated with a post-test probability of having PE of less than 1.85% and PE can be excluded here without the use of diagnostic imaging. The D-Dimer level of 500ng/mL can be further adjusted in patients who are over 50 years old, where the limit is adjusted to be the age of the patient multiplied by 10. This rule can also be applied to patients who have a low clinical risk of having PE. Patients who show a high probability of having PE don’t necessarily have to undergo D-dimer testing because the diagnostic imaging can’t be excluded in that case anyway. (11)

2.8.1 Wells score in patients with suspected pulmonary embolism

Wells score for pulmonary embolism is a clinical pretest probability score that aims to determine the chance of having pulmonary embolism. The criteria for which points are given in Wells score are: 1. Clinical signs and symptoms of having deep vein thrombosis (minimal leg swelling and pain upon palpation of deep veins) – 3 points; 2. No alternative diagnosis- 3 points; 3. Heart rate over 100 – 1.5 points; 4. Immobilisation or surgery in the past 4 weeks- 1.5 points; 5. Previous deep vein thrombosis – 1.5 points; 6. Hemoptysis – 1 point; 7. Malignancy (on treatment or

treated in the last 6 months) 1.0 point (see Table 2). Some clinical symptoms of pulmonary embolism that are common, such as dyspnea, chest pain, and high respiratory rate, had no significance in step-by-step logistic regression analysis. (27) Patients who had less than 2 Points had an overall 3.6% chance of having PE. Patients with 2-6 points had 20.5% and those with >6 points had an overall probability of having PE of 66.7%. These 3 groups were named as having low, moderate, and high probability, respectively. If we add the negative D-Dimer test to these patients, the probability of having PE would go down to 1.5%, 7.6% and 20% in groups, respectively. Using this Score helps in diagnosing otherwise clinically challenging cases of pulmonary embolism. (27)

TABLE 2: WELLS SCORE FOR PE

Wells-Score in PE	**Points**	
	Original	**Simplified**
Clinical signs and symptoms of having deep vein thrombosis	3	1
No more plausible alternative diagnosis	3	1
Previous deep vein thrombosis	1,5	1
Heart rate over 100	1,5	1
Immobilisation or surgery in past 4 weeks	1,5	1
Hemoptysis	1	1
Malignancy	1	
Simplified version: 0–1: PE unlikely; ≥2: PE likely *Original Wells Score:0–1: low probability; 2–6: moderate probability; ≥7: high probability*		

Adapted from: Wells P, Anderson D, Rodger M. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000 Mar; 83(3): 416-20.

2.8.2 Revised Geneva Score for ruling out pulmonary embolism

The revised Geneva score is a pulmonary embolism prediction tool based completely on clinical variables, and, unlike the Wells Score, it does not have subjective parameters such as “likelihood of alternate diagnosis being higher than having PE”. The Revised Geneva Score has 10 Factors. Those include age of 65 and higher giving 1 Point; Previous history of DVT or PE giving 3 points; Surgery with general anesthesia or fracture of lower limbs in past 1 Month giving 2 points; active malignant condition (either active or considered cured in past 1 Year) giving 2 points; Unilateral lower limb pain giving 3 points; Hemoptysis giving 2 points; Heart rate of 75 to 94 beats per minute (BPM) giving 3 points or if higher than 94 giving 5 points; Pain of lower limb deep venous palpation and unilateral edema giving 4 points. Based on the summary of points score of 0-3 is considered low, 4-10 intermediate, and more than 10 a high clinical probability score. The probability of each group (low, intermediate, and high risk groups) of having pulmonary embolism is 8%, 29% and 74 % respectively. (30)

TABLE 3: REVISED GENEVA SCORE FOR PULMONARY EMBOLISM PROBABILITY

Variable	**Points**
Age ≥ 65 years	+1
Previous DVT or PE	+3
Surgery or fracture within the past month	+2
Active malignant disease	+2
Unilateral lower-limb pain	+3
Hemoptysis	+2
Heart rate 75–94 bpm	+3
Heart rate ≥ 95 bpm	+5
Pain on deep vein palpation and unilateral edema	+4

Total Score	**Clinical Probability**	**Estimated Probability of PE**
0–3	Low	~8%
4–10	Intermediate	~29%
≥11	High	~74%

Adapted from: Le Gal G, Righini M, Roy P. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006 Feb; 144(3): 165-71.

2.9 Diagnostic imaging for deep vein thrombosis

The gold standard for diagnosing Deep vein thrombosis is ultrasonography. There are two distinct ways for diagnosing DVT with ultrasonography: point-of-care compression ultrasonography (POCUS) and whole leg ultrasonography (WLUS). In POCUS, the two points are inspected: the common femoral vein at the groin and the popliteal vein in the popliteal fossa, with the inclusion of trifurcation (the most proximal part of the tibial and peroneal veins). In WLUS, the whole segment of veins starting from the femoral vein, going through the popliteal veins, and then the distal veins is inspected. POCUS is simple and quick, and because of that is widely used, whereas WLUS often demands more specialized personnel and more specialized machines. POCUS testing should be performed again after 7 days if symptoms are stable or disappearing, or earlier if symptoms get worse. In cases with low D-dimer or low clinical probability, the DVT can be safely excluded with one negative POCUS. A few randomized controlled studies showed that there is no statistically significant difference between using serial POCUS testing or one-time WLUS, even though there was a significantly higher initial prevalence of DVT in patients examined by WLUS. In both diagnostic approaches, there is one important criterion for diagnosing DVT, and that is the compressibility of the veins. If the vein can be compressed, then the DVT is ruled out, and if not, the DVT is ruled in. (32)
The sensitivity of compression ultrasonography in diagnosing DVT is thought to be around 95% but it can vary depending on the experience and expertise of the physician who is performing compression ultrasonography. For a normal examination with compression ultrasonography of DVT, there are a few minimal points that should be assessed. These include: gray scale images with and without compression of common femoral vein, junction of the common femoral vein with the great saphenous vein, proximal deep femoral vein separately or along with the proximal femoral vein, proximal femoral vein, distal femoral vein, popliteal vein additionally color spectral doppler in long axis should be done on- right common femoral or external iliac vein, left common femoral or external iliac vein, popliteal vein on symptomatic side or on both sides if the examination is bilateral. Lastly,

the compression should be done every 2 centimeters, and especially the pathologic findings should be documented. (8)
A thrombus on ultrasound looks hyperechoic to the blood that flows around it. In comparison between acute and chronic thrombi, the acute ones are hypoechoic, are softer (can be deformed by the probe), the vessels around them are enlarged, and the walls are smooth and thin. The chronic thrombi usually appear hyperechoic, are rigid, the vessels around them are shrunken, and the wall is thick and irregular. The color Doppler comes in use when detecting smaller vessels and can detect complete versus incomplete obstruction. Spectral Doppler can examine phasicity, giving information about more proximal vessel obstruction, for example, in external iliac or femoral veins. (33)
Normal findings on these examinations can exclude DVT in most cases and especially distal DVT, but if the patient was assessed as having a high risk of DVT, ultrasonography should be repeated after 1 week, as mentioned. Venography is also an option in diagnosing DVT, however, the not widespread use, discomfort, and increased complication possibility make it not needed in most cases. However, it does have a lower false positive rate and should be considered in some complicated cases. (8)

2.10 Computed tomography pulmonary angiography

CTPA is a medical imaging procedure where a computed tomography (CT) scan is performed with intravenous contrast material, targeted at pulmonary arteries. The diagnosis of PE is the main goal of the examination. The focus of the CTPA scan is pulmonary embolism, however, it can also diagnose conditions such as musculoskeletal injuries, malignancies, pneumonia, vascular pathologies, cardiac pathologies, and others. The injected contrast material (usually 60-150ml, injected at the pace of 5ml/s) is a high-concentrated iodine bolus, followed by a saline chaser (to reduce beam hardening artefacts and reduce the volume of contrast material needed). There are 3 distinct methods of determining the optimal bolus timing: bolus tracking, empirical (predetermined time amount), and test bolus. In the bolus-tracking method, a region of interest (ROI) is predetermined, and when a predetermined amount of Hounsfield Units (HU) is reached (for example, 100 HU),

the scanning is initiated with a preset delay, allowing for optimal opacification. In the test bolus method, a small bolus of around 10ml contrast material is injected, and the time for opacification is calculated over the ROI, with some seconds being added to account for a larger amount of contrast material for the diagnostic bolus. The bolus-tracking method is usually the preferred choice. When performing the scan, the patients are usually instructed to perform a deep breath hold, or if dyspneic, a relaxed shallow breath hold, in order to reduce motion artifacts. Maximum intensity projection (MIP) is a tool that reconstructs the vessels from the volume of CTPA images to get an angiography-like presentation of vessels, by displaying only voxels of maximum intensity. Peripheral clots would appear here as less enhanced areas compared to neighbouring vessels of the same size. (34) (35)

When diagnosing PE on CTPA images, the thrombus appears as a filling defect that is surrounded by high contrast material within a vessel. By inspection in the longitudinal axis of the vessel, a “railway sign” can be seen where the thrombus appears as a hypodense line next to contrast flowing on either side. A “polo mint” sign can be seen in the cross-section of a vessel, where a hypodense central thrombus is surrounded by a thin layer of contrast material. If the vessel is completely occluded, no contrast material would flow past the thrombus. The thrombus that is very large and spreads over the pulmonary trunk bifurcation is called “saddle embolus”. Pleural effusions sometimes develop when having acute PE and can be seen on CTPA. Pulmonary infarctions can also sometimes develop in acute PE and are wedge-shaped, with the wedge apex pointing to the hilum. Chronic PE shows calcifications, intraluminal webs, thrombus recanalization, mosaic perfusion patterns, and bronchial anomalies. Right ventricular strain is an important finding for risk stratification of PE and is measured with the right ventricle/left ventricle ratio (>1 in the axial plane, and >0.9 in the four-chamber view). Chronic thromboembolic pulmonary hypertension (CTEPH), on CTPA, can show signs such as dilatation of central pulmonary arteries (cutoff is 29mm for men and 27mm for women), eccentric organized thrombi, partial or total occlusions, mosaic perfusion pattern of the lung, right ventricle enlargement, and thickening of the right ventricular wall. (34) (35) (36)

2.11 D-dimer

D-Dimer molecules are created in the process of degradation of cross-linked fibrin during endogenous fibrinolysis. The level of D-dimer is increased when thrombosis is present. D-Dimer creation requires 3 enzymes: plasmin, thrombin, and activated factor XIII. Plasmin digestion of the fibrin clot results in the liberation of degradation products, including D-dimer. The analysis of D-dimer is critical in the modern diagnosis of pulmonary embolism and DVT. (37)

For VTE patients who are in the low-risk group using the Wells score, the D-Dimer testing with a usual level of 500ng/ml has a negative prediction value near 100% and is considered to be safe. Negative predictive value for VTE of D-Dimer level of 500 ng/ml in patients with high pretest probability showed to be 92% in one study. Because of that, it can't be used alone to exclude the VTE without assessment of pretest probability in patients with high clinical probability, and its specificity is too low for it to be used alone in patients with low clinical pretest probability. (38) (39)

A diagnostic strategy is suggested to be considered safe by the International Society on Thrombosis and Hemostasis if it misses under 2% of patients with PE. (40)

The patients who have less than 4 Wells Score and under 500ng/ml D-Dimer make up 30-40% of those suspected with PE, and in cases where it was ruled out with this combination, the 3-month follow-up shows less than 1% failure rate. (38)

However, this strategy is not completely reliable in Patients with cancer because they have a higher chance of getting thrombosis. They show higher DVT presence in conjunction with low pretest probability and negative D-dimer. Diagnostic imaging should be considered directly in this case. (39)

The conventional threshold for PE exclusion is 500ng/ml, but with a new age-adjusted threshold of patients' age x 10ng/ml, the proportion of patients who didn't require anticoagulation without the need for imaging was effectively increased from 28% to 33%. (27)

2.12 Tumor-associated thrombosis

Currently, it is estimated that patients with active cancer have an incidence 7 times higher than the general population, and patients with unprovoked idiopathic VTE are shown to have a 5.2% likelihood of occult malignancy. (1) (41) Patients who have active cancer are considered to have a 20% incidence of VTE, and 2-15% patients with cancer are thought to have clinically evident VTE, depending on the cancer type. Venous thromboembolism is the second most prevalent cause of death in patients with cancer, the progression of the malignant disease being first. (1) (42)

The types of cancer with the highest risk for VTE in patients with cancer are pancreatic, brain, ovarian, and lung cancers. There have been reports of high risk also for lymphomas, myelomas, kidney and bone cancers, with breast and prostate cancer having relatively lower risk for VTE (43). It should be mentioned that novel therapeutics like targeted therapeutics, immune checkpoint inhibitors, as well as chemotherapeutics, are associated with increased risk of VTE (systemic therapy appears to be a risk factor for VTE). (1)

The therapy of choice for cancer-associated thrombosis is low molecular weight heparin and factor Xa inhibitor (Apixaban), where the newer DOACS show at least as good prophylaxis for VTE and do not show any higher risk of bleeding than low molecular weight heparin (LMWH). There seems to be quality of life improvements with Apixaban because it is taken orally, unlike LMWH. (44)

2.13 Recurrent venous thromboembolism

Recurrent venous thromboembolism is the reappearance of either pulmonary embolism or deep vein thrombosis after having a previous venous thromboembolism. Patients who had a provoked venous thromboembolism are at much lower risk of having recurrent VTE than patients who had a first unprovoked venous thromboembolism after discontinuation of anticoagulation therapy.

