

2015



The Royal Australian
and New Zealand
College of Radiologists®

Education Modules for Appropriate Imaging Referrals

SUSPECTED PULMONARY EMBOLISM

PUBLICATION INFORMATION:

©Royal Australian and New Zealand College of Radiologists® 2015

More information is available on The Royal Australian and New Zealand College of Radiologists website:

URL: <http://www.ranzcr.edu.au/quality-a-safety/program/key-projects/education-modules-for-appropriate-imaging-referrals>

For educational purposes only.

The preferred citation for this document is:

Goergen S, Tran H, Jong I, Zallman M. Suspected Pulmonary Embolism. *Education Modules for Appropriate Imaging Referrals*: Royal Australian and New Zealand College of Radiologists; 2015.

ACKNOWLEDGEMENTS:

The *Education Modules for Appropriate Imaging Referrals* project is fully funded by the Australian Government Department of Health and Ageing under the Diagnostic Imaging Quality Projects Program.

The project has supported by the RANZCR's Quality and Safety Program Team:

Administrative support:

Madeleine Bromhead

Jessica Brown

Claire King

Project management:

Jane Grimm

TABLE OF CONTENTS

Authors:	3
1. Introduction	3
What is Pulmonary Embolism?	3
How can clinical decision rules help to standardise pre-test risk evaluation of patients with suspected pulmonary embolism?	4
What else do you need to think about when you consider imaging a patient with suspected PE apart from estimating the risk of serious pathology?.....	5
2. Clinical Decision Rules.....	6
How can clinical decision rules help to standardise pre-test risk evaluation of patients with possible pulmonary embolism?	6
The Wells Score and Simplified Wells Score.....	8
The Revised Geneva And Simplified Revised Geneva Scores.....	12
The Charlotte Rule	14
The Pulmonary Embolism Rule-out Criteria (PERC) Rule.....	15
Suspected PE in the pregnant/postpartum patient:.....	17
Principles Guiding the Diagnostic Evaluation of Possible Pulmonary Embolism in Pregnancy	17
3. What else do you need to think about, other than pre-test probability of pulmonary embolism, when you are considering performing diagnostic imaging in a patient with suspected PE?	21
Urgency:.....	21
Is imaging the best test?.....	21
Is there a generally accepted first line imaging test for Pulmonary Embolism, and if so what is it? Does this depend on the presence of markers of potentially more serious pathology?	21
Radiation dose:	21
Modality Table	22
References:	25
Appendix One: Evidence Summary Table	26
Appendix Two: Using CDRs for Suspected PE and selecting the investigative pathway.....	35
Appendix Three: Wells Score	36
Appendix Four: Simplified Wells Score	37
Appendix Five: The Charlotte Rule	38
Appendix Six: The PERC Rule	39

AUTHORS:

Stacy Goergen, MBBS, FRANZCR, MClInEpi

Director of Research, Department of Diagnostic Imaging, Monash Health, Melbourne, Australia
Adjunct Clinical Professor, Monash University, Department of Surgery, Southern Clinical School

Huyen Tran, MBBS, FRACP, PhD

Director, The Ronald Sawers Haemophilia Centre and Clinical Thrombosis Service,
Australian Centre for Blood Diseases, Melbourne, Australia
Adjunct Clinical Associate Professor, Monash University, Department of Medicine, Central and Eastern Clinical School

Ian Jong, MBBS, FRACP

Nuclear Medicine Physician, Monash Health, Melbourne, Australia

Michaela Zallman, MBBS

Royal Melbourne Hospital, Melbourne, Australia

1. INTRODUCTION

WHAT IS PULMONARY EMBOLISM?

Pulmonary embolism (PE) occurs with an incidence of 2-3 per 1000 adults per year. It is frequently fatal if left untreated, more often in hospitalised people than outpatients. The “classical” symptoms and signs, at presentation, of acute onset pleuritic chest pain with dyspnoea and/or hypotension and tachycardia are non-specific and diagnostic testing is needed to confirm or exclude the diagnosis of PE. This is important because undiagnosed PE can result in death while anticoagulant therapy is associated with an increased risk of haemorrhagic complications.

