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Falster, Casper; Hellfritzsch, Maja; Gaist, Thomas Agerbo; Brabrand, Mikkel; Bhatnagar, Rahul; Nybo, Mads; Andersen, Niels Holmark; Egholm, Gro

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Comparison of international guideline recommendations for the diagnosis of pulmonary embolism

Casper Falster, MD[1,2], Maja Hellfritzsch, MD[3,4], Thomas Agerbo Gaist, MD[5], Prof. Mikkel Brabrand[6,7], Rahul Bhatnagar, MD[8,9], Mads Nybo, MD[10], Niels Holmark Andersen, DMSc[11], Gro Egholm, MD[12]

Affiliations:

1. Odense Respiratory Research Unit (ODIN), University of Southern Denmark, Odense, Denmark
2. Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark
3. Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
4. Danish Society of Thrombosis and Hemostasis
5. Department of Neurology, Odense University Hospital, Odense, Denmark
6. Department of Emergency Medicine, Odense University Hospital, Odense, Denmark
7. Accident and emergency medicine academic unit, Chinese University of Hong Kong, SAR China
8. Respiratory Medicine Department, North Bristol NHS Trust, Southmead Hospital, Bristol, UK
9. Academic Respiratory Unit, University of Bristol, Bristol, UK
10. Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark
11. Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
12. Department of Cardiology, Odense University Hospital, Odense, Denmark

Corresponding author:

Casper Falster

Odense Respiratory Research Unit (ODIN)

Kløvervænget 18, entrance 122

Odense, Denmark

Casper.falster@rsyd.dk

+45 6013 9562

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ABSTRACT

Pulmonary embolism is one of the leading causes of death due to cardiovascular disease. Timely diagnosis is crucial but challenging, as the clinical presentation of pulmonary embolism is unspecific and easily mistaken for other common medical emergencies. Clinical prediction rules and D-dimer measurement allow stratification of patients into groups of expected prevalence and are key elements in adequate selection of patients for diagnostic imaging. However, the strengths and weaknesses of the multiple proposed prediction rules, when to measure D-dimer, and which cut-off to apply may be elusive to a significant proportion of physicians. Thirteen international guidelines authored by medical societies or expert author groups provide recommendations on facets of the diagnostic work-up in suspected pulmonary embolism, some of which are hallmarked by pronounced heterogeneity. This review summarizes key recommendations of each guideline, considers the most recent evidence on the topic, compares guideline recommendations on each facet of the diagnosis of pulmonary embolism, and provides a synthesis on the most common recommendations.

MAIN MANUSCRIPT

INTRODUCTION

Globally, pulmonary embolism (PE) is a common cause of death from cardiovascular disease, surpassed only by heart attack and stroke[1]. Even with timely and adequate treatment, mortality of PE is described as ≥15% in the presence of hemodynamic instability or right ventricular dysfunction with elevated cardiac troponin concentrations[2]. Obtaining a timely diagnosis is challenging as the clinical presentation of PE is hallmarked by non-specific symptoms such as dyspnoea, chest pain, or syncope[3,4].

When suspicion of PE persists following a thorough clinical assessment, stratification of patients into groups of expected prevalence may aid the next diagnostic step. Several approaches have been proposed, ranging from physician gestalt to clinical prediction rules, such as the Wells' criteria or revised Geneva score[5,6]. Furthermore, multiple cut-off values for the subsequent interpretation of D-dimer for ruling out PE suspicion have been suggested[7–9]. For confirmation of PE, the historical gold standard pulmonary angiography is rarely performed due to less-invasive alternatives with similar diagnostic accuracies, such as CT pulmonary angiography (CTPA) or ventilation perfusion scintigraphy (V/Q)[10](FIGURE 1). Considering the numerous possible adjuncts to diagnosis of suspected PE, a standardized approach to the diagnostic work-up, meticulously considering the quality of the available evidence, is paramount.

Thirteen international guidelines address the diagnosis of PE[11–23]. While each cover all or some aspects surrounding the diagnostic work-up, they vary in structure and content. Recently, a thorough comparison of international societal guidelines on the diagnosis of PE in pregnancy revealed noteworthy discrepancies, highlighting the importance of an overview, aiding informed decision making in relation to PE diagnosis[24]. In this review, we extend upon this idea by assessing and comparing recommendations of international guidelines on diagnosis of PE in the emergency setting, while reviewing these in the light of the most recent evidence.

GUIDELINES

The guidelines identified for this review were authored by the American College of Emergency Physicians (ACEP), American College of Physicians (ACP), American Society of Hematology (ASH), British Thoracic Society (BTS), A collaboration of Spanish medical societies (SPAIN), the European Association of Nuclear Medicine (EANM), European Society of Cardiology and European Respiratory Society (ESC/ERS), Japanese Circulatory Society (JCS), the National Institute for Health and Care Excellence (NICE), the investigators of the PIOPED II-study (PIOPED II), the Pulmonary Embolism Response Team consortium (PERT), the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) and UpToDate [11–23]. While not all guidelines provide recommendations on each aspect of PE-diagnosis, key topics include assessment of pre-test probability, D-dimer interpretation, empirical treatment, and diagnostic imaging. Recommendations and

their level of evidence on each topic are compared in (TABLE 1). An overview of proposed clinical pathways for each guideline is available in (TABLE 2) and method of reporting level of recommendation is available in the (Appendix p. 1-2).

DIAGNOSTIC APPROACH

Assessment of pre-test probability

All guidelines acknowledge that the clinical presentation of PE is highly unspecific, and that suspicion may arise due to presence of for instance dyspnoea, chest pain, or tachycardia, which may be observed in a broad range of medical conditions. As such, emphasis is put on the importance of a thorough medical history with focus on risk factors for PE and physical examination to exclude other obvious explanations for the patient's symptoms. If PE is still considered a diagnostic possibility, all guidelines recommend subsequent assessment of pre-test probability, as the expected prevalence of PE significantly impacts predictive values of diagnostic imaging and by extension the interpretation[11–23]. While physician's gestalt has been demonstrated of use in this regard, clinical prediction rules such as the Wells' criteria, revised Geneva score, and PERC rule are often recommended as adjuncts for improving selection of patients for diagnostic imaging[5,6,25]. The Wells' criteria constitute a point-based system developed by Wells and colleagues[6]. The approach stratifies patients into low, intermediate, or high clinical probability based on the presence of clinical parameters such as tachycardia, active cancer, or haemoptysis (Appendix p. 3).

In the initial study, PE was diagnosed in seven of 527 low probability patients (1% [95% CI 0·5–2·7]), 55 of 339 intermediate probability patients (16% [12·5–20·26]), and 24 of 64 high probability patients (38% [28·7–53·7])[6]. The Wells' criteria have since been validated and supplemented with a dichotomized stratification, grouping patients into PE unlikely or likely, showing a prevalence of 3% and 28%, respectively[25].

The revised Geneva score by Le Gal and colleagues is an alternate approach to assessment of pre-test probability[5]. It also incorporates characteristics such as age, active cancer, and haemoptysis (Appendix p. 3). In the derivation study, PE was diagnosed in 32 of 354 patients with low probability (9% [6·6–12·5]), 151 of 549 with intermediate probability (27·5% [23·9–31·4]), and 38 of 53 with high probability (71·7% [58·4–82]). While similar in several respects, the principal difference between Wells' criteria and the revised Geneva score is the former's heavy weighting of the subjective measure of PE being considered the most or equally likely diagnosis. However, meta-analyses and studies applying both approaches on the same patient population report comparable predictive accuracies[26–28]. These findings are reflected in the guidelines, where 11 of 13 recommend the Wells' criteria[11–16,18–20,22,23] and nine recommend the revised Geneva score (the BTS-guideline predates the Geneva score)[11,13–16,18–20,22]. Only five guidelines recommend clinical gestalt as a viable approach to assessment of pre-test probability (UpToDate, ESC/ERS, ACP, JCS, and PIOPED II)[11,13,19,21,22]. Most often, gestalt alone is not recommended due to the concern that lack of standardization would lead to significant

interrater variability. This notion has however been questioned in a retrospective study on 1,038 patients in which gestalt showed superior predictive accuracy compared to clinical decision rules[26].