Provoked VTE is considered to be the one in those individuals with following persistent factors: active cancer (meaning cancer that hasn’t received potential curative therapy, ongoing cancer therapy or evidently not curative therapy); major

transient factors such as major transient surgery (having anesthesia for more than 30 minutes), being confined to bed for more than 3 days “bathroom privilege only” with acute disease, caesarean section; or minor transient factors such as surgery with general anesthesia less than 30 minutes, acute illness in hospital for less than 3 days, hormone therapy, pregnancy, puerperium, confined to bed for less than 3 days with acute disease or reduced mobility associated with leg injury for at least 3 days. Patients who have VTE receive anticoagulation therapy, usually for 3-6 months after having VTE, with the aim of preventing the recurrence of the disease. In patients with first unprovoked VTE who had at least 3 months of anticoagulation therapy, the risk of having recurrent VTE after discontinuation of anticoagulation therapy was 10% in the first year 16% in 2 years, 25% at 5 years, and 36% at 10 years. The case fatality rate of recurrent VTE was 4%. (45)

2.14 Postthrombotic syndrome

Postthrombotic syndrome (PTS) is a form of chronic venous insufficiency that happens after a deep venous thrombosis. PTS is the most common long-term complication after a DVT, and while prevalence varies in the literature, in 20% - 50% cases, the PTS occurs as a complication after having a proximal DVT. (46) Post-thrombotic syndrome can range from being mild to severe, ranging from mild ankle swelling to debilitating venous claudication or leg ulcers. (5)
There is no gold standard for diagnosing PTS. Usually, PTS is diagnosed with clinical signs and symptoms in patients with previous DVT, and diagnosing PTS should be refrained from 3-6 Months after acute DVT. Usual signs and symptoms are pain, swelling, heaviness, itching, cramping, telangiectasia, edema, redness, hyperpigmentation, venous eczema, and skin thickening. The Villalta score is most widely used to assess PTS, and it incorporates the said symptoms and signs as well as the presence of ulcers on the affected DVT leg. (47) Therapy of PTS is usually the use of medical compression stockings and pharmacomechanical catheter-directed thrombolysis, but the effects are questioned in randomized controlled studies where evidence of its benefits is lacking. Anticoagulation therapy for DVT appears to be the only unquestionably effective therapy in the prevention of PTS occurrence. (46)

2.15 Chronic pulmonary hypertension as a complication of pulmonary embolism

A more severe form of post-PE syndrome is chronic pulmonary hypertension. About 3% of patients suffer this long-term complication after having pulmonary embolism, and nearly half of them experience high exercise and functional limitation 1 year after the diagnosis of acute PE. (5)
Chronic pulmonary hypertension can lead to right heart failure and death. Pulmonary hypertension is usually confirmed with right heart catheterisation, which is also used to determine the treatment. The therapy of choice is usually pulmonary endarterectomy, and in cases where not possible, targeted PH medication therapy or balloon pulmonary angioplasty in centers with the required expertise. (48)

2.16 Treatment of VTE

Anticoagulation Treatment for DVT and PE includes anticoagulation medications such as direct oral anticoagulants (DOAC) with Dabigatran, Rivaroxaban, Apixaban, or Edoxaban, low molecular weight heparin (LMWH), or in some rare cases with Vitamin K antagonists (VKA). VKAs seem to be associated with the highest major bleeding risk out of the 3 said anticoagulation options, where DOACs and LMWH seem to have comparable risk of major bleeding, but are generally considered to be safer than VKAs. In newer guidelines, the tendency is to use DOAC over VKA in most cases, as they are at least as safe to use as VKA when it comes to major bleeding and at least as potent in preventing recurrent VTE. In patients with cancer and more severe symptoms, guidelines suggest treating the patients with LMWH over DOAC and VKA, however, some studies show that Apixaban is just as safe as LMWH and isn’t associated with an increase in clinically significant major bleeding events. (49)
For supportive therapy and potentially prevention of post-thrombotic syndrome (PTS), the use of compression stockings is commonly used however, studies don’t show data to support the benefits of this type of therapy for VTE. One other

therapy option for PE prevention in patients with VTE is an inferior vena cava filter, which may reduce early mortality in patients with VTE, but its use is not supported in guidelines. The use of VKA has been highly diminished with the use of DOACs, which showed better results in most patients. However, VKAs still have a place in use with patients who have antiphospholipid syndrome (especially a triple-positive one), mechanical prosthetic heart valves, rheumatic mitral stenosis, patients with severe renal failure, and extremely obese patients. VKAs are also less expensive than DOACs. DOACs offer greater ease of use, per os, where LMWH is given subcutaneously and VKAs require constant monitoring of INR (2-3) and individual adjustment of dose. In pregnancy, LMWH is used over DOACs because they do not cross the placenta, unlike DOACs. Usual anticoagulation therapy lasts 3 to 6 months after the thromboembolic event. If the VTE was provoked, the 3 months of anticoagulation are preferred, and then the anticoagulation therapy is discontinued. In individuals who have unprovoked VTE or other persistent risk factors such as cancer, a longer time of use of anticoagulation therapy should be considered. Similarly, in individuals who have a higher risk of bleeding out, the shorter therapy time should be preferred (3 months) because all anticoagulants increase the chance of major bleeding. (50) (49) (51)

2.16.1 Treatment of pulmonary embolism

In the treatment of VTE in hemodynamically stable patients, the standard therapy up until recently was a start with low molecular weight heparin (LMWH) and follow-up with a vitamin K antagonist such as Warfarin. However, the direct oral anticoagulants like Apixaban, Rivaroxaban, Edoxaban, and Dabigatran have shown to be non-inferior to standard therapy in treating VTE. DOACs have shown a reduction in risk of major bleeding, with a 0.62 relative risk compared to standard therapy. (52) Having these results and with their ease of use, DOACs have largely overtaken VKAs in the therapy of patients with PE and are usually the overall preferred choice in outpatient management of PE. Thrombolysis, which includes thrombolytic systemic therapy and catheter-based thrombus removal, is reserved for patients with acute high-risk PE, hypotension (systolic blood pressure

90<mmHg), hemodynamic instability, and present clinical symptoms. It is associated with a 1.6 reduction in mortality, from 3.9% to 2.3%. (11) (50) (49)
In patients who have a high or intermediate clinical pretest assessment, the initial anticoagulation should already be started while waiting for diagnostic tests. Besides the anticoagulation with DOACs, heparin, or VKA in some cases, rescue thrombolytic therapy, surgical embolectomy, or percutaneous catheter-directed treatment can be considered in patients with hemodynamic deterioration on anticoagulant therapy. Moreover, initial supportive therapy needs to be given. Oxygen therapy is needed, preferably non-invasive, if the oxygen levels are under 90% SaO_2. Vasopression with norepinephrine or dobutamine in hemodynamically unstable patients are beneficial. Volume should be loaded carefully. In extreme cases, the Veno-arterial extracorporeal membrane oxygenation/extracorporeal life support can come in use. (36)

2.17 Prognosis of pulmonary embolism

In patients with PE, there seems to be a high correlation between their clinical outcome and their echocardiographic findings of right ventricular (RV) dysfunction. In case of suspected or diagnosed right ventricular dysfunction, further evaluation of hemodynamic stability should follow. A study performed by Grifoni et al. from 2000 suggests that patients who are hemodynamically stable and have RV dysfunction are statistically much higher at risk than patients without RV dysfunction. However, the biggest prognostic factor is still hemodynamic stability. (53)
Massive pulmonary embolism or high-risk PE is classified by the presence of shock from right ventricular failure or hypotension, systolic blood pressure (SBP) under 90 mm Hg, a drop in SBP over 40 mm Hg over 15 minutes from baseline, or hypotension requiring vasopressor support. This group of patients has high mortality, especially for the first 2 hours and up to 3 days after presentation. On the other hand, patients who do not have RV dysfunction and are hemodynamically stable are classified as having low-risk PE. However, patients who have an increased risk of decompensation in this low-risk PE group should be filtered and observed further. There are validated risk stratification tools for this

stratification, such as the Pulmonary Embolism Severity Index (PESI) and a simplified version of it (sPESI) (see Table 4). (54)
PESI score takes into consideration 11 patient-related factors: age, male sex, cancer, heart failure, chronic lung disease, pulse >= 110/min, SBP< 100mm Hg, respiratory rate >= 30/min, temperature< 36 degrees Celsius, altered mental status, and oxygen saturation < 90mm Hg. Mortality for PESI ranged between 1.1% to 24.5% between PESI I and PESI V. (55)

3 *Current diagnostic imaging for pulmonary embolism and guidelines*

3.1 Diagnostic imaging for pulmonary embolism

CT Pulmonary angiography (CTPA) and ventilation/perfusion (V/Q) scan were traditionally the most often used diagnostic imaging methods for diagnosing pulmonary embolism. CT pulmonary angiography has largely replaced ventilation/perfusion scanning in clinical practice over the years when using diagnostic imaging for pulmonary embolism. In the year 2004, the usage rates of CTPA and V/Q scans were approximately the same. However, going forward, the use rate of CT pulmonary angiography overtook the usage rate of V/Q in a large proportion. The biggest increase in CTPA use was in the first years, meaning from 2004 to 2010. Since 2010 and onwards, a less steep percentual increase of CTPA use was observed, however, still increasing. The use rate of V/Q scans decreased going forward from 2004, but the total number of diagnostic imaging, CTPA and V/Q scans combined, for pulmonary embolisms increased by a big margin in total. (56).
One big study performed by Wang et al. concludes that from 2004 to 2016 the use of CTPA increased by 450% and the use of V/Q scans decreased by 47% in this time period. This raises concerns of potential risks and problems, such as increased unnecessary medical costs by overusing CTPA, increased ionizing radiation in patients, overdiagnosing, and incidental findings, which could potentially lead to unnecessary or even harmful procedures. There have been

tools and scores to prevent the overusage of CTPA, such as the PERC score and YEARS criteria, but the use of CTPA in diagnosing pulmonary embolism is still on the increase (56).

Patients who have a high enough Wells score or Geneva Score, or those who have a D-dimer above the age-adjusted limit, should receive imaging for PE. Both CTPA and planar ventilation perfusion lung scan (V/Q lung scan) are very validated imaging tests for diagnosing pulmonary embolism. (40) (12) (36) Both should be used in appropriate situations in conjunction with clinical probability scores and D-dimer tests to more accurately interpret results. At three months after CTPA excluded PE, the incidence of venous thromboembolism is 1.2% and the negative predictive value of 98.8% where a ventilation-perfusion lung scan does not perform worse. Also, patients who have VTE excluded with compression sonography, D-dimer, ventilation-perfusion lung scan, and clinical probability scores had a three-month incidence of VTE at 0.1% with a negative predictive value of 99.5%. (57) One RCT by Anderson et al. showed that CTPA, in comparison to V/Q lung scan, detected 5% more PEs, but the incidence of VTE at three months post diagnostic imaging was not higher in patients who received V/Q lung scan. (49)

3.2 Comparison between current guidelines considering diagnostic imaging and treatment of PE

When comparing English language guidelines for diagnosing and treatment of PE one review by Zuin et al. considers the following guideline societies: European Society of Cardiology and European Respiratory Society (ESC/ERS) (36), Pulmonary Embolism Respiratory Response Team Consortium (PERT) (10), the American College of Chest Physicians (CHEST) (58), American Heart Association (AHA) (59), American Society of Hematology (ASH) (60), and the National Institute for Health and Care Excellence (NICE) (61). (62)

Most current guidelines prefer the stepwise approach when diagnosing PE, starting with validated pretest probability scores, such as the Wells or Geneva score, with guidelines sometimes having a different preference for such diagnostic tools. All guidelines recommend D-Dimer testing to exclude acute PE when pretest

probability is low or intermediate. ESC/ERS and PERT suggest using age-adjusted or probability-adjusted (YEARS criteria <1 means 1000 μg/L) D-dimer cutoff ranges, where NICE and ASH recommend only age-adjusted D-dimer cutoffs in patients aged more than 50 years old. ESC/ERS considers PERC rule-out criteria for CT imaging in pulmonary suspicion in low pretest probability patients to be unsafe and does not recommend it, whereas ASH, NICE, and PERT suggest that PERC can be used. ESC/ERS, NICE, and PERT recommend that CTPA is the first diagnostic imaging of choice when indicated by suspicion of PE, where ASH suggests that V/Q scanning could be used as first-line diagnostic imaging in centers where the required expertise is present and the V/Q scan can be performed in a timely manner, to reduce the radiation exposure. When this is not the case, ASH recommends the use of CTPA. In case of contraindication or inability to perform CTPA, ESC/ERS and PERT recommend the use of V/Q scanning, transthoracic echocardiography (TTE), and pulmonary angiography. The use of lower extremities ultrasonography, when other imaging techniques are not available, is supported by ESC/ERS, and other societies have not expressed an opinion on this approach. Societies didn’t express their views on imaging methods priority when it comes to cancer patients. When considering pregnancy, ESC/ERS suggests the primary use of X-ray scan and, in case of abnormalities, the use of low-dose radiation protocol CTPA, because of a higher likelihood of the V/Q scan not being accurate. ESC/ERS also recommends of additional use of YEARS algorithms to limit unnecessary CTPAs, because in pregnancy, D-dimer cutoffs are usually elevated in pregnancy. ASH considers the V/Q scan here to be the primary diagnostic option. All guidelines suggest that a combination of negative D-dimer and low or moderate pretest probability score can safely exclude pulmonary embolism. A high pretest probability score or positive D-dimer should be followed up with diagnostic imaging. Imaging should be done in consideration of which procedures are readily available at a given time and center, and also based on whether the required expertise is available at the given institution, with CT being readily available at most centers and V/Q scanning expertise diminishing over time. (62)