The usual source of PE is thrombosis in the deep veins (DVT) of the lower limbs or pelvis. However, only 30-40% of patients with PE will have demonstrable DVT at the time of presentation, so absence of DVT does not rule out PE. Predisposing factors include prolonged bed rest (due to prior surgery and hospitalisation or other causes, including long standing paralysis of one or both lower limbs), major trauma, and heritable or acquired prothrombotic tendencies. Examples of heritable thrombophilia include deficiency of natural anticoagulants (Protein C and Protein S and antithrombin) and factor V Leiden mutation. Causes of acquired thrombophilia include malignancy, hormone replacement/hormonal oral contraceptive and antiphospholipid antibody syndrome.

Diagnosis of PE is made using diagnostic imaging by direct (CT pulmonary angiogram) or indirect (ventilation/perfusion or “V/Q” lung scanning) demonstration of the emboli within the pulmonary arterial tree. The main challenge in the investigation of PE is to avoid unnecessary performance of imaging, which involves ionising radiation, in anyone with symptoms that might be due to PE. **Chest pain, cough, dyspnoea, and tachycardia are common presentations in the emergency department and most often are not due to PE.**

Clinical decision rules (CDRs) can help you to improve your specificity in identifying patients who are very unlikely, unlikely, and likely to have PE and to avoid performing imaging in the first two groups. Lucassen et al¹, in a 2011 systematic review comparing the use of CDRs to clinical gestalt in the diagnosis of PE, found CDRs, and in particular the Wells Score, to be more specific, but no less sensitive, than a gestalt impression of whether or not the patient had PE. Thus the use of CDRs in patients who might have PE can reduce unnecessary imaging, and the reduction in the need for imaging has been shown to be 20-25% in many studies. This represents an important way to prevent your patients being unnecessarily exposed to radiation and saves time and health care expenditure.

HOW CAN CLINICAL DECISION RULES HELP TO STANDARDISE PRE-TEST RISK EVALUATION OF PATIENTS WITH SUSPECTED PULMONARY EMBOLISM?

When evaluating patients with suspected PE, establishing the pre-test probability of PE is fundamental to determining which test, if any, to perform next in the diagnostic process.

At first, it might seem simpler, quicker, and safer simply to perform an imaging test on everyone with possible PE. When the pre-test probability of PE is not very low, the costs and risks of diagnostic imaging are more than outweighed by the considerable benefits of earlier diagnosis of a potentially serious disorder. These benefits can include simpler, less invasive treatment or guidance for surgical or medical therapy that prevent severe disability or death.

However, there are a number of disadvantages to the practice of referral of patients for imaging without first considering what the pre-test probability of PE is likely to be. They include:

- **Unnecessary exposure to ionising radiation.** This is particularly important in younger women with suspected PE who are more sensitive to the breast carcinogenic effects of exposure to ionising radiation than are women over 60. CT scanning is associated with around 100 times the dose of radiation delivered by a plain radiograph (or chest x-ray).
- **Financial cost to the patient and health system of unnecessary testing.** These costs are both direct and indirect (the latter due to waiting time in emergency departments, prolonged length of stay in a hospital, time away from work and other responsibilities waiting for imaging to be performed, having it performed, and then waiting for the result).
- **Incidental findings on imaging frequently have no clinical significance for the patient but trigger further imaging follow up to exclude the very small possibility of something significant.** An example of this includes a lung nodule demonstrated in a person at low/negligible risk of lung cancer discovered incidentally on a CT pulmonary angiogram performed to diagnose or exclude PE. The flow on costs to the patient and health system and the anxiety produced in some patients by follow up testing may not be considered when imaging is requested in a situation where pre-test probability of a condition is very low and imaging likely, therefore, to be unnecessary.
- **A test other than medical imaging may be a faster, less expensive way of ruling out clinically important pathology.** An example of this is the performance of D dimer in patients with suspected venous thromboembolism (either lower limb deep vein thrombosis or PE) when the pre-test risk is assessed as being low.