The Pulmonary Embolism Rule out Criteria (PERC) rule was published with the intention to reduce unnecessary diagnostic testing[29]. In patients with a pre-test probability of PE <15%, who do not exhibit any of eight predefined traits associated with presence of PE, suspicion may be dismissed with no further diagnostic work-up (Appendix p. 3). The original study was conducted on 1,809 patients and reported a false negative rate of 1·4% [0.5-3.0] corresponding to five out of 362 low-risk patients, which was below the predefined threshold of 1·8%[29]. These findings were supported by a validation study on 8,138 patients with a false negative rate of 1·0% [0.6-1.6] in the low-risk population, corresponding to 16 of 1,666 patients[30]. As such, incorporation of the PERC rule for dismissing PE-suspicion in patients with low pre-test probability is recommended by eight guidelines[11,12,14–19]. However, one notable exception is the 2019 ESC/ERS-guideline, which mentions that the low overall prevalence of PE in these studies (6·8% and 5·9%, respectively) does not support generalizability of the results, as PE-prevalence in recent European studies is approximately 20%[13,31].

As the mentioned pre-test probability assessment tools are thoroughly validated and their use recommended by all guidelines except for JCS, it would seem reasonable to assume a widespread application. However, adherence to assessment of pre-test probability varies in the clinical setting, as exemplified by a study on 974 patients referred for CTPA in whom Wells' score was only documented in 127 (13%)[32]. The same authors subsequently assessed the impact of mandatory use of the Wells' score which resulted in a statistically significant increase in positive scans of 6·6% and a decrease in negative scans of 3·1%[33].

Empirical treatment

Since delayed administration of anticoagulants in relation to PE is associated with venous thromboembolism (VTE) and death at 3-months follow-up[34], multiple guidelines offer recommendations on appropriate use of anticoagulation prior to final diagnosis. However, none refer directly to literature supporting their recommendations, and no studies have assessed the optimal approach to empirical treatment in suspected PE. As such, the recommendations on this topic are characterized by significant heterogeneity and low evidence levels when reported: Three guidelines (NICE, EANM, and JCS) advice initiation of anticoagulant treatment in all patients with suspected PE, regardless of pre-test probability[12,14,21]. EANM and JCS recommend identical approaches: administer heparin as soon as PE is suspected. In the NICE-guidelines, patients who are deemed unlikely to have a PE by a Wells' score of ≤4 should be offered low-molecular weight heparin (LMWH), apixaban or rivaroxaban if a D-dimer result cannot be obtained within four hours[12]. For patients with Wells' score >4, anticoagulation should be offered if diagnostic imaging is not immediately available. Four guidelines

(ESC/ERS, SPAIN, PIOPED II, and BTS) recommend empirical treatment only in patients with moderate to high pre-test probability[13,20,22,23]. Besides the 2003 BTS-guidelines which recommend heparin, further specification of a preferred anticoagulant is not provided[23]. The PERT-guidelines recommend empirical treatment only in patients with high pre-test probability but emphasizes consideration of bleeding risk[15]. Four guidelines (THANZ, ACEP, ASH, ACP) do not provide any recommendations on empirical treatment[16–19]. The heterogeneity on this topic is further underscored by a comprehensive 2012 guideline on antithrombotic treatment of VTE, authored by the American College of Chest physicians[35]. Like in the guidelines on diagnosis of PE, the authors were not able to identify trials addressing empirical treatment. Instead, recommendations are based on the principles that the higher the clinical suspicion, the shorter the acceptable interval between treatment and diagnostic imaging, and conversely, the higher the risk of bleeding, the longer the acceptable interval without treatment prior to diagnostic imaging. Consequently, empirical anticoagulation is not recommended in cases of low clinical suspicion, provided diagnostic imaging can be performed within 24 hours. However, LMWH is recommended in cases of intermediate clinical suspicion when diagnostic imaging is delayed for more than four hours or in high clinical suspicion, regardless of when conclusive diagnostics is expected.

Altogether, while empirical treatment is often recommended and may even be considered intuitive (taking bleeding risk into account), prospective studies comparing risks and benefits of empirical treatment approaches are warranted.

D-dimer testing

Following assessment of pre-test probability, D-dimer is commonly measured to select patients for diagnostic imaging by ruling out PE if the value is below a predefined threshold. Indeed, the sensitivity of current D-dimer assays are approximately 95%[33], yielding high negative predictive values in the context of sufficiently low pre-test probability. While it may seem reasonable to measure D-dimer systematically in patients presenting with dyspnoea or chest pain, interpretation of the result is complicated by the specificity[36]: In patients ≤40 years of age, specificity is ≈67%, while in patients ≥80 years of age or in the presence of comorbidities such as cancer, infection, or inflammatory disease, specificity decreases to ≈10%, resulting in a significant proportion of false positive results[36]. The concern of excessive use of D-dimer measurements leading to substantial unnecessary diagnostic imaging predates contemporary guidelines and was highlighted in a 2003 editorial by the chairmen of the PE working party and standards of care committee from BTS, who suggested prohibiting inexperienced doctors from requesting D-dimer measurements[37].

To reduce the proportion of false positive D-dimer results and subsequent unnecessary testing, 12 out of 13 guidelines[11–16,18–23] recommend that D-dimer should only be measured following assessment of the pre-test probability, preceded by a clinical assessment, often encompassing electrocardiogram, chest x-ray, and arterial

blood gas, providing no other explanation for the patients' symptoms. The final guideline published by ACEP does not provide a recommended algorithm for the diagnostic work-up of suspected PE[17].

All 13 guidelines recommend D-dimer measurement only in low, moderate, or unlikely pre-test probability scenarios[11–23]. Acknowledging that in patients with likely or high pre-test probability for PE (≈70% if applying the revised Geneva score), a negative predictive value of 81% (given a sensitivity of 95% and specificity of 50%) is insufficient to rule out PE and delays further diagnostic work-up. As such, all guidelines recommend that patients with high pre-test probability are referred directly to diagnostic imaging.

Several research groups have attempted to accommodate the decreasing specificity of D-dimer related to comorbidities and increasing age, like Righini and colleagues who proposed an age-adjusted cut-off in 2014[9]. In the ADJUST-PE-study, 3,346 patients with suspected PE were selected for diagnostic imaging using an age-adjusted cut-off, defined as age x 10 µg/L in patients ≥50 years, instead of the conventional cut-off at 500 µg/L. The results were especially encouraging in 766 patients ≥75 years with low to intermediate pre-test probability[9]. Here, PE was excluded in 200 patients (29.7% [26.4-33.3]), as opposed to 43 (6.4% [4.8-8.5]) had the conventional cut-off been applied, with no increase in proportion of false negatives[9]. In 2017, van der Hulle and colleagues contributed with a cut-off adjusted by pre-test probability[38]. In the YEARS-study, 3,465 patients with suspected PE were assessed for presence of three items: clinical signs of DVT, haemoptysis, and PE as the most likely diagnosis. If none of these were present, D-dimer cut-off was increased to 1000 µg/L; however, if one or more of the items were present, the conventional cut-off was applied. Consequently, a reduction of 14% in referral to CTPA was observed with similar false negative rates at 3-months follow-up compared to the age-adjusted cut-off at 0·6% [0·4–1·0] and 0·3% [0·1–1·7], respectively. Lastly, the 2019 PEGeD-study on 2,197 patients by Kearon and colleagues assessed an approach allowing dismissal of PE suspicion in patients with a low pre-test probability (Wells' criteria score <2) and concomitant D-dimer <1000 µg/L[8]. For patients with intermediate pre-test probability (Wells' 2-6) the conventional cut-off was used. This approach reduced referral to diagnostic imaging by 17% with no instances of symptomatic VTE in the 3-month follow-up period. A recent comprehensive meta-analysis comparing diagnostic strategies for ruling out PE concluded that the age-adjusted D-dimer, the YEARS algorithm, and the pre-test-adjusted D-dimer can all be considered safe across their predefined patient subgroups, which does not allow favouring one over the others[39].