3.3 ESC/ERS guidelines on diagnosis and management of pulmonary embolism

The ESC/ERS guidelines of 2019 for pulmonary embolism diagnosis cover many different aspects of the disease, like its predispositions, epidemiology, diagnostic process, treatment, and more. As of today, only 5% of CTPA examinations show an actually positive result, which is a lot less than it was in the past, for example, in 1980 the reported number of positive scans was 50%. (36)

3.3.1 Predisposition factors for developing or having VTE

ESC/ERS states strong, moderate, and weak predisposing risk factors for VTE.
Strong factors: Fracture of lower limbs, hip or knee replacement, atrial fibrillation/flutter or hospitalization for heart failure in the last 3 months, myocardial infarction in the last 3 months, major trauma, certain types of cancer, previous history of VTE, and spinal cord injury.
Moderate risk factors: Arthroscopy knee surgery, autoimmune diseases, blood transfusions, intravenous catheters, chemotherapy, congestive heart failure or respiratory heart failure, hormone replacement therapy, postpartum period, infections, inflammatory bowel disease, paralytic stroke, superficial vein thrombosis or thrombophilia.
Weak risk factors: bed rest for over 3 days, diabetes mellitus, varicose veins, obesity, pregnancy, laparoscopic surgery, increased age, arterial hypertension, and prolonged inactivity. (36) (63)

3.3.2 ESC/ERS on PE clinical diagnostic and D-dimer

ESC/ERS suggests the following signs and symptoms that can potentially be more often present in an event of PE: syncope and presyncope (even when explained by an alternate diagnosis), chest pain, dyspnea, and hemoptysis. Hemodynamic instability is rarer at clinical presentation as it is often a complication of PE that develops over an extended period of time. The use of clinically validated pretest

probability scores like the Geneva and Wells scores and their simplified versions can help in clinical practice, however, the clinical gestalt proved to be just as good as these scores. Age-adjusted D-dimer testing is recommended. Pulmonary Embolism Rule-out Criteria (PERC) are suggested to be used to reduce the number of unnecessary diagnostic imaging performed, their complications, and the high costs, however, ESC/ERS suggests that there is a lack of evidence supporting the safe use of this tool. (36) (27) (30)

3.3.3 ESC/ERS on high-risk 30-day mortality PE cases

ESC/ERS defines high-risk 30-day mortality in patients who have hemodynamic instability. This means that they either have 1) cardiac arrest and the need of cardiopulmonary resuscitation, 2) obstructive shock, meaning systolic blood pressure of under 90 mmHg or require vasopressors support and 3) having persistent (over 15 minutes) systolic blood pressure under 90mmHg or the fall of systolic blood pressure by 40 mmHg from baseline and is not caused by arrythmia, hypovolemia or sepsis. (36)

3.3.4 ESC/ERS guidelines on diagnostic imaging in PE

3.3.4.1 Computed tomography pulmonary angiography (CTPA) by ESC/ERS guidelines

CTPA is the first choice diagnostic imaging when it comes to diagnosing PE as it is widely spread, fast, and can detect pulmonary embolism down to the subsegmental level. The PIOPED II study, which is a prospective study, found that CTPA has 83% sensitivity and 96% specificity. Pretest probability mattered here in a major way, where CTPA seemed to have 96% and 89% negative predictive value in groups with low and intermediate risk respectively, and the high-risk group showed 60% negative predictive value. This could also be seen in the positive prediction value (PPV), with the high and intermediate group showing 96% and 92% predictive value respectively, but the low pretest probability group showed a

PPV of 58%. ESC/ERS notes that even though chronic thromboembolic pulmonary hypertension is a complication of PE, it shouldn't be overlooked when diagnosing acute PE. (64) (36)
On CTPA, the stratification of 30-day mortality risk can be further assessed. In either the four-chamber view or the transverse view, the right ventricle diameter and the right ventricle to left ventricle ratio (RV/LV ratio) should be measured. ESC/ERS suggests that an RV/LV ratio bigger and equal to 1 suggests increased overall early mortality by a 2.5 odds ratio and a 5 times increased PE-related mortality odds ratio. Other parameters that can be looked at in CTPA are the RL/VL volume ratio (cut-off >1.2), RA/LA volume ratio (cut-off >1.2), and if inferior vena cava reflux is present, having 6.5, 2.1, and 2.2 odds ratios for early mortality, respectively. (36)

3.3.4.2 Planar ventilation/perfusion scan (V/Q scan) by ESC/ERS guidelines

In planar V/Q scans, the perfusion test is done, where multiple different tracers can be used. These include substances like xenon 133 gas, krypton 81 gas, technetium 99m labeled aerosols, or technetium 99m labeled carbon microplates called technegas. A ventilation scan is also done because it allows for the test to have increased specificity. In the case of present acute pulmonary embolism, the ventilation would be normal in a hypoperfused lung segment. ESC/ERS suggests that sometimes, when having a normal X-ray done prior, only the perfusion scan needs to be performed, where having any perfusion defect would be considered pathological. New single photon emission computed tomography (SPECT) V/Q scan (with or without CT) shows better results than planar V/Q scan, however, large prospective studies are needed to support this claim. V/Q scan is also a well-established PE diagnostic imaging, however, compared to CTPA, it is less often performed. Its strengths are that it has lower radiation exposure burden (mSv), spares on the use of contrast medium, and because of this, it is used in younger women (where radiation to breast tissue could be problematic), pregnant women, patients who have severe renal failure, and patients with a history of contrast medium induced anaphylaxis. V/Q scanning has the weakness in that a relatively

high amount of tests that are performed are non-diagnostic. Furthermore, the absence of alternative diagnosis when PE is excluded, not being readily available, and the results being reported as likelihood ratios (Excluded PE, low, intermediate, and high probability scan, and non-diagnostic scan) are also some of its shortcomings. (36)

3.3.4.3 Pulmonary angiography ESC/ERS guidelines

Pulmonary angiography (an invasive procedure where a catheter is inserted in pulmonary arteries, with entry usually through the internal jugular vein), not to be confused with computed tomography pulmonary angiography, was the historical gold standard for diagnosing PE for decades. The thrombus would be recognized with a filling defect or an amputation of a pulmonary artery branch. However, with CTPA having similar accuracy to it, it is not performed as often in recent past. It is invasive and has shown a 0.5% mortality rate, while having 1% major and 5% minor complications. Its effective radiation dose is also very high, with 10-20 mSv. Overall, these shortcomings usually outweigh the benefits. (36) (65)

3.3.4.4 Magnetic resonance angiography (MRA) by ESC/ERS guidelines

ESC/ERS suggests that MRA could be a promising diagnostic test for PE, however, it has shown a large proportion of inconclusive scans and is not readily available in an emergency setting. There are studies still being done to see if MRA can safely exclude PE and whether it can do so in combination with the absence of proximal deep vein thrombosis on compression ultrasonography. (36)

3.3.4.5 Echocardiography by ESC/ERS guidelines

Echocardiography can be used in patients with suspected PE to determine if there is right ventricular (RV) pressure overload and dysfunction. Transthoracic echocardiography (TTE) negative predictive value is too low (40-50%) for it to be

able to exclude PE because RV overload or dysfunction can be found, even if PE is not present, in other cardiac or respiratory diseases. ESC/ERS specify signs on echocardiography suggestive of PE: enlarged right ventricle on long axis view; in four chamber view- RV/LV basal ratio of > 1.0 and McConell sign (RV free wall hypokinesis); flattened intraventricle septum in short axis; distented vena cava inferior in subcostal view; pulmonary ejection < 60 ms and midsystolic notch with mildly elevated < 60 mmHg peak systolic gradient on tricuspid valve; right heart mobile thrombus; decreased tricuspid annular plane systolic excursion (TAPSE) lower than 16 mm and decreased peak systolic velocity of tricuspid annulus of <9.5 cm/s. (36)
Echocardiography is useful in differential diagnosis in patients with dyspnea. It can relatively safely exclude the high-risk PE when signs of RV strain are absent. Differential diagnoses of hemodynamically unstable patients that could cause shock include conditions such as aortic dissection, pericardial tamponade, acute valve dysfunction, LV dysfunction, or hypovolemia. Patients who have a high clinical probability and show to be hemodynamically unstable on echocardiography should receive emergency reperfusion treatment for PE if emergency CTPA is not available and there is no other clear cause of RV pressure overload. (36)

3.3.4.6 Compression ultrasonography (CUS) by ESC/ERS guidelines

Because thrombi that cause PE originate from DVT of the lower limbs most of the time, DVT is present in 70% of cases of PE. When PE is present, a four-point compression ultrasonography (CUS) can be performed on both sides in the groin and popliteal fossa. ESC/ERS suggests that the only reliable sign of thrombus presence is incomplete compressibility of the vessel and that flow measurements are not reliable. Positive proximal CUS has a positive predictive value of 96%, and can detect a higher percentage of thrombosis in patients who are symptomatic. This can be combined in an emergency setting with echocardiography and electrocardiogram (signs of RV dysfunction) for better diagnostic performance. DVT found in CUS warrants the use of anticoagulation treatment with no further testing. One study suggests that patients with normal venous ultrasound and

absence of RV dysfunction signs on electrocardiogram could safely exclude DVT in 96% of cases. (36)

3.3.4.7 Chronic Thromboembolic Pulmonary Hypertension (CTEPH) signs on CTPA by ESC/ERS guidelines

ESC/ERS elaborates further on how to diagnose a pre-existing CTEPH on CTPA:
Direct vascular signs: eccentric wall adherent filling defects which could calcify and are different than central filling defects seen in acute PE, abrupt tapering and truncation, complete occlusion and pouch defects, linear intraluminal filling defects with intravascular webs and bands, presence of stenosis and dilatation distal to it, and intima irregularities and vascular tortuosity.
Indirect vascular signs: Right ventricular hypertrophy and dilatation, pericardial effusion, dilatation of the pulmonary artery with a cutoff of 29mm for men and 27mm for women, with the possibility of its calcification, and systemic collateral arterial supply.
Parenchymal changes: Mosaic attenuation of the lung parenchyma, which then results in geographical variation in given perfusion. (36)

3.4 Preferred diagnostic tests for suspected pulmonary embolism by the American College of Radiology (ACR)

The American College of Radiology (ACR) suggests the following rules when deciding which diagnostic test to use in PE diagnosis:
Chest radiography is not included in this ruleset because it is usually done before advanced imaging is performed. Chest radiography is useful in exploring into differential diagnosis of dyspnea, usually: pneumothorax, pneumonia, or other conditions. X-ray can also be used as an aid in the interpretation of the (V/Q) scan to exclude other diseases that also cause perfusion defects, such as atelectasis. ACR discloses that for the diagnosis of PE alone, CT with intravenous contrast material should always be performed in the form of CT pulmonary angiography

(CTPA). ACR gives 4 scenarios when suspecting PE and suggests which imaging should be performed in which cases. These 4 scenarios are as follows: 1. Suspected pulmonary embolism where pretest probability is low or intermediate and D-dimer is negative; 2. Suspected PE where pretest probability is low or intermediate and D-dimer is positive; 3. Suspected PE and high pretest probability; 4. Pregnant patients with suspected PE. When there is a low or intermediate pretest probability of having PE and a negative D-dimer is present, ACR suggests that no advanced imaging is done and that PE can be safely excluded as a diagnosis. If pretest probability is low or intermediate with a positive D-dimer, ACR suggests CT pulmonary angiography as the first-line diagnostic imaging tool. In this variant V/Q lung scan is also considered to be appropriate. MRA is considered to maybe be appropriate, and the CT triple rule out (that is used to rule out pulmonary embolism, coronary artery disease, and aortic dissection) is considered to be maybe appropriate to a lesser extent. In variant 3, where there is high pretest probability and positive D-dimer, CTPA is a first-line diagnostic technique, V/Q is usually appropriate, MRA may be appropriate, transthoracic echocardiography (TTE) may be appropriate, and ultrasound duplex doppler of lower extremities might be appropriate to a lesser extent. In variant 4, where PE is suspected in pregnant patients, the methods with lower radiation doses are more suitable. In some cases, if the perfusion scan is normal, the ventilation scan can be left out. CTPA and lower extremity ultrasound duplex Doppler are also recommended in this case. (66)

3.5 Computed tomography pulmonary angiography (CTPA)

The CT pulmonary angiography (CTPA) is the gold standard for diagnosing PE and by far the most commonly used method for diagnosing PE, as stated before. Inadequate scans with CT pulmonary angiography are few, and as a benefit, it can provide an alternative diagnosis if one is present. (23) (67) The CTPA showed relatively high sensitivity (83%) and specificity (96%) for diagnosing PE, where sensitivity can be affected by motion artifacts, reader accuracy, and contrast injection timing. CTPA is not only useful for diagnosing PE but also for assessing

the prognosis and risk stratification. It can show the right ventricle/left ventricle ratio, septum position, right ventricular response to acute PE, and show real-time response to treatment. (12) (36)
It has the benefit over most of the other diagnostic imaging methods in that it can be used in an acute setting, even in patients who are hemodynamically unstable. The clot in submassive or massive pulmonary embolism shows at CT angiography as a central non-enchancing clot in the pulmonary artery system. Emboli can get clogged in central (lobar), segmental, or subsegmental pulmonary arteries, and therefore, PE is classified as central, segmental, or subsegmental. If it is caught between two pulmonary branches, it can be called a “saddle embolus”, or it may be a solitary endoluminal filling defect. Often, in obstruction of either the left or right pulmonary artery, or partial occlusion of both, it leads to right heart strain. (56) (68)

3.6 Ventilation/Perfusion lung scan (V/Q scan) and ventilation/perfusion single photon emission computed tomography (SPECT)