Continued increases in healthcare costs are a global problem. More than ever before, medical practitioners are being asked to be accountable for utilisation of finite health care resources and to add value and reduce waste in the care they deliver to patients. Reducing inappropriate use of diagnostic imaging in situations where it is highly unlikely to result in a net benefit to the patient is an important way to reduce waste and improve quality of care.

Please see the Clinical Decision Rules Module for more information about:

- **what CDRs are;**
- **how they are developed; and**
- **what the characteristics of a high quality CDR are.**

Resources: Something that will become apparent as you work through these modules is the difficulty involved in trying to commit the elements of CDRs to memory. It is a good idea to refer to an electronic or hard copy of the CDR each time you use it to ensure that you are applying it correctly. To support this, the following resources are provided:

- Printable PDFs of all of the CDRs including inclusion and exclusion criteria
- “Pocket-sized” PDFs suitable for printing, lamination, and attachment to a lanyard
- Links to the website MDCalc where you will find a calculator that allows you to enter clinical data for your patient into a clinical decision rule. This website does not feature all published CDRs for patients with suspected PE and does not discuss the reasons for featuring some and not others. However, this module will help you develop an understanding of the advantages and disadvantages as well as relative performance of the various CDRs. Go to the website now and try out the calculator for the Wells and PERC CDR:
 - www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/
 - www.mdcalc.com/perc-rule-for-pulmonary-embolism/
- For more information about specific imaging tests and procedures please see – www.insideradiology.com.au

WHAT ELSE DO YOU NEED TO THINK ABOUT WHEN YOU CONSIDER IMAGING A PATIENT WITH SUSPECTED PE APART FROM ESTIMATING THE RISK OF SERIOUS PATHOLOGY?

- **Test performance** (sensitivity, specificity, LR+ and LR-) in relation to the pathological process(es) you are trying to diagnose or exclude.
- **What is available locally, especially after hours or in an emergency?**
- **Radiation dose** – This is different for VQ scanning and CTPA and is discussed in more detail later in this module.
- **Financial and other costs to the patient and health system of one diagnostic strategy compared with another.**
- **Renal function** in the case of CTPA that uses iodinated contrast medium to demonstrate emboli within the pulmonary arteries.
- **History of anaphylactoid reaction to iodinated contrast media** – this would require an alternative test to CTPA (such as VQ) or alternatively premedication of the patient with corticosteroids.
- **Patient preferences** – if two diagnostic tests perform equally well at confirming or excluding the presence of a particular condition, patients may have a preference for one over another for reasons of cost, convenience, risk, or real/perceived discomfort associated with a particular diagnostic test or diagnostic strategy.

QUESTION 1.

Why is it important to assess a patient's pre-test risk of pulmonary embolism when you are considering this in your differential diagnosis? Select the SINGLE best answer.

- 1A. Patients at low risk do not require imaging as the first diagnostic test
- 1B. Patients at very low risk do not require further investigation at all
- 1C. Patients at higher risk are best evaluated with diagnostic imaging rather than D dimer assay
- 1D. Risk assessment helps you to interpret the results of subsequent diagnostic testing
- 1E. All of the above

CORRECT ANSWER:

1E. All of the above

2. CLINICAL DECISION RULES

HOW CAN CLINICAL DECISION RULES HELP TO STANDARDISE PRE-TEST RISK EVALUATION OF PATIENTS WITH POSSIBLE PULMONARY EMBOLISM?

Clinical assessment of the probability of pulmonary embolism is a crucial step in the diagnostic approach to patients with possible PE because performance and interpretation of subsequent tests depends on this assessment.

Because clinicians do not want to miss the diagnosis of PE, but also do not want to perform imaging on every patient with non-specific and common chest symptoms that might be due to PE, a great deal of effort has been expended over the past 15 years in developing CDRs for use in this situation.