However, while it may then seem intuitive to apply the pre-test-adjusted cut-off going forward, it is important to consider that each proposed D-dimer cut-off for ruling out PE harbours an inherent trade-off between efficiency in reducing use of diagnostic imaging and proportion of false negative results. Indeed, while the pre-test-adjusted approach used in combination with the Wells' score is characterized by an efficiency of 47%, it simultaneously suffers from a failure rate of 2·8%[40]. Conversely, if the conventional cut-off is applied, the failure rate reduces to approximately 0·4% albeit with a simultaneous reduction in efficiency to 26%.

The efficacy and safety of the alternate cut-off values are reflected by the guidelines, where seven out of nine guidelines published after 2014 recommend an age-adjusted D-dimer cut-off (NICE, ESC/ERS, EANM, PERT, ACEP, ASH, ACP)[12–15,17–19]. The remaining post-2014 guidelines constitute THANZ, which does not provide any recommendation on cut-off, and UpToDate, which prefers the conventional cut-off at 500 µg/L but proposes that an age-adjusted cut-off may be considered in low pre-test probability[11,16]. Regarding other alternative cut-offs, ESC/ERS and PERT also endorse the YEARS-approach[13,15]. While the PERT-guideline does not specifically mention YEARS, but rather risk-adjusted cut-off, it was published prior to the PEGeD-study making referral to this approach unlikely[15]. Not surprisingly, all guidelines published prior to 2014 do not provide any recommendations other than the conventional cut-off (SPAIN, JCS, PIOPED II, and BTS)[20–23]. Lastly, a well-considered use of different D-dimer assays should be emphasised. While most current assays exhibit high sensitivities, recent studies have found varying performance around the diagnostic cut-off[41].

Echocardiography as part of diagnostic work-up

Point-of-care echocardiography is an established adjunct in the diagnostic work-up of patients presenting with dyspnoea or chest pain and its use by non-cardiologists has been endorsed by the ESC and the European Association of Cardiovascular Imaging, who also provide a core curriculum[42,43]. While of obvious use in pathology such as pericardial tamponade or acute heart failure, the utility of echocardiography in the hemodynamically stable patient with suspected PE is disputed. As most echocardiographic signs of right ventricular strain have sensitivities below 70%, their absence cannot rule out PE[44]. Conversely, as right ventricular strain can be present due to other cardiorespiratory ailments, echocardiography in the stable patient is not considered diagnostic of PE by any guidelines except for ESC/ERS, who state that identification of a right heart thrombus essentially confirms the diagnosis of PE[13]. However, in the hemodynamically unstable patient with suspected PE, the utility of echocardiography is endorsed by eight guidelines (UpToDate, ESC/ERS, EANM, PERT, SPAIN, JCS, PIOPED II, and BTS)[11,13–15,20–23]. While only BTS recommends finally accepting PE-diagnosis when right ventricular strain is detected, all eight guidelines recommend that echocardiography supports the decision of administering fibrinolytic treatment[11,13–15,20–23]. As such, in the hemodynamically unstable patient with suspected PE, echocardiography is not recommended as a replacement for CTPA or V/Q scan, but rather as an essential tool in the decision to administer thrombolytic treatment prior to finalizing diagnosis. While not all guidelines clearly define right ventricular strain, common examples include right ventricular dilation, the D-sign (septal deviation towards the left ventricle due to right ventricular pressure overload), and McConnell's sign (akinesia of the right ventricular free wall with normal or hyperkinetic apical motion). The D-sign and McConnell's sign in particular are specific for PE with recent meta-analysis data revealing specificities in hemodynamically stable patients of 96·2% [93·1–98·0] and 98·6% [96·7–99·4], respectively[44].

Deep venous and lung ultrasound as part of diagnostic work-up

Besides echocardiography, two other ultrasound modalities have gained notable scientific attention in relation to suspected PE. Venous ultrasound allows visualization of a potential source thrombus and lung ultrasound can detect subpleural infarctions, the downstream effect of PE[45].

A recent meta-analysis of 22 studies comprising 4,708 patients reported a sensitivity of 43·7% [36·3–51·4] and a specificity of 96·7% [95·4-97·6] of a proximal deep venous thrombus (DVT) acknowledged by ultrasound in suspected PE[44]. Thus, given a sufficient pre-test probability, identification of a DVT results in a high positive predictive value, as acknowledged by the ESC/ERS, PERT, ACP, PIOPED II, and BTS-guidelines, who all recommend accepting diagnosis of PE or stop further diagnostic work-up, if a proximal DVT is detected[13,15,19,22,23]. While less decisive, the guidelines from UpToDate, ASH, and SPAIN recommend that PE diagnosis should be accepted if a DVT is detected following an inconclusive CTPA or V/Q scan[11,18,20]. The main rationales behind these recommendations are that since DVT and PE are both manifestations of VTE, they often require identical treatment, and that "silent" PEs are often present in patients with proximal DVTs, who do not exhibit concomitant cardiopulmonary symptoms. A 2010 meta-analysis reported a prevalence of 32%, and a subsequent prospective study on 103 patients with proximal DVT, using CTPA as the sole reference standard, identified silent PEs in 66% of patients[46,47]. Thus, it is likely that the combination of a proximal DVT and dyspnoea or chest pain is highly predictive of PE as suggested by the meta-analysis[44].

Lung ultrasound may be of particular use in patients with suspected PE and pleuritic chest pain. A retrospective analysis of 217 patients reported a sensitivity of 81·5% [70–90·1] and a specificity of 95·4% [90·7–98·1] of subpleural infarctions located at the site of the chest pain[48]. Meta-analysis suggests a sensitivity of 44·2% [38–50·6] and a specificity of 96·5% [93·2–98·5] for the presence of PE when at least two subpleural infarctions are detected in patients with suspected PE regardless of the presence of chest pain – diagnostic values which are on par with those of DVT[44]. A monograph on thoracic ultrasound by the ERS even suggests that presence of at least two subpleural infarctions should rule in suspicion of PE when a CTPA is not available[45]. However, lung ultrasound is only mentioned in the 2003 BTS-guideline, which states that the technique is not widely used and should be considered as an adjunct rather than an alternative to other imaging techniques[23].

Diagnostic imaging

All guidelines recommend that patients of low to intermediate pre-test probability with elevated D-dimer or those of high pre-test probability are referred to final diagnostic imaging. Nine guidelines recommend CTPA as the primary imaging choice, regardless of pre-test probability (UpToDate, NICE, ESC/ERS, PERT, THANZ, ACP, SPAIN, JCS, PIOPED II, and BTS)[11–13,15,16,19–23]. ASH recommends CTPA only in patients with high probability and V/Q scan in low to intermediate, while JCS considers CTPA and V/Q-scan equal[18,21].

While only few guidelines discuss the interpretation of CTPA-results in relation to pre-test probability, it should be considered that the PIOPED II-study reported a sensitivity and specificity of (mainly four-detector) CTPA at 83% [76–92] and 96% [93–97], respectively[49].

The ESC/ERS-guideline emphasizes that these test characteristics yielded a modest positive predictive value of 58% in low pre-test probability, with the lowest values in patients with segmental or subsegmental PE. Further, the negative predictive value was 60% in high pre-test probability, leading to the recommendation that additional testing should be considered in cases of discordance between clinical judgement and the CTPA result[13]. The low negative predictive value of a negative CTPA in relation to a high pre-test probability is also acknowledged by the NICE, ASH, SPAIN, and PIOPED II guidelines, which all recommend supplementing with V/Q scan or deep venous ultrasound prior to finally dismissing suspicion of PE[12,18,20,22]. Conversely, PERT, THANZ, ACP, JCS, and BTS do not address this clinical conundrum and consider a negative CTPA dismissive of PE, regardless of pre-test probability[15,16,19,21,23].