Nuclear medicine V/Q scans used to be as common as CT pulmonary angiography for diagnosing PE historically, but over the years, the usage of V/Q scans has been reduced, and it has been largely replaced by CTPA. The patients with massive or submassive pulmonary embolism usually show very limited lung perfusion, but they don’t have decreased lung ventilation. Single photon emission CT (SPECT) is a new nuclear medicine diagnostic method, and it is replacing the planar V/Q scan. It shows higher sensitivity and specificity, but is yet to be massively adopted in diagnosis of PE. SPECT V/Q scan allows the presentation of lung perfusion and ventilation, unlike the dual energy CT (DECT), in that aspect, which only depicts the lung perfusion. In retrospective studies, V/Q SPECT scan shows higher sensitivity and specificity when diagnosing PE than planar V/Q scan (97% and 91% for SPECT V/Q and 76% and 85% for planar V/Q scan, respectively). Even though V/Q SPECT alone is a lower dose of radiation than CT usually, the optimal imaging strategy is still to be discussed. Some studies show

high negative predictive value when diagnosing PE with V/Q scanning. (69) (70) Among the weaknesses of V/Q scan is that there is a high amount of non-diagnostic imaging, and when a V/Q scan is performed, it is usually hard to provide an alternative diagnosis if PE is not present. This problem of its inability to provide an alternate diagnosis has been compensated partially with SPECT V/Q scan, which could also detect conditions such as radiation therapy-caused changes in the lung, emphysema, neoplasms, and mediastinal adenopathy. (66) Left to right heart shunting can also be detected on V/Q scans by looking at the non-lung uptake and then dividing it by the dose of technetium-99m macroaggregated serum albumin given. It was proposed that the radiation dose reduction could be beneficial to pregnant women and younger people in general, however, there are more and more emerging strategies that reduce the radiation dose of CT. Moreover, sometimes non-contrast CT is added to V/Q SPECT, in which case there is no reduction of overall radiation dose. Between V/Q SPECT with or without non-enhanced CT or only perfusion SPECT (Q SPECT) with or without non-enhanced CT, it is not yet clear which method is most beneficial and efficient, considering all the benefits and drawbacks. Large prospective studies are needed to assess the effectiveness and benefit of the V/Q SPECT scan. (69) (70)

3.7 Magnetic resonance angiography (MRA)

Magnetic resonance (MR) has proven to be a successful imaging technique in many parts of the body, however, it remains challenging and not practical to perform MR angiography for diagnosing PE. One reason is due to the long time period needed to acquire MR images and the inability for patients with dyspnea to hold breath for a longer period of time. Magnetic resonance angiography is not widely available, has higher costs, and due to longer acquisition times, is not well suited for cases of acute pulmonary embolisms. MRA imaging does not require any use of ionizing radiation, which is beneficial. The PIOPED III study that was performed from 2006 to 2008, showed that MRA has a sensitivity of 78% among participants with adequate MRA scans, but due to a quarter of patients not getting adequate MRA scans, when looking at the whole participant group, the MRA had a sensitivity of 57% when diagnosing PE. Largely, the reasons for inadequate MRA

scans were motion artifacts and poor vascular opacification. Other studies, like the IRM-EP study, showed similar results with 28-30% of MR scans being inconclusive, 69% sensitivity when including the not interpretable MR scans, and 79-85% when looking at only adequate MRA scans. Gadolinium-based contrast material is usually used when performing MRA, however, it is not advised to be used in pregnant women because of the possible long-term side effects on the fetus. Instead, potentially ferumoxytol could be used, which is considered safe in pregnancy, however, it is not a standard contrast material suggested for use in diagnosing pulmonary embolisms. One more issue with MRA scans in patients with hemodynamic instability is that in the case where resuscitation is needed, the patient and the MR imaging table would need to be both removed from the scan room. (70) (69) (71)

Some retrospective studies show higher accuracy, sensitivity, specificity, negative predictive value, and positive predictive value, and propose that MRA could be more suited for diagnosing PE than it is suggested in PIOPED III and IRM-EP studies, when performed technically adequately. (72)

3.8 Radiographic signs of pulmonary embolism

The differentiation of PE is challenging and usually not possible with radiographic imaging. However, in massive pulmonary embolisms, there can be some signs, like Westmark and Palla signs, that can suggest the presence of massive PE, where some aggressive treatments like systemic thrombolysis might prove beneficial. Westmark sign describes the lack of vascularity in the affected part of the lung (oligemia), and Palla sign describes the enlargement of the right descending pulmonary artery mimicking a sausage-like appearance on radiograph. If these signs are present, then acute further clarification via CT should be performed to clarify the presence of PE. Chest radiography also contributes to excluding other conditions that are common causes of acute chest pain, tachycardia, and respiratory distress. These conditions in emergency cases are often pneumonia, pneumothorax, pericardial effusion, or heart failure. Radiography is also useful as an aid for the interpretation of V/Q scans, excluding

some other causes of perfusion defects. The main benefits of X-ray are in that it is cheap to perform, quick, and has low radiation exposure. (69) (73)

3.9 Echocardiography

Performing transthoracic echocardiography (TTE) can be done quickly in an emergency setting, and it can provide some useful information when stratifying PE mortality risk. When having pressure overload caused by pulmonary embolism right ventricle shows increased strain and decreased contraction at TTE. The right free wall might begin to balloon outward, and a McConnell sign could present itself, meaning free wall hypokinesis in relation to the apex. Other signs would be tricuspid regurgitation, septal ventricular bowing at systole, and volume overload with septal ventricular bowing at inspiration. Secondary signs of central venous hypertension can be seen in echocardiography. These include atrial septal bowing, right atrial enlargement, atrial septal aneurysm, and little or no respiratory variation in the vena cava inferior diameter. Transosophageal echocardiography (TEE) provides better imaging options, however, it is more complicated to perform. TEE can also show the presence of the embolic clot directly in the right pulmonary artery because it can visualize pulmonary arteries much better than TTE. (69)

3.10 Stratification of pulmonary embolism mortality risk

Some major guidelines committees, like the European Society of Cardiology, American Heart Association, and American College of Chest Physicians, all use similar tools for predicting the rate of mortality of pulmonary embolisms. The American Heart Association differentiates massive, submassive, and low-risk pulmonary embolisms when it comes to mortality risk stratification. These groups show 25%-65%, 3% and less than 1% mortality, respectively. (69) A massive PE is differentiated by a patient having sustained hypotension of >90 mmHg for over 15 minutes or requiring vasopressor support. The submassive PE is defined as having right heart strain, dysfunction, dilatation, or ischemia. Here, the right heart

dysfunction and strain can be diagnosed with echocardiography, and the right ventricle (RV)/left ventricle(LV) ratio can also be assessed using echocardiography or CT. The RV/LV ratio should be reported when diagnosing PE on CT images because it shows a significant hemodynamic factor. The diameter of RV and LV is measured from the free to septal endocardium, meaning the myocardium is excluded, and then the maximum diameter of RV measured in the axial plane is divided by the maximal LV diameter. Having increased brain natriuretic peptide or troponin would also classify the PE as being submassive. Some electrocardiography changes, like right bundle branch block, anteroseptal ST-changes, or anteroseptal T wave inversion, can classify the patient as potentially having submassive PE. The low-risk patient group would show no signs of hypotension, right heart dysfunction, or dilatation. One additional important criterion of stratification of pulmonary embolism prognosis is the localization of the thrombus. The thrombi that are localized centrally (in the left or right main pulmonary artery) show higher mortality than those that are located more peripherally. However, it seems that the clot burden (for example, Qanadli score) does not correlate to a great extent with 30-day mortality in patients with PE. (69) Usage of validated prognostic stratification scores, like the Pulmonary Embolism Severity Index (PESI) is endorsed by guidelines from ESC/ERS, PERT, and ASH. This score is composed of 11 prognostic factors and classifies the patients then as having low, moderate, or high mortality risk and divides them into 5 classes (I and II having low risk, III as moderate, and IV and V as high risk). The simplified version of the PESI score exists, called sPESI, because of the relative complexity of the PESI score. Simplified PESI takes into account age, cancer presence, chronic cardiopulmonary disease, tachycardia, low systolic blood pressure, and arterial oxygen saturation. Simplified PESI is often used to identify patients in a low-risk 30-day mortality group. (62) (69)

3.10.1 Pulmonary Embolism Severity Index (PESI) and simplified (sPESI) scores

TABLE 4: ORIGINAL PESI AND sPESI SCALES

Parameter	Original Scale (No. of Points)	Simplified Scale (No. of Points)
Age	Actual age	1 if > 80 years
Male sex	10	0
Cancer	30	1
Chronic heart failure	10	1*
Chronic pulmonary disease	10	*
Pulse > 110 beats/min	20	1
Systolic blood pressure < 100 mm Hg	30	1
Respiratory rate > 30 breaths/min	20	0
Temperature < 36°C	20	0
Altered mental status	60	0
Arterial oxygen saturation < 90%	20	1

Note:
Point interpretation for the original scale:
- *Class I < 65 points, very low 30-day mortality (up to 1.6%)*
- *Class II 66–85 points, low 30-day mortality (up to 3.5%)*
- *Class III 86–105 points, moderate 30-day mortality (up to 7.1%)*
- *Class IV 106–125 points, high 30-day mortality (up to 11.4 %)*
- *Class V > 125 points, very high 30-day mortality (up to 24.5%)*

Point interpretation for the simplified scale:
- *0 points, 1% mortality*
- *1 point or more, 10% 30-day mortality*

(*) These two variables are combined into one category in the sPESI.

Adapted from: Sista A, Kuo W, Schiebler M. Stratification, Imaging, and Management of Acute Massive and Submassive Pulmonary Embolism. Radiology. 2017 Jul; 284(1): 5-24.

3.11 Follow-up imaging after pulmonary embolism

The ESC/ERS and PERT guidelines recommend 3 to 6 months follow-up visits to assess the presence of pulmonary embolism complications such as post-PE

syndrome and chronic thromboembolic portal hypertension, recurrent VTE events, quality of life, efficacy of anticoagulation, and recovery progress. ESC/ESR, AHA, and PERT support the use of noninvasive tests such as TTE, 6-minute walk tests, and sometimes natriuretic peptides to determine if pulmonary hypertension is present, especially in patients who have not otherwise explained shortness of breath and trouble with exercise tolerance after 3 months of an embolic event. V/Q scanning and TTE could be done in cases where this is suspected, however, guidelines don’t recommend the routine use of CTPA and V/Q scanning. (62) (36)

4 *Future perspectives of pulmonary embolism diagnostic imaging.*

4.1 Dynamic chest radiography (DCR)

Dynamic chest radiography (DCR) is a relatively new and possibly promising method of detecting chronic thromboembolic pulmonary hypertension (CTEPH). DCR is a functional X-ray imaging that utilizes flat-panel detectors and a pulsed X-ray generator. It can visualize pulmonary perfusion by evaluating the temporal changes in X-ray translucency in sequential images that are captured in 7 to 10 seconds of breath hold. In one retrospective study by Yamasaki et al., 350 patients underwent DCR imaging in the course of 1.5 years. Of these 350 patients, 81 had pulmonary hypertension (PH) confirmed by right heart catheterization, and they were included in this study. Of these 81 patients, 31 were excluded due to not having performed a V/Q scan in a period of two months from DCR, having pulmonary endarterectomy or balloon pulmonary angioplasty, chest surgery, and one case due to severe motion artifacts, leaving 50 patients included in the study. Of these 50 patients, 29 showed chronic thromboembolic pulmonary hypertension, and 21 of them had pulmonary hypertension due to other reasons. DCR scans were evaluated by two experienced radiologists with 13 and 15 years of experience, having well circumscribed wedge-shaped abnormality on a dynamic perfusion image or lung perfusion map as the main diagnostic criteria. This was

compared to anterior and posterior planar and SPECT V/Q scan images, which were evaluated by two nuclear physicians with 14 and 20 years of experience. The DCR showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 97%, 86%, 90%, 95%, 92% respectively, having the corresponding values of 100%, 86%, 91%, 100% and 94% for V/Q scans. The patients had to hold their breath for 7-10 seconds during examination, and the dynamic perfusion images and lung perfusion maps were created with the help of a radiologic technologist. This data suggests that the DCR had almost comparable diagnostic ability to the V/Q scan when diagnosing CTEPH in patients with pulmonary hypertension. Dynamic chest radiography has some advantages over other imaging techniques when diagnosing CTEPH. It does not require any contrast material, which is beneficial in patients who have allergies to contrast materials, those where intravenous access is difficult, or those who have renal impairments. The radiation dose is much less than that of a V/Q scan or a CT scan. DCR radiation dose is 0.2-0.3 mSv, where V/Q scan is usually 2 mSv and CT angiography is 3-10 mSv, and low radiation dose CT is 0.9-1.3 mSv, meaning that DCR has around one-tenth the radiation dose of V/Q scan and one twentieth of standard CT imaging. DCR is also very fast to perform, with around 10 seconds of scanning and about 1 minute of post-processing. The installation costs of DCR units are estimated to cost one-tenth of the cost of CT/SPECT, are lower than V/Q scanners, and also take less space than it is required for V/Q scanning. Additionally, the costs are reduced by not using the radioisotopes in each examination. DCR units could be used as conventional chest radiographs when not used in dynamic chest radiography. Dynamic chest radiography could potentially be used as an alternative to magnetic resonance imaging (MRI), CT, and V/Q scanning in some cases of lung imaging, however, further testing is needed to support the real clinical value of DCR. The application of DCR in diagnosing acute PE is a potential point of research in the future. (74) (75)