When you are assessing a patient who might have PE, it is useful to think of the diagnostic process as consisting of 4 questions:

- 1. Is pulmonary embolism likely or unlikely? The definition of “likely” and “unlikely” in this context is a pre-test probability of PE of about 10% or less (“unlikely”) or greater than this (“likely”).**
- 2. If PE is “unlikely”, is the pre-test probability so low (2% or less) that I do not need to do further diagnostic tests?**
- 3. If PE is “unlikely” but not 2% or less, what test should I do next?**
- 4. If PE is “likely” what test should I do next?**

Although many clinical decision rules for pulmonary embolism have been developed, this module focusses on the four best performing and most validated tools. These are:

1. The Wells Score (and more recently the Simplified Wells Score);
2. The Geneva Score (and more recently the Simplified Revised Geneva Score);
3. The Charlotte Rule; and
4. The Pulmonary Embolism Rule-out Criteria.

For each CDR, you will find a summary statement that provides:

- an overview of the performance of the rule;
- general inclusion and exclusion criteria;
- precautions about routine clinical use of the CDR;
- more detailed information about these aspects of these CDRs can be found in the evidence table (Appendix One) at the end of the module. It allows rapid comparison of the performance, inclusion and exclusion criteria for each CDR.

Throughout this module, you will be presented with questions that will evaluate module content and also your ability to apply this to real clinical situations.