Naturally, when interpreting these guidelines, it should be considered that the quality of CT-scanners have improved since the 2006 PIOPED II-study, and radiologists are now increasingly able to detect contrast filling defects in even the peripheral parts of the pulmonary vasculature, some of which may be flow artifacts which do not represent PE or require treatment[50]. As CT-scanners have become more available, concerns that anticoagulation would be initiated in an excess of patients with low pre-test probability and presumed subsegmental PE has fuelled a rigorous scientific discussion in recent years[51,52]. To clarify the significance of subsegmental PE, a 2022 study withheld anticoagulation in 292 patients with a single or multiple isolated subsegmental PE and no DVT[53]. The study was discontinued prior to completion after a predefined stopping rule was met, with the upper bound of the 95% confidence interval of the 90-day rate of recurrent VTE exceeding 5·0%. Of all enrolled patients, 90-day VTE-recurrence occurred in eight (3·1% [1·6–6·1]). However, recurrence was lower the in 191 patients below 65 years (1.8% vs 5.1%), and in the 209 patients with only one subsegmental PE it was 2·1% [0·8–5·5]. Subsequent discourse signifies that the approach to subsegmental emboli is not yet definitely answered[54,55]. As such, to increase the yield of CTPA for suspected PE, clinicians should not only adhere to recommended diagnostic protocols prior to referral, but also carefully include pre-test probability into the interpretation of the results while considering the uncertain significance of single subsegmental contrast defects[33].

V/Q with single-photon emission CT (SPECT) is considered the primary imaging choice in all pre-test probability strata by the 2019 EANM guideline[14]. The society highlights a sensitivity of 96% which is superior to that of CTPA, and a lower rate of non-diagnostic studies (1-4% vs. 4-10%), but simultaneously acknowledges that CTPA is indispensable due to the limited availability of V/Q-SPECT. The NICE and ESC/ERS-guidelines also address V/Q-SPECT[12,13]. NICE recommends SPECT over planar V/Q when CTPA is not feasible, but ESC/ERS caution that most studies reporting on the diagnostic accuracy of SPECT are

limited by a retrospective design or the inclusion of SPECT itself in the reference standard and highlights that large-scale prospective studies are needed for final validation[56–58].

In cases of indeterminate primary imaging or contraindications to CTPA, eleven guidelines recommend referral to V/Q-scan[11–16,18–20,22,23]. While only NICE, EANM and ESC/ERS discern between planar and SPECT V/Q, it is safe to assume that most guidelines refer to planar V/Q, which has been established as a diagnostic alternative to pulmonary angiography for decades[59].

Although planar V/Q is validated in prospective management outcome studies and has almost no contraindications, the guidelines highlight several reasons for the choice planar V/Q as secondary imaging[60]. For instance, the limited availability and lack of utility in situations of hemodynamic instability, and the inability to provide alternative diagnoses if PE is excluded. Based on large, older studies with high sensitivity and negative predictive value especially with low pre-test probability, a normal V/Q scan has generally been considered sufficient to rule out PE, but diagnostic accuracies vary which may be attributed to different interpretation criteria (e.g. PIOPED I & II and PISA-PED). For instance, the original PIOPED I reported sensitivity of 98% [96-100] and a specificity of 97% [96-98] (albeit not at the same time), whereas PIOPED II found a sensitivity of 77·4% [69·7–85·0] and specificity of 97·7% [96·4–98·9][4,61]. Older studies usually employed the invasive pulmonary angiography as reference standard and it was often omitted in patients with normal or low-probability scans for ethical reasons, which may have resulted in selection bias with overestimated sensitivity[62,63]. PIOPED II excluded the 26·5% of patients who had non-diagnostic scans[64]. Indeed, the high rate of inconclusive V/Q-scans has led ESC/ERS, THANZ, ASH, and SPAIN to further recommend that in low pre-test probability patients with inconclusive planar V/Q, an ultrasound examination devoid of a DVT allows withholding of anticoagulation[13,16,18,20].

Approach to future diagnostic studies on pulmonary embolism

Multiple guidelines emphasize that following a diagnostic algorithm including assessment of pre-test probability and D-dimer testing reduces unnecessary testing and radiation exposure. However, despite largely similar recommendations across the last 20 years, a recent communication from the International Society on Thrombosis and Haemostasis (ISTH) reported that the prevalence of PE in patients referred to CTPA continuously diminishes, from approximately 25% in 1990 to 20% in 2015[31].

As such, the conundrum posed by Gregoire Le Gal and Henri Bounameaux in 2004: "*The question may be no more how should we investigate pulmonary embolism but rather in whom?*", still seems relevant today[65]. Research groups considering conducting prospective management studies on algorithms improving selection of patients for diagnostic imaging should preferably design their studies with 3-month failure rate as the primary outcome measure, defined as incidence of VTE in the three months following study inclusion. Historically, the applied safety threshold has been 1·7%, with an upper limit of the 95% confidence interval of

2·7%, based on a meta-analysis of eight management studies pooling data from 1050 consecutive patients with suspected PE undergoing pulmonary angiography[66].

However, as PE prevalence in studies is declining, the accepted failure rate of new diagnostic tests or algorithms should be lowered along with it. The ISTH recommends a novel approach to calculation of acceptable failure rate threshold, which incorporates expected prevalence in the study population: 1·82+0·00528*prevalence[31]. To accommodate for over- or underestimation of PE prevalence, the ISTH further encourages interim analysis and applying an adaptive study design, allowing adjustment of the sample size. It should be noted that the communication contains a minor inconsistency in the example calculation, which may cause confusion when attempting a practice replication of the method.

In the example, the authors expect a failure rate of 1·2%, anticipate a baseline prevalence of 30%, and the goal is to keep the point estimate of the failure rate below a 1.98% safety threshold (1·82+0·00528*30). The authors apply power of 80% and a one-sided significance level of 5% and calculate that 1444 patients with PE ruled out are needed and conclude a total sample size of 1877 patients.

However, the correct total population would be 2063 patients, as the 1444 accounts for 70%, due to an expected prevalence of 30%. We have corresponded with the authors on this matter who acknowledge this inconsistency.

Further, when designing a diagnostic study on PE, it must be considered if the study participants should represent the average emergency department population or a more specific group of patients such as those with pregnancy or chronic obstructive pulmonary disorder (COPD), as it is questionable whether common algorithms are safe in such groups. Noteworthy examples of trials applying rigorous methodology for assessing more specific populations with suspected PE are the CT-PE-Pregnancy study by Righini and colleagues as well as the Artemis study by van der Pol and colleagues, which both demonstrated acceptable safety of bespoke diagnostic algorithms for suspected PE during pregnancy[67,68]. Likewise, as exacerbation of COPD may easily raise suspicion of PE and lead to measurement of D-dimer, it is no surprise that this patient category has also been the subject of scientific attention. Perhaps most notably in the recent SLICE-study by Jiménez and colleagues, which demonstrated that active search for PE in patients with COPD exacerbation did not improve outcome compared to standard care[69].

CONCLUSION

This review provides an overview of the 13 most recent guidelines on diagnosis of suspected pulmonary embolism and highlights important recent literature. A synthesized diagnostic approach based on the most common recommendations constitutes that in the hemodynamically stable patient, a clinical assessment not providing an alternate explanation for the patient's symptoms should be followed by assessment of pre-test probability, either by use of the Wells' criteria or the revised Geneva score. Subsequently, D-dimer with an age-adjusted cut-off is measured in instances of low to intermediate pre-test probability. When D-dimer is

elevated or pre-test probability is high, patients should be referred to CTPA. If CTPA is contraindicated, patients may be referred to V/Q scan.

In the hemodynamically unstable patient with suspected pulmonary embolism, if CTPA is not immediately feasible, echocardiography should be performed. If presence of right ventricular strain, consider administering thrombolysis prior to finalizing the diagnosis.

Major discrepancies between guidelines encompass empirical treatment regimens and the role of ultrasound in the hemodynamically stable patient with suspected pulmonary embolism. Adequately powered prospective management studies are warranted to further explore the efficiency and safety of these aspects of pulmonary embolism diagnostics.

CONTRIBUTORS

CF, MH, TAG, MB, RB, MN, NHA, and GE were involved in conceiving the study. CF performed article search and data-extraction. TAG painted visual abstract. CF wrote the initial draft. CF, MH, TAG, MB, RB, MN, NHA, and GE made critical revision and approved the final manuscript. CF is responsible for the overall content as guarantor.

CONFLICTS OF INTEREST

CF, MN, and GE have received honoraria as speakers from Bristol-Myers-Squibb. MH, MN, and GE have received honoraria as speakers from Bayer. MN is Chair of the Danish Society of Clinical Biochemistry. The other authors declared no conflicts of interest .