4.1.1 Magnetic resonance direct thrombus imaging (MRDTI) in PE patients

Magnetic resonance direct thrombus imaging is an imaging method that does not require contrast material and is non-invasive. It is based on the detection of methemoglobin in fresh thrombi. On T1 weighted sequences against the suppressed background tissues, methemoglobin causes T1 shortening and produces high signal intensity from the intravenous thrombi. This high signal appears to be present mostly at the start of thrombus formation, starting from 8-12 hours up to the first days after the symptoms onset. The signal intensity reduces over time, which could be used to potentially track its age and the effect of antithrombotic and other therapies. The higher signal reaches its peak in the first 3 weeks and is observed to normalize in approximately 6 months. Some benefits that are achievable with MRDTI are imaging of clots that are hard to access, such as the pelvical region, limbs where plaster casts are present, in pregnant women, or the presence of contraindications for contrast material. Originally, MRDTI was tested in studies for DVT in which it showed a sensitivity of 94-96% and specificity of 90-92%. Pulmonary embolism, being essentially another manifestation of the same disease, could be researched as a next step. MRDTI of the chest was performed in 13 patients who were suspected of having PE. It showed a positive signal in every patient who was diagnosed with PE using conventional pulmonary angiography or the combination of other standard PE diagnostic tests like V/Q scan, ultrasonography of lower limbs, laboratory test, and clinical follow-up. Here, the diagnostic ability of MRDTI in the detection of smaller subsegmental clots remains unknown. The benefit of MRDTI to estimate the clot age could prove useful in differentiating whether the PE is chronic or acute, and the disease follow-up, which could be relevant for decisions regarding therapeutic procedures. MRDTI could also play a role in diagnostic work-up and operability assessment of patients with CTEPH, where pulmonary endarterectomy is considered. Further research is needed to assess the clinical value of MRDTI in DVT and PE diagnosis. (70)

4.2 Artificial intelligence (AI) in diagnosing pulmonary embolism

The emergence of artificial intelligence (AI) has prompted many new research ideas and is potentially a new revolutionary tool that could have widespread use in health care. Diagnostic imaging is no exception here, and using AI is a central theme of many new studies in the field of radiology. If and the ways in which AI could be brought to clinical practice are being extensively and rapidly tested and investigated. (76) While computed tomography pulmonary angiography (CTPA) is currently the gold standard for diagnosing pulmonary embolism, with it being non-invasive and giving high sensitivity and specificity of 0.67 to 0.87 and 0.89 to 0.99, respectively, according to older studies (higher in newer studies), sometimes radiologists are not widely available at the event of acute pulmonary embolism. The new tools for assisting in this diagnostic process would likely prove beneficial. Some recent studies show that artificial intelligence has high sensitivity and accuracy in diagnosing pulmonary embolism on CTPA, and some such AI tools are already approved by the Food and Drug Administration (FDA) for use in clinical practice. Retrospective studies show that artificial intelligence could prove useful in assisting the diagnosis of pulmonary embolism on CTPA; however, prospective real-life studies are still lacking to confirm this. One study of 1526 examinations, where around half of them were performed with radiologists using CTPA without AI, and then the other half with AI, showed mild improvements when the AI was added to the work of radiologists. However, the difference was clinically statistically not significant considering sensitivity, accuracy, miss rates, turnaround times, and wait times of CTPA studies. AI alone performed significantly worse than radiologists alone, however, as mentioned, combined with the use of AI, radiologists performed slightly better in diagnosing PE in CTPA at this point in time. In this study, radiologists without AI had accuracy and miss rates of 97.6% and 12.3% and 98.6% and 6.1% with AI, respectively. (77)
Deep learning (DL) models have a well-known issue of them not being applicable with the same performance metrics in between different hospitals. This phenomenon is well known in deep learning research and hinders the safe use of developed deep learning models before extensive validation on new data sets.

This makes the development of generalizable deep learning models more difficult and requires the fine-tuning of DL models, testing them before their deployment in a clinical setting. Even then, if the DL model is deployed, further controlling of its performance and further fine-tuning at a specific hospital is required. The amount of images required for fine-tuning is still unknown, and further research is needed in this aspect of DL development. (78)

One prospective study by Schmuelling et al., which was the first study to test deep learning (DL) algorithms in real clinical practice, showed that even though deep learning based detection has good performance, with a sensitivity of around 80% and specificity of 95%, it does not have a significant impact on clinical performance. This study was possibly limited by things such as not integrating deep learning in standard operating procedures and non-trained personnel, low transition time, and a low time amount of training for doctors to use these new procedures in their clinical workflow. The future artificial intelligence software detection might show better results, because this was one of the first prospective studies of deep learning based PE detection. AI being in a relatively early development stage means that it naturally has big potential for improvement. Better integration of the clinical system and standard procedures could improve clinical effectiveness. (79)

A study from 2020 by Weikert et al. examined retrospectively the performance of AI in diagnosing PE. From examined 1499 patients, the AI showed 92.7% sensitivity, 95.5% specificity, a positive predictive value of 79.6% and a negative predictive value of 98.6%. Here, it was also shown that AI had better results with diagnosing central emboli with 95.7% detection rates, then segmental emboli with 93.3% detection rates, and lastly, it was more difficult for it to diagnose subsegmental emboli with 85.7% detection rate. It is uncertain if the treatment of subsegmental emboli is correlating with significantly reduced mortality rates. The authors argue that AI has good potential to be a clinical decision support tool based on the results of this and other studies. (80)

A study from 2022 by Cheikh et al., where 1202 patients were included, had similar findings as the study by Weikert et al. The sensitivity of AI showed to be 92.6%, specificity 95.8%, positive predictive value of 80.4% and negative predictive value of 98.6%. In this study survey was given to radiologists to grade how AI impacted their workflow 9 months after its implementation in clinical

routine. 72.2% found that AI impacted their diagnostic confidence either positively or strongly positively. AI is suggested to be good at excluding false negative diagnostic results, and radiologists stressed here the importance of the ability to confirm negative findings. In this study, AI detected 19 new pulmonary embolisms in 19 individual patients, which means that AI detected 1 misdiagnosed pulmonary embolism in every 63 CTPAs performed. This high negative predictive value and sensitivity, but relatively low positive predictive value and specificity, suggest that AI could be used as a safety net and supportive tool to strengthen diagnostic confidence when diagnosing PE. The authors of this retrospective study support the use of AI in clinical practice as an augmentation to radiologists' workflow. (81) Other study by Ayobi et al. had similar findings, suggesting that AI PE detection on CTPA can be used as a safety net PE detection, where AI has a relatively low PPV of 76.0 % and a relatively high negative predictive value (NPV) of 98.9%. In this study, it is also suggested that AI was able to reduce the number of missed PEs by 11.8%. This could especially prove useful to on-call radiologists in those environments where the workload is high and during the night shifts. (82)

4.2.1 Effect of AI in the reduction of turnaround, read, and wait times

In one retrospective study by Batra et al., with 2501 examinations in 2197 patients, it was looked into at how an AI triage program affects the turnaround, read, and wait times in patients who have undergone CTPA. The program is supposed to make prioritization of exams, where after scanning the examination, it would mark the examination on the radiologist's workflow as high priority if it found an increased possibility of the patient having PE. There were two groups in the study, one pre AI and one post AI, composed of 1335 and 1166 patients, respectively. In the pre AI group, there were 15.1% of PEs diagnosed, and 12.7% in the post AI group. The mean turnaround, read, and wait times were 47.6 minutes, 21.4 minutes, and 26.3 minutes for the post AI group. The corresponding numbers for examinations without the use of AI were 59.9 minutes, 33.4 minutes, and 26.5 minutes. This suggests that when using AI to triage the CTPAs performed and making prioritization on radiologists' workflow based on the increased possibility

that the examination will show the presence of pulmonary embolism, the reduction in mean turnaround time could be achieved by 12.3 minutes, mean wait time by 12 minutes, and the mean read time could not be reduced and was approximately the same. This study was done during regular working hours, and it is assumed that this approach would be more beneficial in institutions with a shortage of radiologists. (83) However, in the study by Schmuelling et al., which was done in an emergency department setting prospectively, there was no difference in time to anticoagulation or turnaround times when using AI. (79)

4.2.2 AI pulmonary embolism diagnosis and differentiation of embolus location

One newer study by Zsarnoczay et al. researched retrospectively the diagnostic performance of machine deep learning image analysis in diagnosing PE in CTPA images and stratifying their location. Initially, 1000 cases were included in this study, and then 97 were excluded due to reasons of incomplete data transfer, insufficient contrast detected in the pulmonary trunk, failure of postprocessing algorithms, or inconclusive radiology report, leaving a final cohort of 903 cases. This study, in addition, differentiated the location of pulmonary embolism between: central branches (main pulmonary artery and left and right pulmonary arteries), lobar branches (right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingula, and left lower lobe), and peripheral regions (segmental and subsegmental). The ground truth was taken from clinical reports, and in case of AI meeting false positive or false negative results, cases were further reviewed by a board-certified radiologist with 6 years of experience and a radiology resident with 3 years of experience. The overall performance of AI in diagnosing PE on CTPA images in this study had the following values for sensitivity, specificity, positive prediction value, negative prediction value, and accuracy: 84.6%, 95.1%, 70.5%, 97.8%, and 93.8% respectively. These values remain similar in both obese and non-obese patient groups, which is beneficial because in patients with higher BMI, the CTPA images usually have lower quality due to elevated X-ray absorption. When looking at location-specific detection of pulmonary embolism, the sensitivity increases to 100% in central PE (21 true positive and 0 false negative), 96.7% in

lobar PE (29 true positive and 1 false negative), and 72.9% in peripheral PE (43 true positive and 1 false negative). The treatment and detection of small peripheral segmental and subsegmental PE may not be clinically of great relevance since its detection is tied to minimal decline of mortality. This suggests that AI gives better performance in detecting more clinically important PEs relative to its ability to detect less clinically important PEs. Authors stress that new tools in PE diagnosis, like AI, could prove beneficial because the number of performed CTPA is growing by 3-4% every year, and thorough examination of CTPA is tedious, time consuming, and requires review from expert radiologists. They also support the stance that the AI technology could triage patients, with the possibility of reducing the time to early diagnosis, and that it could potentially serve as a second reader. (84)

4.2.3 Artificial intelligence in incidental pulmonary embolism detection

Many Patients receive CT imaging without the main question focus being on pulmonary embolism. For example, oncology patients often have the comorbidity of pulmonary embolism, with cancer being the main risk factor for acquiring PE. These incidental pulmonary embolisms (IPE) are detected when routine CT is performed, where the main focus of examination is not the detection of thromboembolic disease. Incidental pulmonary embolisms can have a poor outcome and a serious role in a patient's overall survival, even the ones that are asymptomatic and clinically unsuspected at first. In some such cases, the timely proper diagnosis and treatment are beneficial. In a prospective study from Topff et al. that included 11,736 CT scans, the artificial intelligence was used to diagnose incidental pulmonary embolisms. The miss rate for diagnosing incidental pulmonary embolism was reduced from 44.8% without the AI assistance to 2.6% with AI assistance. However, 58.3% of IPEs that were missed by radiologists and diagnosed with AI were segmental, and here, there could be a risk of overdiagnosing and overtreating. That would still leave a big portion of the patients who had central or lobar PE, where treatment would likely be beneficial. This study also had some other limitations, like underestimating the number of false positive

incidental pulmonary embolisms because negative findings by both AI and radiologists were not reviewed, the reason being the large number of CTs performed. Also, the population that is not oncologic patients has a lower incidence of PE than the oncologic one, therefore, the clinical relevance might be less significant than it is proposed in this study. (85)
The AI in this study also studied prioritization and flagged the studies that it determined to be highly probable of having PE. It improved the median detection and notification time significantly from one to several days in the normal workflow routine to 87 minutes (time for the radiologist to open the study from its appearance in the worklist) with AI-assisted prioritization in IPE cases. The data is therefore similar with turnaround time (time from which the study appears in the radiologist's worklist to finalization of report) being reduced from several days to 1.5 hours when assisted with AI, because of the aforementioned reduced time to open the study. (85)

4.3 PCCT compared to EID CT in diagnosing pulmonary embolism

Photon counting computed tomography (PCCT) is a new and emerging technology in computed tomography. Unlike the energy integrating detectors (EIDs) that are currently the standard of conventional and dual energy CT scanners, the photon counting detectors (PCDs) are made of substances like cadmium telluride, cadmium zinc telluride, or silicon. They convert each X-ray photon directly into an electric pulse. The small detector element size used in PCCTs leads to a decrease in pixel size, being 50 micrometers in preclinical and 200 micrometers in clinical systems. In these systems, each photon can be spectrally decomposed at the detector level and then counted and sorted according to its energy. This process allows for increased detail of spectral decomposition, achieving up to seven energy bins, as well as reducing the electronic noise. This inherent ability of spectral decomposition by PCCT allows it to produce different types of spectral reconstruction similar to those obtained with DECTS systems using EIDs. Another benefit of PCCT systems is the detection and quantification of elements with spikes in their attenuation curves at specific energetic levels, which corresponds to

the binding energy level of the K shell. This process is known as K-edge imaging. The ability of K-edge imaging could result in the development of new contrast materials, which could allow for the emergence of new methods of detecting pathologies and could open up a bigger spectrum of diseases that are detectable with CT. (86)

One study, concluding of 64 Patients, showed that PCCT can produce subjectively better diagnostic images (rated by four radiologists) using considerably less effective radiation dose (1.4 vs 3.3 mSv). However, objective image quality was measured to be significantly higher in the EID group using the previously mentioned effective radiation dosage. None of the images in this study proved to be “non-diagnostic”, and it shows that PCCT can considerably reduce the contrast material dose and radiation dose while still providing good to excellent image quality compared to conventional EID CTPA. (87)