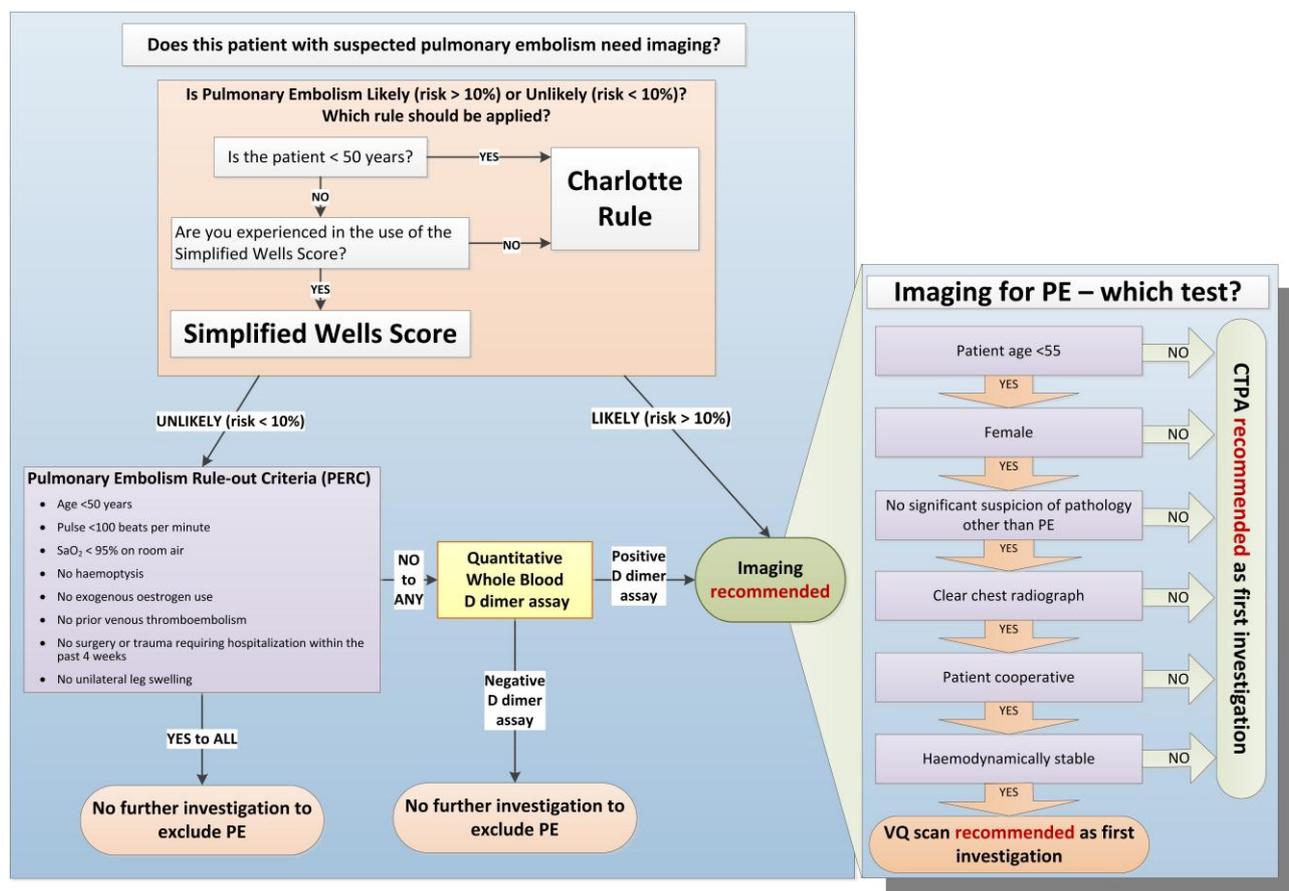


FIGURE 1: USING CDRS TO SELECT THE APPROPRIATE INVESTIGATIVE PATHWAY

If the D dimer is positive in a low likelihood patient OR a patient has a higher score with one of these CDRs, making the patient “unsafe” to be tested with D dimer alone, what test should I do?

- **CT pulmonary angiogram** – this involves a CT scan with injection of iodinated contrast medium into a peripheral vein. It is performed in the radiology/diagnostic imaging department.
- **Ventilation / Perfusion (VQ) lung scan** – this involves inhalation and intravenous injection of radioisotopes. It is a nuclear medicine test and may be performed either within a diagnostic imaging department / facility or the nuclear medicine department

Details about how you would decide about performing one test rather than the other are provided in a table later in this module.

Regardless of which one you choose, **it is important to perform a chest radiograph first** in any patient you suspect of having PE unless the patient is haemodynamically unstable due to possible massive PE and requires urgent CT scanning. The chest radiograph will help to show other diagnoses that may be the cause of the symptoms e.g.

- pneumothorax
- pneumonia
- larger lung cancers

It is also true that patients with an abnormal chest radiograph due to lung or pleural disease will most often have an indeterminate result on VQ scanning and so you should choose to do CTPA first in this situation as the result of VQ is likely to be unhelpful.

QUESTION 2.

Why is a chest radiograph an important first step in imaging patients with possible PE? Select all possible answers.

- 2A. A normal chest radiograph (x-ray) allows you to rule out pulmonary embolism in a patient who is at low risk (less than 10% pre-test probability of PE)
- 2B. The chest radiograph can allow you to make an alternative diagnosis as the cause for chest pain or shortness of breath
- 2C. There are specific chest radiograph abnormalities in most patients with PE
- 2D. Lung disease, such as pneumonia, on a chest radiograph makes it more likely that a VQ scan result will be indeterminate and thus CT pulmonary angiography becomes the preferred imaging modality to diagnose PE.
- 2E. All of the above

CORRECT ANSWER:

Chest radiography is an important first step in imaging patients with possible PE because:

- 2B. The chest radiograph can allow you to make an alternative diagnosis as the cause for chest pain or shortness of breath.
- 2D. Lung disease, such as pneumonia, on a chest radiograph makes it more likely that a VQ scan result will be indeterminate and thus CT pulmonary angiography becomes the preferred imaging modality to diagnose PE.

FEEDBACK: The plain chest radiograph is almost always normal in patients with PE and when it is abnormal the abnormality is most often non-specific.

THE WELLS SCORE AND SIMPLIFIED WELLS SCORE.