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Search strategy and selection criteria

PubMed.org was searched on the 15th of November 2022 to identify guidelines on the diagnosis of pulmonary embolism. We used the following search string: *Pulmonary Embolism"[Mesh] OR pulm* embol* or pulm* thromboembol* AND "Guideline" [Publication Type]*. Guidelines specifically aimed at primary care, patients with cancer, pregnancy or COVID-19 were not considered, neither were guidelines not written in English or published prior to the year 2000. Only the most recent versions of guidelines from the same authors were eligible, unless different versions described separate aspects of PE-diagnosis. This approach yielded 11 clinical guidelines which were extracted and compared. We further included UpToDate, a widely used point-of-care medical resource. By evaluating reference lists of included guidelines, we further identified a guideline by the National Institute for Health and Care Excellence. When available, we also registered and compared reported evidence level of recommendations.

LEGENDS

Figure 1:

Overview of recommended items in each part of the diagnostic work-up of pulmonary embolism: Clinical evaluation (blue), assessment of pre-test probability (green), D-dimer measurement (yellow), and diagnostic imaging (red).

Table 1:

Guideline endorsements for each clinical diagnostic component for pulmonary embolism with extracted grade or evidence.

*No grading of strength or level of recommendation.

PERC: Pulmonary Embolism Rule Out Criteria. DVT: Deep Venous Thrombus. PE: Pulmonary Embolism. CTPA: CT Pulmonary Angiography. V/Q: Ventilation/perfusion scan.

NICE: National Institute for Health and Care Excellence. ESC/ERS: European Society of Cardiology/European Respiratory Society. EANM: European Association of Nuclear Medicine. PERT: Pulmonary Embolism Response Team consortium. THANZ: Thrombosis and Haemostasis Society of Australia and New Zealand. ACEP: American College of Emergency Physicians. SPAIN: Spanish Medical Societies (Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Society Española Internal Medicine (SEMI). Spanish Society of Thrombosis and Haemostasis (SETH). Spanish Society of Cardiology (ESC). Spanish Society of Medicine Accident and Emergency (SEMES). Spanish Society of Angiology and Surgery Vascular (SEACV)). JCS: Japanese Circulatory Society. PIOPED II: Prospective Investigation of Pulmonary Embolism Diagnosis investigators. BTS: British Thoracic Society.

Table 2:

Summary of suggested approach for diagnostic work-up of suspected pulmonary embolism for each guideline.

CTPA: CT Pulmonary Angiography. DVT: Deep Venous Thrombosis. LMWH: Low Molecular Weight Heparin. PE: Pulmonary Embolism. PERC: Pulmonary Embolism Rule Out Criteria. SPAIN: Spanish Medical Societies (Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Society Española Internal Medicine (SEMI). Spanish Society of Thrombosis and Haemostasis (SETH). Spanish Society of Cardiology (ESC). Spanish Society of Medicine Accident and Emergency (SEMES). Spanish Society of

Angiology and Surgery Vascular (SEACV)). V/Q: Ventilation/perfusion scan. TEE: Trans Esophageal Echocardiography. TTE: Trans Thoracic Echocardiography.

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	Guideline endorsements	Number of endorsements (out of 13)
Assessment of pre-test probability		
Clinical judgement	UpToDate*, ESC/ERS (I), ACP*, JCS*, PIOPED II*	5
Wells' criteria	UpToDate*, NICE*, ESC/ERS (I), EANM*, PERT*, THANZ (strong), ASH*, ACP*, SPAIN*, PIOPED II*, BTS (C)	11
Revised Geneva score	UpToDate*, ESC/ERS (I), EANM*, PERT*, THANZ (strong), ASH*, ACP*, SPAIN*, PIOPED II*	9
PERC rule in low pre-test probability	UpToDate*, NICE (consider), EANM*, PERT*, THANZ (strong), ACEP (B), ASH*, ACP*	8
Risk stratification following assessment of pre-test probability		
PE likely or unlikely	NICE*, ERS/ESC*, THANZ*, ASH*, SPAIN*,	5
Low, intermediate, or high clinical probability	UpToDate*, ERS/ESC*, EANM*, PERT*, ACEP*, ASH*, ACP*, SPAIN*, JCS*, PIOPED II*, BTS*	11
Empirical treatment prior to diagnosis		
No recommendation	THANZ, ACEP, ASH, ACP	4
In all pre-test probability strata	NICE (offer), EANM*, JCS*	3
In intermediate to high pre-test probability	ESC/ERS (I), SPAIN*, PIOPED II*, BTS (C)	4
In high pre-test probability and low risk of bleeding	PERT*	1
Under consideration of pre-test probability and risk of bleeding	UpToDate*	1
Time of D-dimer measurement		
No recommendation	ACEP	1
Prior to assessment of pre-test probability	No recommendations	0
Following assessment of pre-test probability	UpToDate*, NICE (offer), ESC/ERS*, EANM*, PERT*, THANZ*, ASH*, ACP*, SPAIN*, JCS*, PIOPED II*, BTS (B)	12
In all pre-test probability strata	No recommendations	0
In low and intermediate or "unlikely" pre-test probability	UpToDate*, NICE (offer), ESC/ERS (I), EANM*, PERT*, THANZ*, ACEP*, ASH (strong), ACP*, SPAIN*, JCS (I), PIOPED II*, BTS (B)	13
D-dimer cut-off		
No recommendation	THANZ, JCS, PIOPED II, BTS	4
Conventional cut-off (500 µg/L)	UpToDate*, SPAIN*	2
Age-adjusted cut-off (age * 10 µg/L) when > 50 years	NICE (consider), ESC/ERS (IIa), EANM*, PERT*, ACEP (B), ASH*, ACP*	7
Clinical probability-adjusted cut-off	ESC/ERS (IIa), PERT*	2
Echocardiography and other ultrasound as part of diagnostic work-up		
No recommendation	NICE, ACEP	2
Lower extremity scan without DVT excludes PE in low-probability patients if inconclusive V/Q scan	ESC/ERS*, THANZ*, ASH*, SPAIN*	4
Proximal DVT confirms PE-suspicion	ESC/ERS (I), PERT*, ACP*, PIOPED II*, BTS (B)	5
Proximal DVT confirms PE-suspicion if inconclusive V/Q or CTPA	UpToDate*, ASH*, SPAIN*	3
DVT allows fibrinolysis in hemodynamic instability and suspected PE	UpToDate*, ESC/ERS*, PERT*, PIOPED II*	4
RV dysfunction allows diagnosis of suspected massive PE	BTS (B)	1
RV dysfunction or right heart thrombus allows fibrinolysis in hemodynamic instability and suspected PE	UpToDate*, ESC/ERS (I), EANM*, PERT*, SPAIN*, JCS*, PIOPED II*, BTS (B)	8
Primary diagnostic imaging		
No recommendation	ACEP	1
CTPA regardless of pre-test probability	UpToDate*, NICE (offer), ESC/ERS*, PERT*, THANZ (strong), ACP*, SPAIN*, JCS (I), BTS (B)	9
CTPA in high pre-test probability, V/Q scan in low to intermediate	ASH (very low)	1
CTPA and CT venography of the proximal leg veins	PIOPED II*	1
V/Q scan	EANM*, JCS (I)	2
Secondary diagnostic imaging		
No recommendation	ACEP, JCS	2
CTPA	EANM*, ASH (very low)	2

V/Q scan	UpToDate*, NICE*, ESC/ERS*, EANM*, PERT*, THANZ*, ASH (very low), ACP*, SPAIN*, PIOPED II, BTS (B)	11
Lower extremity venous ultrasound	PIOPED II*	1

Table 1: Guideline endorsements for each clinical diagnostic component for pulmonary embolism with extracted grade or evidence.
*No grading of strength or level of recommendation.