4.4 Dual energy computed tomography (DECT) and its use in diagnosing pulmonary embolism

Dual energy computed tomography (DECT) has been commercially available for some years now. Its primary advantage over conventional CT is that it can differentiate materials based on their absorption characteristics. DECT has made some meaningful changes in diagnostic computed tomography practices and has improved diagnostic performance in some cases. Some of these changes include, but are not limited to, reduction of the amount of contrast material dosage needed to perform the examination, increased vessel opacification, and sometimes lowered radiation doses due to virtual noncontrast (VNC) reconstruction. Some of the tradeoffs and limitations of DECT are limited spatial resolution and high electronic noise. Adding to that, the spectral resolution of DECT could be improved upon because it uses two X-ray spectra or two layers of detectors, which have energetic overlaps, and they do vary in amplitude depending on the used DECT technology. (86) (88)

When diagnosing pulmonary embolism, dual energy computed tomography has an advantage because it can present the steady-state lung perfusion by displaying the iodine distribution within the lung. This means that with one scan of dual

energy CT, it is possible to get information about the presence and position of the clot within the pulmonary arteries and to get information about perfusion of the lung, similarly to that of a ventilation/perfusion scan. It has been understood that a non-occlusive clot does not necessarily cause a reduction of lung perfusion. In practice on DECT, the user is often faced with perfusion defects without the signs of having pulmonary embolism. This is due to perfusion defects being caused by other reasons besides pulmonary embolism, including the pathologies of lung parenchyma or the pleural space. In most cases, these pathologies relate to emphysematous and fibrotic changes, pleural effusions, infiltration, and interstitial edema. The perfusion defects follow mostly 3 different patterns: Circumscribed wedge-shaped, circumscribed not wedge-shaped, and diffuse patchy patterns. Perfusion defects that are not caused by PE are connected mostly to a circumscribed and patchy pattern of perfusion on DECT. Only the circumscribed wedge-shaped pattern showed a high correlation to patients having pulmonary embolism, and in this case, further radiological research of the pulmonary arteries is needed. However, not every wedge-shaped lung perfusion deficit is caused by pulmonary embolism, and a small number of them remain with an unidentifiable cause. Even though in over 70% of cases of wedge-shaped lung perfusion pathologies, the underlying cause was pulmonary embolism, it could also be caused by segmental infiltration or hilar tumor. The absence of a wedge-shaped perfusion defect does not exclude PE since it can be non-occlusive PE. This pattern of wedge-shaped lung perfusion defect is logical from an anatomical standpoint because of the typical pyramidal branching of the arteries from center to periphery, and is known from pulmonary catheter angiography and ventilation scintigraphy. (89)

One study by Weidman et al. researched the ability of DECT to diagnose PE. In lungs, as previously stated, the pattern of iodine enhancement at DECT angiography shows to matches the lung blood volume at planar scintigraphy and single photon emission CT, meaning that DECT angiography allows simultaneous view of pulmonary vasculature and also parenchymal iodine distribution. In this case, the effective radiation dose is less than that of a total conventional imaging procedure. In this study with 1144 examinations, the DECT and its iodine maps found 2.3% new pulmonary embolisms (33 new PEs) and gave an increase of PE diagnosis in 1.1% more patients. These findings also match those that were

conducted in animal studies. Even though 89% of newly detected PEs were occlusive, all of them were either segmental or subsegmental, and therefore, here the clinical significance is questionable. (88)
DECT also has other use advantages than diagnosing PEs. As a summarization of examples of other clinical cases where dual or multi energy computed tomography could prove useful are: automated bone removal (for example when wanting to directly visualize and evaluate iodinated vessels in CT angiography); perfused blood volume presentation (for example to visualize the areas of myocardial ischemia and lung perfusion deficits); production of virtual noncontras images (which could then remove the need of some scans where both contrast and noncontrast phase is required like in examinations of bladder, ureter and kidneys where noncontrast image is beneficial to asses stone formation); removal of atherosclerotic plaques to better determine the real vessel lumen; differentiating silicone breast implant leakages from nearby soft tissue; differentiation of gout and pseudogout by better discrimination of uric acid from calcium; virtual noncalcium images which remove calcium for assessing bone marrow edema; the ability to differentiate the types of stones based on material they are composed of. (90)

4.4.1 Computer-aided detection of pulmonary embolism when using DECT

A study by Langius-Wiffen looked retrospectively at computer-aided detection (CAD) of pulmonary embolisms. In this study, which included 124 Patients suspected of having PE, it was looked at computer-assisted PE detection between conventional polychromatic images (CPIs) and virtual monochromatic images (VMI), the latter being acquired by DECT. Sensitivity was high in both CPI and VMI imaging sets, with 97% for both (37/38 cases), however, the specificity for CPI images was 23% and 47% for the VMI technique. The number of false positive detections was significantly reduced by using VMI, increasing its accuracy by a big margin. Increased accuracy is presumably partially due to increased image quality, making it easier to differentiate the Embolisms. This could potentially also reduce radiologists’ reading time for VMI in comparison to CPI, as proposed by the authors of the study. (91)

5 *Future perspectives of DVT diagnostic imaging*

5.1 Magnetic resonance direct thrombus imaging (MRDTI) of deep vein thrombosis

Even though CUS has high sensitivity and specificity, there are some cases where the examination is non-diagnostic. In the follow-up, when determining the presence of recurrent Thrombosis after a year, many examinations are non-conclusive, reaching up to 30% of the cases. This happens mostly due to a lack of images from the previous ultrasounds. MRDTI is a diagnostic imaging method with high sensitivity and specificity for DVT. In a study by Van Dam et al., it is proposed that MRDTI should be used as a tool with non-conclusive CUS DVT examinations and for the follow-up of recurrent DVT presence. This would also then include decisions concerning the need of anticoagulation therapy. Van Dam et al. propose in their study that MRDTI can give a clear distinction between acute and chronic DVT. Further strengths of MRDTI are that it is non-invasive, takes about 10 minutes to acquire images, and does not require contrast material. Limitations are that it is relatively expensive and not readily available. (92)

5.2 AI in DVT diagnostic imaging

5.2.1 AI-guided DVT imaging acquisition with ultrasound by non-expert operators

In a study by Speranza et al., the imaging device was connected to the smartphone, and then AI AI-guided CUS scan was performed by nurses, proceeding to be then uploaded for further review by Radiologists and POCUS certified emergency medicine (EM) physicians. Radiologists and POCUS EM physicians found 80% of these images to be sufficient for the diagnosis, and the sensitivity was above 90% suggesting that this method might be sufficient to exclude DVT in cases with a negative result. In 20% of cases where images were

found insufficient for diagnosis, it is proposed that further CUS needs to be performed. This method of diagnosing DVT could potentially prove beneficial in areas where expert-led ultrasound is unavailable. (93)

5.2.2 AI in analysing ultrasonography DVT images

In a study by Kainz et al., the AI model was trained to analyse the ultrasonography images for the presence of DVT. The images were acquired by experienced radiologists and sonographers. This is a pioneering study for DL model DVT ultrasound analysis. The DL model used here, AutoDVT, has 2 uses. The first use case is to guide the non-ultrasound-trained staff to perform DVT ultrasound and acquire images that can be later used for analysis. The second option is for the AutoDVT to analyse the images itself. In this case, only the second option was used, and images were of high quality, acquired by radiologists and sonographers. This deep learning model was able to achieve sensitivity within a 95% confidence interval of 0.82 to 0.94 and specificity within a 95% confidence interval of 0.70 to 0.82. (94)

5.3 Fluorodeoxyglucose- positron emission tomography/computed tomography (FDG- PET/CT) molecular imaging for diagnosing DVT in cancer patients

Molecular imaging is often used as a procedure for staging, prognosis acquisition, planning of radiation therapy, and assessment of therapy in cancer patients. These routine scans in patients with cancer can have molecular early signs of venous thromboembolism, before the clinical manifestation of VTE. 2-deoxy-2-fluorodeoxyglucose- positron emission tomography/computed tomography (FDG-PET/CT) is commonly used to detect inflammatory intravascular lesions. Because the process of VTE formation begins with inflammation, it is proposed that here local FDG uptake could be increased. In a retrospective study by Kaghazchi et al. is suggested that signs of thrombus formation can be detected in FDG PET/CT

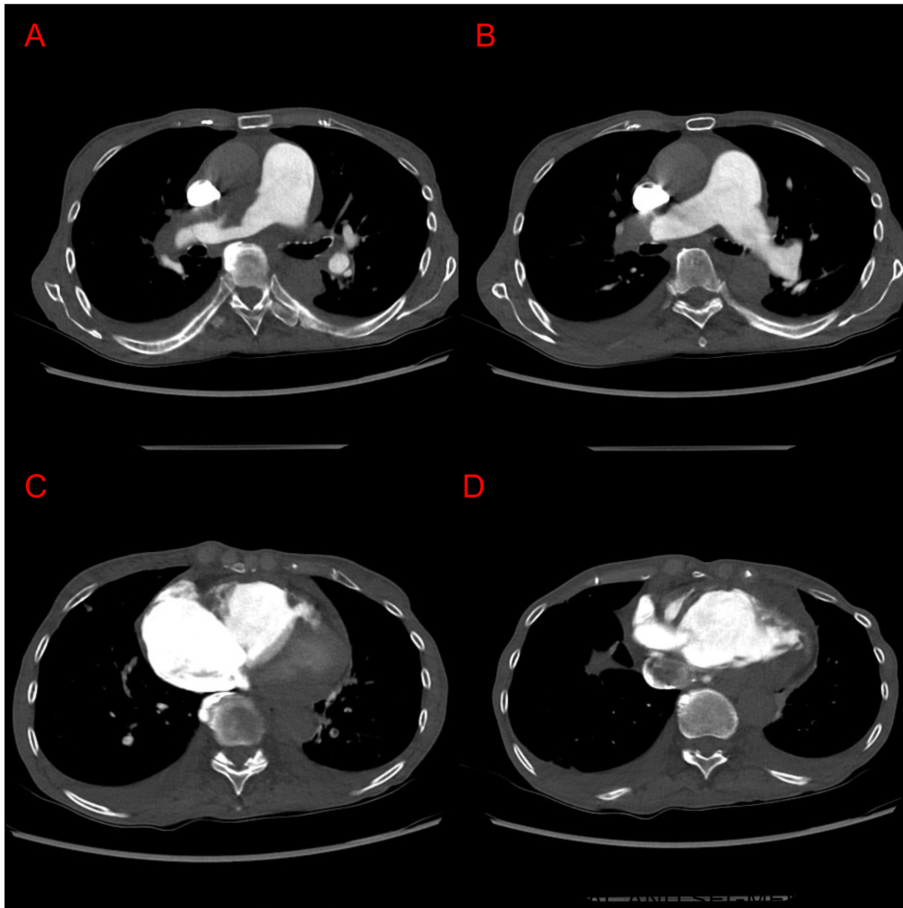
routine imaging and could be evaluated and reported in addition. They propose that in their study of 131 cancer patients with a previous history of VTE, the most common site of thrombosis was the inferior vena cava, with 53.8%, which cannot be diagnosed with conventional means. (95)

6 Clinical Cases

6.1 Case 1

Female, 71 years old.

The patient was known to have CTEPH. She was taken in to perform a right heart catheter examination. On right heart catheter examination, the large increase in pulmonary pressure and pulmonary vascular resistance is shown, together with a decrease of cardiac output. A V/Q scan was performed, and it correlated with segmental and subsegmental pulmonary embolism. CTPA was then performed and showed signs of massive central, segmental, and subsegmental PE (more on the right side than the left) as well as pulmonary infarction with infiltrate in the middle lung lobe, and oral anticoagulation was started (Figure 1). A few months later, the patient presented with pneumonia and pleural effusion. Again, CTPA was performed, however, with no signs of PE, but the truncus, both of the pulmonary arteries, and the right heart were dilated. Later, the patient received balloon pulmonary angioplasty, which moderately improved their condition.



PE, AND PULMONARY HYPERTENSION

A) Central and segmental pulmonary embolism; B) Enlarged truncus pulmonalis and left and right pulmonary arteries; C) Enlarged right atrium; D) Enlarged right ventricle.

Source: Departmant of Radiology, University Hospital LKH Graz

6.2 Case 2

Male, 46 years old.

The patient presented to the emergency department with dyspnea and burning chest pain. D-dimer was elevated over 12 mg/L. On CTPA central, segmental, and subsegmental PE were present (Figure 2). Pulmonary trunk was enlarged, and the RV/LV quotient was 1.6 with septal bowing. On the basal lung parts, a pulmonary infarction with infiltrate could be recognized. The patient received Lysis therapy and anticoagulation, stabilizing after receiving the therapy.