PERC: Pulmonary Embolism Rule Out Criteria. DVT: Deep Venous Thrombus. PE: Pulmonary Embolism. CTPA: CT Pulmonary Angiography. V/Q: Ventilation/perfusion scan.
NICE: National Institute for Health and Care Excellence. ESC/ERS: European Society of Cardiology/European Respiratory Society. EANM: European Association of Nuclear Medicine. PERT: Pulmonary Embolism Response Team consortium. THANZ: Thrombosis and Haemostasis Society of Australia and New Zealand. ACEP: American College of Emergency Physicians. SPAIN: Spanish Medical Societies (Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Society Española Internal Medicine (SEMI). Spanish Society of Thrombosis and Haemostasis (SETH). Spanish Society of Cardiology (ESC). Spanish Society of Medicine Accident and Emergency (SEMES). Spanish Society of Angiology and Surgery Vascular (SEACV)). JCS: Japanese Circulatory Society. PIOPED II: Prospective Investigation of Pulmonary Embolism Diagnosis investigators. BTS: British Thoracic Society.

Recommended approach for diagnosis of suspected pulmonary embolism by guideline

UpToDate:

1. Estimate pre-test probability. Preferably using Wells' score, but Geneva score or clinical gestalt are also appropriate.
2. Consider empiric anticoagulation by taking level of clinical suspicion, risk of bleeding and expected timing of diagnostic test into account.

Low clinical probability

3. Assess PERC criteria, if = 0 rule out PE without D-dimer testing.
4. If PERC > 0, measure D-dimer.
5. If elevated D-dimer (> 500 µg/L) refer to CTPA.
6. If CTPA not feasible or inconclusive, refer to V/Q scan.
7. If V/Q scan is neither feasible, normal or of low probability, revisit feasibility of CTPA or perform lower extremity ultrasound.

Intermediate clinical probability

3. Measure D-dimer.
4. If elevated D-dimer (> 500 µg/L) refer to CTPA.
5. If CTPA not feasible or inconclusive, refer to V/Q scan.
6. If V/Q scan is neither feasible or normal, revisit feasibility of CTPA or perform lower extremity ultrasound.

High clinical probability

3. Do not measure D-dimer. Refer directly to CTPA.
4. If CTPA not feasible or inconclusive, refer to V/Q scan.
5. If V/Q scan is not feasible, or of low or intermediate probability, revisit feasibility of CTPA or perform lower extremity ultrasound.

Hemodynamic instability

3. Perform bedside TTE or lower extremity compression ultrasound.
4. If present new RV strain, right heart thrombus or DVT administer immediate reperfusion treatment without further testing.

National Institute for Health and Care Excellence (NICE):

1. Assess medical history, do a physical examination, and offer chest x-ray to exclude other causes than PE.
2. If clinical likelihood of PE is estimated to be < 15%, consider using the PERC criteria to determine whether any further investigations are needed.
3. If PE is still suspected, use 2-level Wells' score.

PE Unlikely

4. Measure D-dimer
5. If D-dimer cannot be obtained within 4 hours, measure full blood count, renal and hepatic function, prothrombin time and activated partial thromboplastin time, and offer interim therapeutic anticoagulation while awaiting the results.
6. If D-dimer is elevated, offer CTPA immediately if possible.
7. If contraindications to CTPA, assess suitability of V/Q SPECT or V/Q planar, as an alternative.

PE Likely

4. Offer CTPA immediately if possible.
5. If contraindications to CTPA, assess suitability of V/Q SPECT or V/Q planar, as an alternative.
6. If CTPA or V/Q scan cannot be done immediately, offer interim therapeutic anticoagulation. Measure full blood count, renal and hepatic function, prothrombin time and activated partial thromboplastin time.
7. If CTPA or V/Q is negative, consider deep venous ultrasound if suspected DVT.

European Society of Cardiology & European Respiratory Society (ERS/ESC):

1. Assess pre-test probability by clinical judgement (including arterial blood gas, chest X-ray and electrocardiogram if possible) or prediction rules (revised Geneva rule or Wells' rule).

Low or intermediate clinical probability

2. Measure D-dimer. Consider age-adjusted cut-off (age x 10 µg/L, in patients aged >50 years) or clinical probability adjusted cut-off as an alternative to the fixed D-dimer cut-off (500 µg/L).

American Society of Hematology (ASH):

1. Assess clinical probability using a clinical decision rule (Wells' or Geneva score)

Low clinical probability or pulmonary embolism unlikely

2. PERC criteria may rule out PE without D-dimer testing.
3. Measure D-dimer, use age-adjusted cut-off in patients >50 years (age x 10 µg/L).
4. Refer to V/Q scan if elevated D-dimer.
5. If V/Q scan is non-diagnostic, consider lower extremity ultrasound or CTPA.

Intermediate clinical probability

2. Measure D-dimer, use age-adjusted cut-off in patients >50 years (age x 10 µg/L).
3. Refer to V/Q scan if elevated D-dimer.
4. If V/Q scan in non-diagnostic, consider CTPA.

High clinical probability or pulmonary embolism likely

2. Do not measure D-dimer.
3. Refer to CTPA.
4. If negative CTPA, consider V/Q or perform proximal lower extremity ultrasound. If high probability V/Q or present DVT, PE is confirmed.

American College of Physicians (ACP):

1. Assess clinical probability using a clinical decision tool (Wells' or Geneva) or clinician gestalt.
2. Consider lower extremity venous ultrasound as a DVT results in similar treatment.

Low or intermediate clinical probability

3. In low probability patients, PERC criteria can rule out PE without D-dimer testing.
4. If PERC > 0 or intermediate probability, measure D-dimer.
5. If elevated D-dimer (age-adjusted cut-off off in patients >50 years (age x 10 µg/L)), refer to CTPA.
6. If contraindications to CTPA, refer to V/Q scan.

High clinical probability

3. Do not measure D-dimer.
4. Refer to CTPA immediately.

Hemodynamic instability

3. Do not measure D-dimer.
4. Refer to CTPA immediately.
5. If transport to CTPA is problematic, supportive measures and empirical anticoagulation may be required.

Spanish Medical Societies (SPAIN):

1. When chest X-ray, electrocardiogram and arterial blood gas have ruled out alternative diagnoses in the hemodynamically stable patient, use Wells' or Geneva score to assess pre-test probability.
2. Initiate anticoagulant treatment if intermediate or high pre-test probability.

Low or intermediate clinical probability or PE unlikely

3. Measure D-dimer.
4. If elevated D-dimer (>500 µg/L), refer to CTPA.
5. If contraindications to CTPA, refer to V/Q scan.
6. If inconclusive scan or discrepancy between clinical probability and result, consider lower extremity ultrasound.

High clinical probability or PE likely

3. Do not measure D-dimer.
4. Refer to CTPA immediately.
5. If contraindications to CTPA, refer to V/Q scan.
6. If inconclusive scan or discrepancy between clinical probability and result, consider lower extremity ultrasound.

Hemodynamic instability

3. Initiate anticoagulation (preferably LMWH or fondaparinux) in intermediate probability patients while diagnostic work-up is in progress.
4. Refer to CTPA if elevated D-dimer. Consider further testing in case of discordance between clinical judgement and the CTPA result.
5. Planar V/Q may be considered if contraindications to CTPA or in younger patients and in female patients in whom thoracic CT might raise the lifetime risk of breast cancer.
6. If compression ultrasound has been performed, it is recommended to accept PE-diagnosis if a proximal DVT is found.

High clinical probability

2. Do not measure D-dimer (insufficient negative predictive value). Refer to CTPA.
3. If CTPA is negative, consider additional testing.
4. Initiate anticoagulation (preferably LMWH or fondaparinux) while diagnostic work-up is in progress.

Hemodynamic instability

2. Perform bedside TTE, TEE or lower extremity compression ultrasound.
3. If present RV dysfunction, right heart thrombus or DVT administer immediate reperfusion treatment without further testing.
4. When the patient is stabilized, confirm PE by CTPA.

European Association of Nuclear Medicine (EANM):

1. Assess clinical probability of PE by clinical judgement or by clinical prediction rules, foremost Wells' and revised Geneva score.
2. Where acute PE is suspected, administer heparin (unless contraindicated) until test result is known.

Low or intermediate clinical probability

3. Measure D-dimer. Values below a predefined cut-off (i.e., <500 µg/L with correction for age) can be used to exclude PE in patients of low and intermediate probability or who are PE-unlikely. The PERC strategy may reduce the number of D-dimer.
   tests in patients with very low clinical probability of PE, but caution is advised.
4. Refer to V/Q SPECT if elevated D-dimer. Planar V/Q should only be used when a patient for any reason cannot be examined by V/Q SPECT.
5. If V/Q SPECT is not available, refer to CTPA or planar V/Q.

High clinical probability

3. Do not measure D-dimer. Refer to SPECT V/Q.

Hemodynamic instability

3. Perform TTE or perfusion lung scintigraphy.
4. If these examinations suggest massive PE, thrombolytic therapy may be given.
5. If not already performed, a perfusion scan should be performed as soon as possible as a basis for follow-up.

PERT consortium (PERT):

1. After a comprehensive history and physical examination, determine pre-test probability, using Geneva or Wells' score.

Low or intermediate clinical probability

2. In patients with low probability, PERC rule may be used to identify patients for whom no D-dimer testing is indicated.
3. Measure D-dimer. Age- and risk-adjusted testing has higher specificity than the typical cut-off of 500 mg/L and may be useful to exclude PE in those patients with low-probability or PE-unlikely.
4. Refer to CTPA if elevated D-dimer. V/Q scan may be used if contraindications to CTPA.

High clinical probability

2. Do not measure D-dimer. Initiate anticoagulant treatment if bleeding risk is low.
3. Refer to CTPA or V/Q scan (if CTPA contraindicated).

Hemodynamic instability

3. If patient is stabilized, perform CTPA.
4. If patient is unstable preventing transfer to a scanner, perform TTE.
5. If present RV overload, administer fibrinolysis.

Japanese Circulatory Society (JCS):

1. Examine for DVT at once.
2. Start heparin therapy when PE is suspected.
3. Screen for other causes of dyspnea or chest pain using chest x-ray, electrocardiography, arterial blood gas, TTE and blood chemistry.

Mild or moderate suspicion

4. Measure D-dimer (cut-off not specified).
5. If elevated, refer to CTPA or V/Q scan.

Severe suspicion

3. Do not measure D-dimer.
4. Refer directly to CTPA or V/Q scan.

Hemodynamic instability

3. Apply percutaneous cardiopulmonary support and vasopressors.
4. Perform TEE or refer to CTPA.

PIOPED II investigators (PIOPED II):

1. Perform clinical assessment based on an objective method (Wells' or Geneva score). Physicians with experience in pulmonary embolism may apply empirical assessment.
2. Consider performing deep venous ultrasound prior to further diagnostics. Presence of a DVT allows treatment with no further obligatory testing.

Low probability

3. Measure D-dimer (cut-off not specified).
4. If negative D-dimer, additional testing with venous ultrasound or gadolinium enhanced magnetic resonance venography is optional.
5. If elevated D-dimer, perform CTPA in combination with CT venography of the proximal leg veins.
6. If main or lobar PE, administer treatment. In case of segmental or subsegmental PE, reassess certainty of CTPA diagnosis and consider V/Q scan, deep venous ultrasound, or pulmonary digital subtraction angiography.

Moderate probability

3. Consider treatment with anticoagulation while awaiting outcome of diagnostic test.
4. Measure D-dimer (cut-off not specified).
5. If negative D-dimer, additional testing with venous ultrasound or gadolinium enhanced magnetic resonance venography is optional.
6. If elevated D-dimer, perform CTPA in combination with CT venography of the proximal leg veins.
7. If negative CTPA alone, perform deep venous ultrasound.
8. If main or lobar PE, administer treatment. In case of segmental or subsegmental PE, reassess certainty of CTPA diagnosis and consider V/Q scan, deep venous ultrasound, or pulmonary digital subtraction angiography.

High probability

3. Administer anticoagulation while awaiting outcome of diagnostic test.
4. Do not measure D-dimer.
5. Perform CTPA in combination with CT venography of the proximal leg veins.
6. If CTPA is negative and CT angiography/CT venography was not done or was technically inadequate, a venous ultrasound or magnetic resonance venography is recommended.
7. Positive CTPA should lead to treatment regardless of PE location.

Hemodynamic instability

1. Perform bedside TTE or lower extremity compression ultrasound.
2. Enlargement or poor function of the RV and a DVT can be interpreted as resulting from PE.
3. Consider portable perfusion scan.
4. When the patient is stable, perform adequate imaging studies.

2. Perform bedside TTE, lower extremity ultrasound or portable V/Q (if available).
3. If present RV dysfunction, right heart thrombus, DVT or PE administer immediate reperfusion treatment without further testing.

Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ):

1. Apply clinical prediction rule. Most validated are the simplified Wells' and Geneva scores. Stratify as PE "unlikely" or "likely".

PE unlikely

2. In patients <50 years of age and rate of PE <15%, the PERC-criteria may rule out PE without D-dimer testing.
3. If PERC does not rule out PE, measure D-dimer.
4. Refer to CTPA if elevated D-dimer (cut-off not specified). If renal impairment, refer to V/Q scan instead.
5. If V/Q scan is non-diagnostic, perform CTPA or bilateral duplex ultrasound of lower limbs on day 1 and 7.

PE likely

2. Do not measure D-dimer.
3. Refer to CTPA or V/Q scan if renal failure.

American College of Emergency Physicians (ACEP):

1. Use the PERC criteria to rule out PE suspicion without further testing in patients with low pre-test probability.

Low to intermediate pre-test probability

2. In patients older than 50 years, with low or intermediate pre-test probability, a negative age-adjusted D-dimer may rule out suspicion of PE.

British Thoracic Society (BTS):

1. Assess clinical probability using Wells' score.
2. Consider performing deep venous ultrasound prior to further diagnostics. Identification of DVT precludes the need for further tests.

Low clinical probability

3. Measure D-dimer (cut-off not specified).
4. If elevated, refer to CTPA.

Intermediate clinical probability

3. Measure D-dimer (Vidas/MDA is available).
4. If elevated (or not available), initiate LMWH and refer to CTPA.

High clinical probability

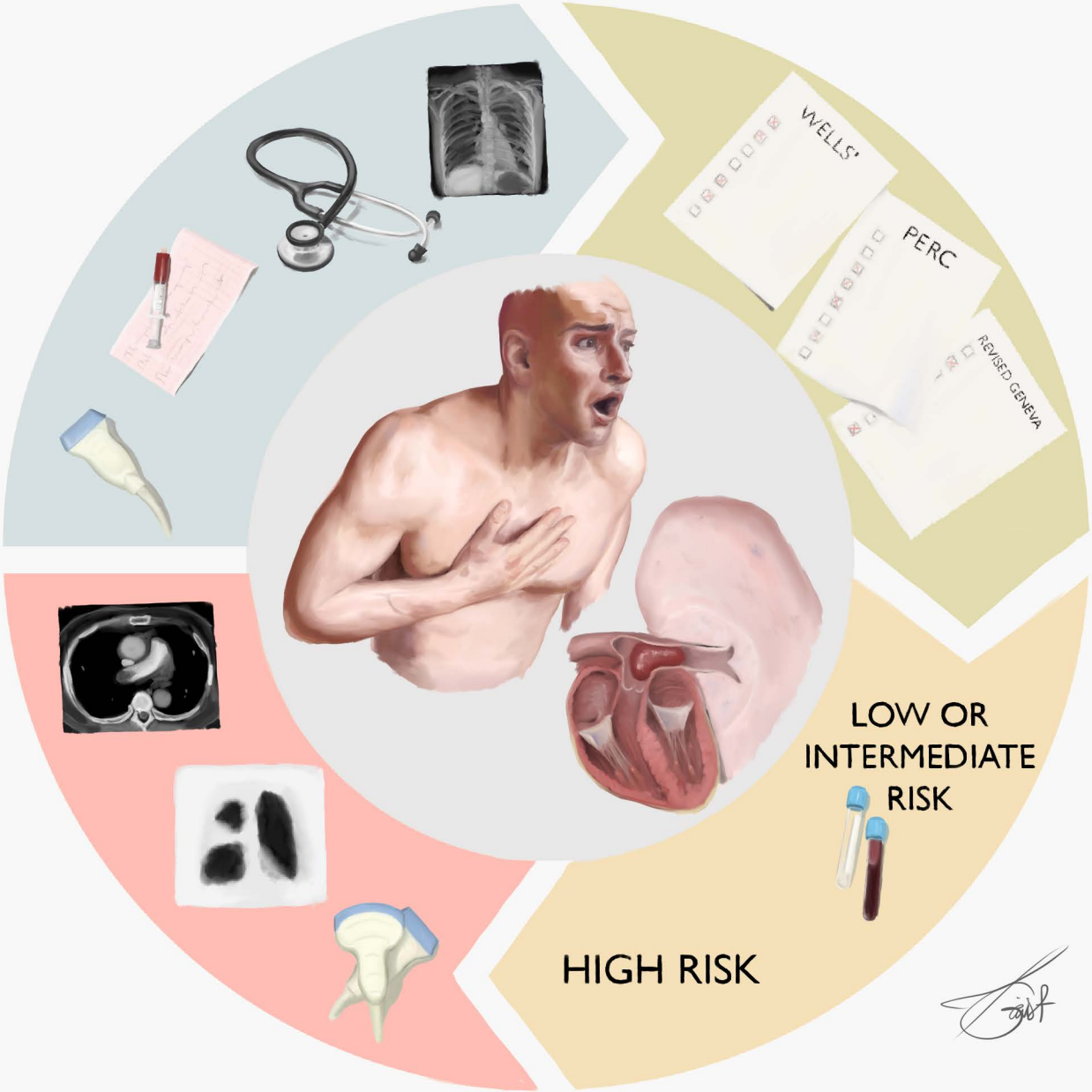
3. Do not measure D-dimer.
4. Initiate LMWH and refer to CTPA.