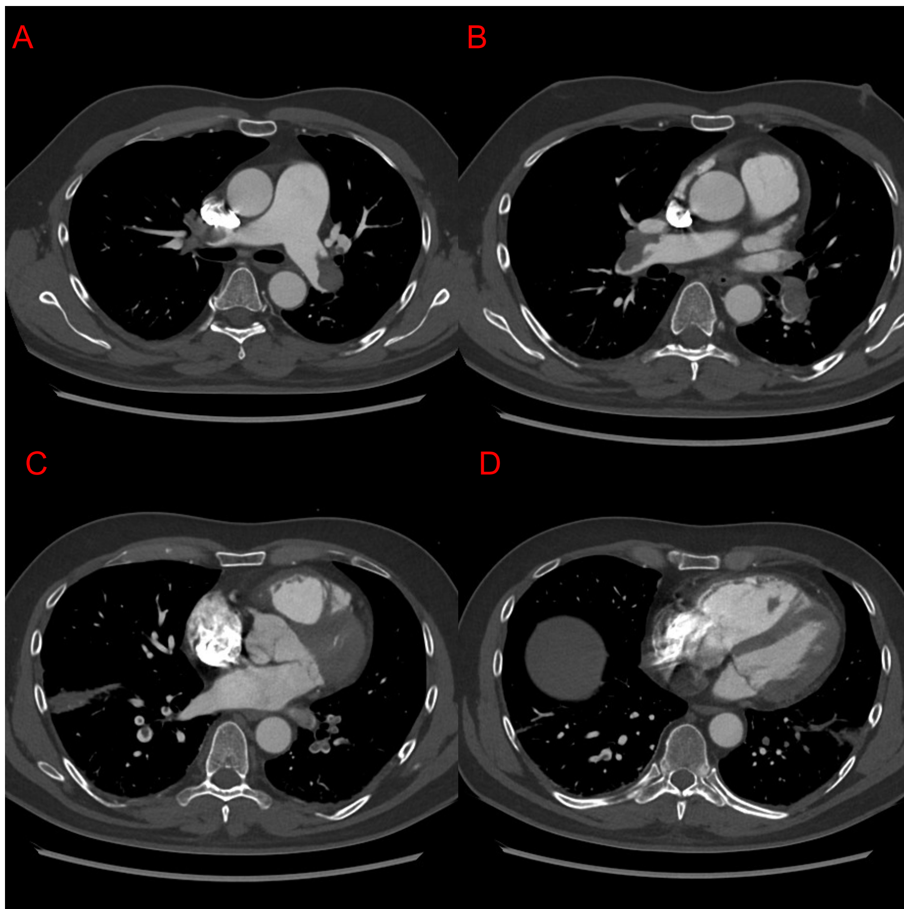


Figure 2: Case 2: Axial CT with septal bowing, enlarged truncus pulmonalis, and PE

A, B) Central, segmental, and subsegmental pulmonary embolism; C, D) wedge-shaped pulmonary infarction in lower lung lobes.

Source: Department of Radiology, University Hospital LKH Graz

6.3 Case 3

Female, 40 years old.

Patient, undergoing estrogen therapy, presented with chest pain in the emergency department. On CTPA, the signs of central and segmental PE were shown (Figure 3). Signs of pulmonary infarction were shown in the lower lung lobes. Moreover small pleural effusion was to be seen bilaterally. No signs of right heart enlargement were present, and the pulmonary trunk was within normal limits. The anticoagulation therapy in the length of three months was prescribed.

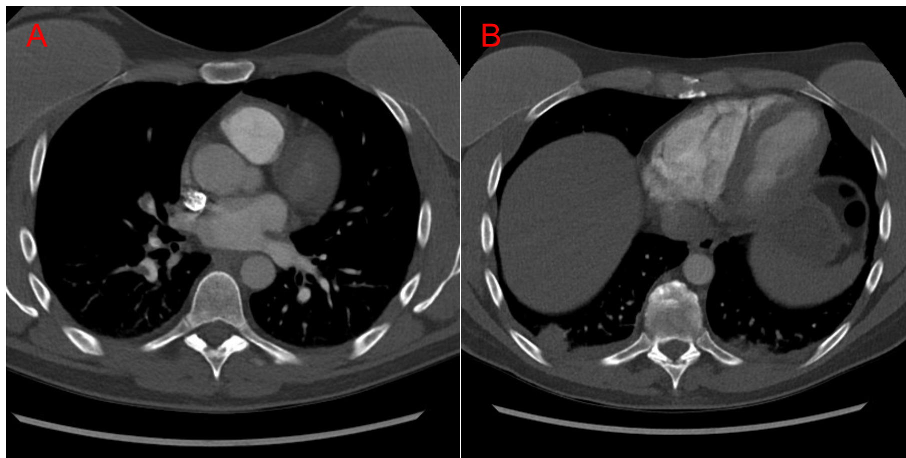


FIGURE 3: CASE 3: AXIAL CT WITH CENTRAL AND SEGMENTAL PE, SIGNS OF PLEURAL EFFUSION, AND PULMONARY INFARCTION

A) Central and segmental PE;

B) Pleural effusion and pulmonary infarction.

Source: Departmant of Radiology, University Hospital LKH Graz

6.4 Case 4

Female, 76 years old.

A patient with known COPD presented with dyspnea. D-dimer was elevated to 15 mg/L. Duplex Doppler sonography of the legs didn’t show the presence of DVT. CTPA showed segmental and subsegmental uncomplicated PE (see Figure 4) and was treated with anticoagulants. The symptoms resolved after receiving anticoagulation therapy.

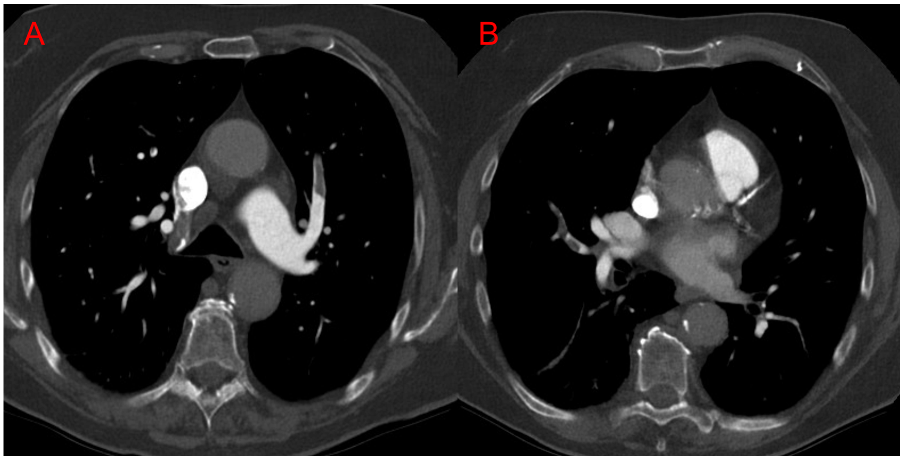


Figure 4: Case 4: Axial CT of CTPA of COPD patient
A, B) bilateral segmental and subsegmental PE

Source: Department of Radiology, University Hospital LKH Graz

6.5 Case 5

Male, 66 years old.

The patient presents with dyspnea, chest pain, and swollen legs (with the right leg being more swollen than the left one) to the emergency department. The patient had a cancer disease in the past, but is currently in complete remission. The D-dimer was over 14 mg/L, and Leg duplex Doppler sonography revealed a deep vein thrombosis. On CTPA, a segmental PE was found (see Figure 5). The patient underwent anticoagulation therapy, and the symptoms stabilized after receiving it.

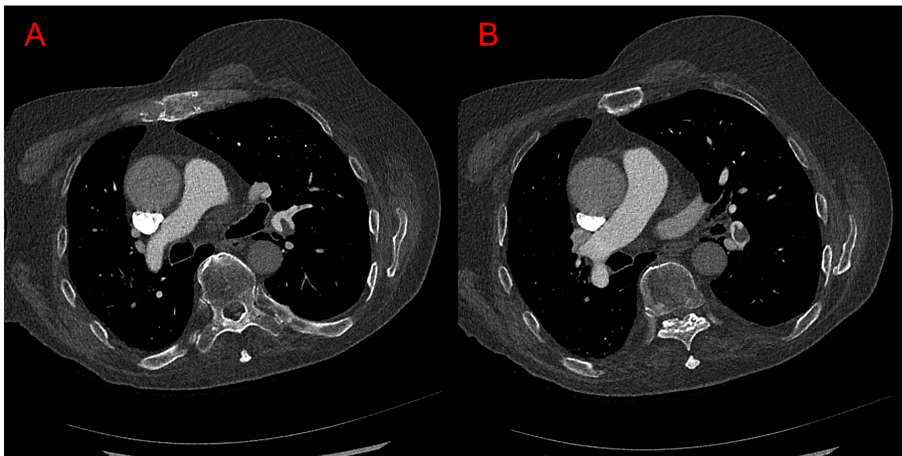


FIGURE 5: CASE 5: AXIAL CT WITH LARGE SEGMENTAL PE
A,B) large segmental PE

Source: Department of Radiology, University Hospital LKH Graz

7 Discussion

With the constantly increasing number of diagnostic imaging performed for suspected PE, especially CTPA, the workload for radiologists is ever-increasing. The percentage of positive CTPA scans for PE is decreasing over time, having been 50% at the time of its introduction and dropping to 5% to 10% at present. This means that the number of performed CTPA scans is increasing at a much higher pace than the number of CTPA scans that are positive for PE. The cost-to-benefit of performing CTPA scan ratio is worsening, over time, on average.
When comparing current guidelines for PE diagnostic imaging, clinical diagnosis, and treatment, they tend to agree on most points. Guidelines support the use of clinical pretest probability scores, such as Wells and revised Geneva scores, and consider this to be the first diagnostic step. PERC rule-out criteria are supported by American guidelines, however, ESC/ERS suggests that it is safe in the low-risk group but lacks evidence in other preclinical probability risk groups. After the clinical pretest risk stratification, the D-dimer test is next to be performed in groups that have low and intermediate pretest probability. In the cases where the patients have high clinical pretest probability, the D-dimer testing can usually be skipped. This happens because the diagnostic imaging, such as CTPA, cannot be avoided even if the D-dimer is under the safe threshold. The next step is the chest X-ray scan, as the first diagnostic imaging that is performed. Chest X-ray is fast to obtain, it provides the baseline imaging, it is cheap to perform, it can exclude other common conditions, and in some cases, it can show some signs of PE or CTEPH. Guidelines mostly agree that CTPA is the gold standard for diagnosing PE, and that the V/Q scan can be considered in some cases. V/Q scan can be performed here instead of CTPA, as the primary PE diagnostic imaging, when the indications are met and sufficient expertise is available at the given clinical center. The indications for a V/Q scan over a CTPA scan are: contrast material allergy, significant renal insufficiency, pregnancy, or young age of the patient (especially in female patients). MRA is not considered to be a first-line diagnostic imaging test for PE. While the MRA scan can diagnose PE, a relatively large proportion of MRA scans are non-diagnostic, and it is not readily available in some centers.

Future perspectives for PE imaging today mainly consist of photon counting CT, dual energy CT, and perhaps most importantly, the use of artificial intelligence. Photon counting CT has the benefits over the conventional CT of having better spatial resolution, the ability to acquire true spectral images, has better contrast-to-noise ratio, and it could reduce the radiation exposure. However, PCCT is a relatively new imaging method that is still largely in the experimental phase and is expensive. Dual energy CT provides the additional benefits of spectral imaging by utilizing 2 or more energy sources, compared to conventional CT. DECT has the ability to acquire lung perfusion images and to detect pulmonary emboli in a single scan, possibly leading to reduced total radiation exposure and better diagnostic capabilities. Artificial intelligence is a promising new technology, which in case of PE diagnosis, could be used as a second reader on CTPA as a safety net with its relatively high negative predictive value. It could also prove beneficial in making prioritizations in the radiologists' worklist, where it could flag potential PE cases as a high priority for evaluation. Other cases where AI could prove useful are in the detection of incidental PE findings on scans where the PE diagnosis is not the focus of the CT examination.

The future perspectives of DVT imaging mostly comprise of AI-guided ultrasound image acquisition by non-ultrasound-trained staff, MRDTI, and molecular imaging. The MRDTI could be used to more precisely diagnose DVT, including in places inaccessible by ultrasound, especially in the iliac (and sometimes pelvic) veins, and in patients with orthopedic casts. Moreover, the MRDTI can also differentiate between acute and chronic thrombi, it can more accurately diagnose recurrent thrombosis, and it allows for better anticoagulation treatment assessment. Molecular imaging could also be used for diagnosing DVT, and it is proposed that DVT assessment could be performed when acquiring the standard FDG-PET in oncologic patients.

8 References

1. Guntupalli S, Spinosa D, Whetington S. Prevention of venous thromboembolism in patients with cancer. BMJ. 2023 Jun; 381: e072715.

2. Beckman M, Hooper W, Ortel T, al. e. Venous thromboembolism: a public health concern. Am J Prev Med. 2010 Apr; 38(4 suppl): S495-501.

3. Mahan C, Borrego M, Woersching A. Venous thromboembolism: annualised United States models for total, hospital-acquired and preventable costs utilising long-term attack rates. Thromb Haemost. 2012 Aug; 108(2): 291-302.

4. Lutsey P, Zakai N. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol. 2023 Apr; 20(4): 248-262.

5. Khan F, Tritschler T, Kahn S, Rodger M. Venous thromboembolism. Lancet. 2021 Jul; 398(10294): 64-77.

6. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. Morbidity and Mortality Weekly Report. 2012 Jun; 61(22): 401-4.

7. Engbers M. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010 Oct; 8(10): 2105-12.

8. Olaf M, Cooney R. Deep Venous Thrombosis. Emerg Med Clin North Am. 2017 Nov; 35(4): 743-770.

9. Thachil J. Deep vein thrombosis. Hematology. 2014 Jul; 19(5): 309-10.

10. Rivera-Lebron B, McDaniel M, Ahrar K, al. e. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. Clinical and Applied Thrombosis/Hemostasis. 2019 Jan; 25.

11. Freund Y, Cohen-Aubart F, Bloom B. Acute Pulmonary Embolism: A Review. JAMA.. 2022 Oct; 328(13): 1336-45.

12. Essien E, Rali P, Mathai S. Pulmonary Embolism. Med Clin North Am. 2019 May; 103(3): 549-564.

13. Mammen E. Pathogenesis of venous thrombosis. Chest. 1992 Dec; 102(6): 640-4.

14. Christiansen S, Cannegieter S, Koster T. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA.. 2005 May; 293(19): 2352-61.

15. Pastori D, Cormaci V, Marucci S, al. e. A Comprehensive Review of Risk Factors for Venous Thromboembolism: From Epidemiology to Pathophysiology. International Journal of Molecular Sciences. 2023; 24(4): 3169.