Hemodynamic instability

1. Perform bedside TTE, TEE or lower extremity compression ultrasound.
2. If present RV dysfunction, right heart thrombus or DVT, PE is confirmed, allowing administration of thrombolysis without further testing.

Table 2: Summary of suggested approach for diagnostic work-up of suspected pulmonary embolism for each guideline.

CTPA: CT Pulmonary Angiography. DVT: Deep Venous Thrombosis. LMWH: Low Molecular Weight Heparin. PE: Pulmonary Embolism. PERC: Pulmonary Embolism Rule Out Criteria. SPAIN: Spanish Medical Societies (Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Society Española Internal Medicine (SEMI). Spanish Society of Thrombosis and Haemostasis (SETH). Spanish Society of Cardiology (ESC). Spanish Society of Medicine Accident and Emergency (SEMES). Spanish Society of Angiology and Surgery Vascular (SEACV)). V/Q: Ventilation/perfusion scan. TEE: Trans Esophageal Echocardiography. TTE: Trans Thoracic Echocardiography.


WELLS'
PERC
REVISED GENEVA
LOW OR
INTERMEDIATE
RISK
HIGH RISK

APPENDIX

Appendix 1: Rationale behind level of recommendation by author group

All guidelines	
*	No level of recommendation
American College of Chest Physicians (ACCP)	
Strong	The panel is highly confident of the balance between desirable and undesirable consequences and make a strong recommendation for or against
Weak	The panel is less confident of the balance between desirable and undesirable consequences and make a weak recommendation for or against
American College of Emergency Physicians (ACEP)	
A	Generally accepted principles for patient care that reflect a high degree of clinical certainty
B	Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty
C	Recommendations for patient care that are based on case series or, in the absence of any adequate published literature, based on expert consensus
American College of Physicians (ACP)	
N/A	No reported grading of recommendations
American Heart Association (AHA)	
I	Procedure/treatment should be performed/administered
IIa	It is reasonable to perform procedure/administer treatment
IIb	Procedure/treatment may be considered
III	Procedure/treatment should not be performed/administered since it is not helpful and may be harmful
American Society of Hematology (ASH)	
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain
British Thoracic Society (BTS)	
A	At least one meta-analysis, systematic review, or RCT rated as high quality with very low risk of bias and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as well conducted with low risk of bias directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as high quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias or Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
C	A body of evidence including studies rated as well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as High quality systematic reviews of case-control or cohort studies or High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
D	Non-analytic studies, e.g., case reports, case series, expert opinion or Extrapolated evidence from studies rated as Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
European Association of Nuclear Medicine (EANM)	
N/A	No reported grading of recommendations
European Society of Cardiology (ESC)	
N/A	No reported grading of recommendations
European Society of Cardiology and European Respiratory Society (ESC/ERS)	
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective

IIa	Weight of the evidence/opinion is in favour of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful
Japanese Circulatory Society (JCS)	
I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
IIa	Conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy.
IIb	Conditions for which the Usefulness/efficacy is less well established by evidence/opinion
III	Conditions for which there is general agreement that a procedure/treatment is neither useful nor indicated and may be harmful.
National Institute of Health and Care Excellence (NICE)	
Offer	Where there is clear and strong evidence of benefit, we will use the word 'offer'.
Consider	Where the benefit is less certain we use the word 'consider'.
Prospective Investigation of Pulmonary Embolism Diagnosis II investigators (PIOPED II)	
N/A	No reported grading of recommendations
Pulmonary Embolism Response Team Consortium (PERT)	
N/A	No reported grading of recommendations
Spanish medical societies (SPAIN)	
N/A	No reported grading of recommendations
Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ)	
Strong	The panel is highly confident of the balance between desirable and undesirable consequences and make a strong recommendation for or against
Low	The panel is less confident of the balance between desirable and undesirable consequences and make a weak recommendation for or against
UpToDate	
N/A	No reported grading of recommendations

Appendix 2: Clinical decision rules

* Values of estimated prevalence are based on meta-analytic data by Ceriani et. al. (2010)

Wells' score

Clinical items	**Score**
Clinical signs and symptoms of DVT	+3
PE is most or equally likely diagnosis	+3
Heart rate > 100	+1.5
Immobilization ≥ 3 days or surgery in the previous 4 weeks	+1.5
Previous PE or DVT	+1.5
Hemoptysis	+1
Malignancy with treatment within 6 months or palliative	+1
Total score (trichotomous)	**Estimated prevalence***
< 2 (low probability)	≈ 6%
2 – 6 (intermediate probability)	≈ 23%
> 6 (high probability)	≈ 49%
Total score (dichotomous)	**Estimated prevalence***
≤ 4 (PE unlikely)	≈ 8%
> 4 (PE likely)	≈ 34%

Revised Geneva score

Clinical items		**Score**
Age >65 years		+1
Previous PE or DVT		+3
Surgery in general anesthesia or lower limb fracture within past month		+2
Malignant condition (active or cured within <1 year)		+2
Unilateral lower limb pain		+3
Hemoptysis		+2
Heart rate	75 – 94	+3
	≥ 95	+5
Pain on lower limb palpation and unilateral edema		+4
Total score		**Estimated prevalence***
< 4 (low probability)		≈ 9%
4 – 10 (intermediate probability)		≈ 26%
> 10 (high probability)		≈ 76%

Pulmonary Embolism Rule out Criteria (PERC)

Clinical items	**Score**
Age ≥ 50 years	+1
Heart rate ≥ 100	+1
O_2 saturation <95% without supplementary oxygen	+1
Unilateral leg swelling	+1
Hemoptysis	+1
Surgery or trauma within ≤ 4 weeks treated in general anesthesia	+1
Previous PE or DVT	+1
Oral contraceptives, hormone replacement or estrogenic hormone use	+1
Total score	**Estimated prevalence**
0	< 2%
≥ 1	≥ 2%

Search strategy and selection criteria

PubMed.org was searched on the 15th of November 2022 to identify guidelines on the diagnosis of pulmonary embolism. We used the following search string: *Pulmonary Embolism"[Mesh] OR pulm* embol* or pulm* thromboembol* AND "Guideline" [Publication Type]*. Guidelines specifically aimed at primary care, patients with cancer, pregnancy or COVID-19 were not considered, neither were guidelines not written in English or published prior to the year 2000. Only the most recent versions of guidelines from the same authors were eligible, unless different versions described separate aspects of PE-diagnosis. This approach yielded 11 clinical guidelines which were extracted and compared. We further included UpToDate, a widely used point-of-care medical resource. By evaluating reference lists of included guidelines, we further identified a guideline by the National Institute for Health and Care Excellence. When available, we also registered and compared reported evidence level of recommendations.