16. Mackman N. New insights into the mechanisms of venous thrombosis. J Clin Invest. 2012 Jul; 122(7): 2331-6.

17. Goldhaber S. Pulmonary embolism. Lancet. 2004 Apr 17;363(9417):1295-305. 2004 Apr; 363(9417): 1295-1305.

18. Milka K, Beate EK. Thrombosis and platelets: an update. European Heart Journal. 2017 Mar; 38(11): 785–791.

19. Patriarcheas V, Tsamos G, Vasdeki D. Antiphospholipid Syndrome: A Comprehensive Clinical Review. J Clin Med. 2025 Jan; 14(3): 733.

20. Hogan M, Berger J. Heparin-induced thrombocytopenia (HIT): Review of incidence, diagnosis, and management. Vasc Med. 2020 Apr; 25(2): 160-73.

21. Goodacre S, Sutton A, Sampson F. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. Ann Intern Med.. 2005 Jul; 143(2): 129-39.

22. ELsaid A, AlQattan A, Elashaal E. he ugly face of deep vein thrombosis: Phlegmasia Cerulea Dolens-Case report. Int J Surg Case Rep. 2019 May; 59: 107-110.

23. Goldhaber S, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012 May; 379(9828): 1835-46.

24. Cohen A, Agnelli G, Anderson F. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007 Oct; 98(4): 756-64.

25. Torbicki A, Perrier A, Agnelli Gea. ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008 Sep; 29(18): 2276-315.

26. Thomson D, Kourounis G, Trenear R. ECG in suspected pulmonary embolism. Postgrad Med J. 2019 Jan; 95(1119): 12-17.

27. Wells P, Anderson D, Rodger M. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the

models utility with the SimpliRED D-dimer.. Thromb Haemost. 2000 Mar; 83(3): 416-20.

28. van der Hulle T, Cheung W, Kooij S. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017 Jul; 390(10091): 289-297.

29. Kline J, Mitchell A, Kabrhel C. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost. 2004 Aug; 2(8): 1247-55.

30. Le Gal G, Righini M, Roy P. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006 Feb; 144(3): 165-71.

31. Penaloza A, Versschuren F, Meyer G. Comparison of the unstructured clinician gestalt, the wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. Ann Emerg Med. 2013 Aug; 62(2): 117-124.

32. Bernardi E, Camporese G. Diagnosis of deep-vein thrombosis. Thromb Res. 2018 Mar; 163: 201-206.

33. Needleman L, Cronan J, Lilly M. Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations From the Society of Radiologists in Ultrasound Consensus Conference. Circulation. 2018 Apr; 137(14): 1505-15.

34. Moore A, Wachsmann J, Chamarthy M. Imaging of acute pulmonary embolism: an update. Cardiovasc Diagn Ther. 2018 Jun; 8(3): 225-243.

35. Hartmann I, Wittenberg R, Schaefer-Prokop C. Imaging of acute pulmonary embolism using multi-detector CT angiography: an update on imaging technique and interpretation. Eur J Radiol. 2010 Apr; 74(1): 40-49.

36. Konstantinides S, Meyer G, Becattini C. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of (ESC). Eur Respir J. 2019 Oct; 54(3): 1901647.

37. Johnson E, Schell J, Rodgers G. The D-dimer assay. Am J Hematol. 2019 Jul; 94(7): 833-39.

38. van der Hulle T, van Es J, van Es N. Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med. 2016 Aug; 165(4): 253-61.

39. Chopard R, Albertsen IE , Piazza G. Diagnosis and Treatment of Lower Extremity Venous Thromboembolism: A Review. Jama. 2020 Nov; 324(17): 1765-76.

40. Dronkers C, van der Hulle T, Le Gal G. Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. J Thromb Haemost. 2017 May; 15(5): 1040-43.

41. Bloom J, Doggen C, Osanto S. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005 Feb; 293(6): 715-22.

42. Fernandes C, Morinaga L, Alves Jj. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019 Mar; 28(151): 180119.

43. Timp J, Braekkan S, Versteeg H. Epidemiology of cancer-associated venous thrombosis. Blood. 2013 Sep; 122(10): 1712-23.

44. MCBane R2, Wysokinski W, Le-Redemacher J. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost. 2020 Feb; 18(2): 411-21.

45. Khan F, Rahman A, Carrier M. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ. 2019 Jul; 24(377): l4363.

46. Makedonov I, Kahn SR, Abdulrehman J. Prevention of the Postthrombotic Syndrome with Anticoagulation: A Narrative Review.. Thromb Haemost. 2022 Aug; 122(8): 1255-64.

47. Rabinovich A, Kahn S. The postthrombotic syndrome: current evidence and future challenges.. J Thromb Haemost. 20017 Feb; 16(2): 230-241.

48. Kim N, Delcroix M, Jais X. Chronic thromboembolic pulmonary hypertension. Eur Respir J.. 2019 Jan; 53(1): 1801915.

49. Duffet L, Castellucci L, Forgie M. Pulmonary embolism: update on management and controversies. BMJ. 2020 Aug; 370: m2177.

50. Kearon C, Akl E, Ornelas J. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb; 149(2): 315-352.

51. Otto C, Nishimura R, Bonow R. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint

Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021 Feb; 77(4): e25-e197.

52. Gómez-Outes A, Terleira-Fernández A, Lecumberri R. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014 Oct; 134(4): 774-82.

53. Grifoni S, Olivotto I, Cecchini P. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000 Jun; 101(24): 2817-22.

54. Carroll B, Larnard E, Pint D. Percutaneous Management of High-Risk Pulmonary Embolism. Circ Cardiovasc Interv.. 2023 Feb; 16(2): e012166.

55. Aujesky D, Obrosky D, Stone R. Derivation and validation of a prognostic model for pulmonary embolism.. Am J Respir Crit Care Med. 2005 Oct; 172(8): 1041-6.

56. Wang R, Miglioretti D, Marlow E. Trends in Imaging for Suspected Pulmonary Embolism Across US Health Care Systems, 2004 to 2016. JAMA Netw Open. 2020 Nov; 3(11): e2026930.

57. Anderson D, Kahn S, Rodger M. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007 Dec; 298(23): 2743-53.

58. Stevens S, Woller S, Kreuziger L. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021 Dec; 160(6): e545-e608.

59. Jaff M, McMurtry M, Archer S. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011 Apr; 123(16): 1788-830.

60. Ortel T, Neumann I, Ageno W. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct; 4(19): 4693-4738.

61. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London. NICE. 2023 Aug.

62. Zuin M, Bikdeli B, Ballard-Hernandez J. International Clinical Practice Guideline Recommendations for Acute Pulmonary Embolism: Harmony, Dissonance, and Silence. J Am Coll Cardiol. 2024 Oct; 84(16): 1561-77.

63. Anderson Fj, Spencer F. Risk factors for venous thromboembolism. Circulation. 2003 Jun; 107(23): I9-16.

64. Stein P, Fowler S, Goodman L. PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006 Jun; 354(22): 2317-27.

65. Bae J, Murugiah K. Invasive Pulmonary Angiogram Performance and Interpretation in the Diagnosis of Pulmonary Thromboembolic Disease. Interv Cardiol Clin. 2023 Jul; 12(3): 299-307.

66. Kirsch J, Wu C, Bolen M. ACR Appropriateness Criteria® Suspected Pulmonary Embolism: 2022 Update. J Am Coll Radiol. 2022 Nov; 19(11S): S488-S501.

67. Di Nisio M, van Es N, Büller H. Deep vein thrombosis and pulmonary embolism. Lancet. 2016 Dec; 388(10063): 3060-3073.

68. Zantonelli G, Cozzi D, Bindi A. cute Pulmonary Embolism: Prognostic Role of Computed Tomography Pulmonary Angiography (CTPA). Tomography. 2022 Feb; 8(1): 529-539.

69. Sista A, Kuo W, Schiebler M. Stratification, Imaging, and Management of Acute Massive and Submassive Pulmonary Embolism. Radiology. 2017 Jul; 284(1): 5-24.

70. de Jong C, Kroft L, van Mens T. Modern imaging of acute pulmonary embolism. Thromb Res.. 2024 Jun;(238): 105-116.

71. Stein P, Chenevert T, Fowler S. PIOPED III (Prospective Investigation of Pulmonary Embolism Diagnosis III) Investigators. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). Ann Intern Med. 2010 Apr; 152(7): 434-43.

72. Schiebler M, Nagle S, François C. Effectiveness of MR angiography for the primary diagnosis of acute pulmonary embolism: clinical outcomes at 3 months and 1 year. Magn Reson Imaging. 2013 Oct; 38(4): 914-25.

73. Abbas A, Joseph E, Mansour O. Radiographic features of pulmonary embolism: Westermark and Palla signs. ostgrad Med J. 2014 Jul; 90(1065): 422-3.

74. Wandtke J, Kaproth-Joslin K. Pulmonary Embolism Can Be Diagnosed with Dynamic Chest Radiography without Using Intravenous Contrast Material. Radiology. 2023 Mar; 306(3): e222507.

75. Yamasaki Y, Abe K, Kamitani T. Efficacy of Dynamic Chest Radiography for Chronic Thromboembolic Pulmonary Hypertension. Radiology. 2023 Mar; 306(3): e220908.

76. Mohanarajan M, Salunke P, Arif A. Advancements in Machine Learning and Artificial Intelligence in the Radiological Detection of Pulmonary Embolism. Cureus. 2025 Jac; 17(1): e78217.

77. Rothenberg S, Savage C, Elkassem A. Prospective Evaluation of AI Triage of Pulmonary Emboli on CT Pulmonary Angiograms. Radiology. 2023 Oct; 309(1): e230702.

78. Kolossváry M, Raghu V, Nagurney J. Deep Learning Analysis of Chest Radiographs to Triage Patients with Acute Chest Pain Syndrome. Radiology. 2023 Feb; 306(2): e221926.

79. Schmuelling L, Franzeck F, Nickel C. Deep learning-based automated detection of pulmonary embolism on CT pulmonary angiograms: No significant effects on report communication times and patient turnaround in the emergency department nine months after technical implementation. Eur J Radiol. 2021 Aug; 141: 109816.

80. Weikert T, Winkel D, Bremerich J. Automated detection of pulmonary embolism in CT pulmonary angiograms using an AI-powered algorithm. Eur Radiol. 2020 Dec; 30(12): 6545-6553.

81. Cheikh A, Gorincour G, Nivet H. How artificial intelligence improves radiological interpretation in suspected pulmonary embolism. Eur Radiol. 2022 Sep; 32(9): 5831-42.

82. Ayobi A, Chang P, Chow D. Performance and clinical utility of an artificial intelligence-enabled tool for pulmonary embolism detection. Clin Imaging. 2024 Sep;(113): 110245.

83. Batra K, Xi Y, Bhagwat S. Radiologist Worklist Reprioritization Using Artificial Intelligence: Impact on Report Turnaround Times for CTPA Examinations Positive for Acute Pulmonary Embolism.. AJR Am J Roentgenol. 2023 Sep; 221(3): 324-33.

84. Zsarnoczay E, Rapaka S, Schoepf U. Accuracy of a deep neural network for automated pulmonary embolism detection on dedicated CT pulmonary angiograms. Eur J Radiol. 2025 Jun; 187: 112077.

85. Topff L, Erik R. R, Annemarieke BR. Artificial Intelligence Tool for Detection and Worklist Prioritization Reduces Time to Diagnosis of Incidental Pulmonary Embolism at CT. Radiology: Cardiothoracic Imaging. 2023 Apr; 5(2): e220163.

86. Douek P, Boccalini S, Oei E. Clinical Applications of Photon-counting CT: A Review of Pioneer Studies and a Glimpse into the Future. Radiology. 2023 Oct; 309(1): e222432.

87. Pannenbecker P, Huflage H, Grunz J. Photon-counting CT for diagnosis of acute pulmonary embolism: potential for contrast medium and radiation dose reduction. Eur Radiol. 2023 Nov; 33(11): 7830-39.

88. Weidman E, Plodkowski A, Halpenny D. Dual-Energy CT Angiography for Detection of Pulmonary Emboli: Incremental Benefit of Iodine Maps. Radiology. 2018 Nov; 289(2): 546-53.

89. Bauer R, Kerl J, Weber E. ung perfusion analysis with dual energy CT in patients with suspected pulmonary embolism--influence of window settings on the diagnosis of underlying pathologies of perfusion defects. Eur J Radiol. 2011 Dec; 80(3): e476-82.

90. McCollough C, Leng S, Yu L. Dual- and Multi-Energy CT: Principles, Technical Approaches, and Clinical Applications. Radiology. 2015 Sep; 276(3): 637-53.

91. Langius-Wiffen E, Nijholt I, de Boer E. Computer-aided Pulmonary Embolism Detection on Virtual Monochromatic Images Compared to Conventional CT Angiography. Radiology. 2021 Nov; 301(2): 420-422.

92. van Dam L, Dronkers C, Gautam G. Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis. Blood. 2020 Apr; 135(16): 1377-85.

93. Speranza G, Mischkewitz S, Al-Noor F. Value of clinical review for AI-guided deep vein thrombosis diagnosis with ultrasound imaging by non-expert operators. NPJ Digit Med. 2025 Mar; 8(1): 135.

94. Kainz B, Heinrich M, Makropoulos A. Non-invasive diagnosis of deep vein thrombosis from ultrasound imaging with machine learning. NPJ Digit Med. 2021 Sep; 4(1): 137.

95. Kaghazchi F, Borja A, Hancin E. Venous thromboembolism detected by FDG-PET/CT in cancer patients: a common, yet life-threatening observation. Am J Nucl Med Mol Imaging. 2021 Apr; 11(2): 99-106.