The **Original Wells Score**² was first published in 2000 and is the most validated and specific of the CDRs for risk assessment in patients with suspected pulmonary embolism. Specificity is important as the more specific the CDR is, the fewer patients there will be who are unnecessarily imaged due to being incorrectly classified as “likely” to have PE rather than “unlikely”.

The **Simplified Wells Score (SWS)**³ was developed so that each element in the CDR scored 1 point, potentially making it easier to use and remember than the original Wells Score. The cut off value distinguishing between “PE likely” and “PE unlikely” is 2, so patients with a score of 1 or 0 are classified as “PE unlikely” and suitable for D dimer testing rather than imaging.

The Simplified and original Wells Score are **associated with low “failure rates”** in that fewer than 0.5% of patients classified as “unlikely” who **also have a negative result on a quantitative D dimer assay** will eventually be diagnosed with PE.

The Wells and Simplified Wells Scores can be used in **inpatients or outpatients** but not people who have been anti-coagulated for 72 hours or more (see the next page for details of other exclusion criteria).

Both versions of the Wells Score have in common a **“gestalt” judgement on the part of the clinician about whether PE is the most likely diagnosis for that patient.** This can be hard to decide when you have limited clinical experience and thus use of this tool will often require consultation with someone with greater clinical experience in diagnosing pulmonary embolism when you lack the experience to make this judgement.

The SWS has been shown to be less specific than the original Wells Score in a systematic review by Lucassen et al in 2011¹. This means that although it is probably easier to use and potentially easier to remember, its use will probably result in more imaging of people without PE compared with the original Wells Score. This review also found that the Geneva Score and Revised Geneva Score were both associated with low “failure” rates, as for the Wells Score, but they were less specific, meaning that their use could be expected to result in more patients without PE being classified as “likely” and therefore more patients without PE imaged instead of being tested with D dimer¹.

THE WELLS SCORE

Predictor	Score
Clinical Signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)	+3
An alternative diagnosis is less likely than PE	+3
Heart rate greater than 100	+1.5
Immobilisation at least 3 days or surgery in previous 4 weeks	+1.5
Previous DVT/PE	+1.5
Haemoptysis	+1
Malignancy	+1
Total	/12.5

Risk of PE	Associated Score
Low (3% risk of PE)	<2
Moderate (28%)	2-6
High (78%)	>6

Risk of PE	Associated Score
Unlikely (5.1-7.8% rate of PE)	≤4
Likely (~40%)	>4

TABLE 1: THE WELLS SCORE

Summary Statement:

Based on the primary derivation study, a Wells' Score of ≤ 4 and a negative whole blood D dimer assay result is associated with a sufficiently low probability of PE that anticoagulation is not required and an alternative diagnosis should be sought.

In addition, the PERC rule may be used with patients with a score of ≤ 4 to determine who should have a D dimer and who requires no further testing for PE.

Inclusion Criteria:

(Unless ALL are satisfied, the Wells Score cannot be applied to assess the pre-test probability of PE)

- Inpatients or outpatients with clinical suspicion for PE
- Symptoms for < 30 days

Exclusion Criteria:

(If ANY these are satisfied, the Wells Score cannot be applied to assess the pre-test probability of PE)

- Suspected upper extremity DVT as source of PE
- No symptoms of PE for more than 3 days before presentation
- Use of anticoagulation for more than 72hrs
- Expected survival <3 months
- Contraindication to contrast media
- Pregnancy

QUESTION 3.

A 39 year old woman returns to Australia in July on a plane from London. 48 hours later she has shortness of breath and pleuritic chest pain and feels unwell. She takes oral contraceptives but has no other relevant past history and in particular has no history of cancer, deep vein thrombosis or pulmonary embolism. Her heart rate is 87 bpm, blood pressure 115 / 75, and examination of both lower limbs shows no abnormality.

Use the link below to the Wells Score calculator to enter relevant parts of the following clinical data.

<http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/>

PART 1 – Is this patient likely or unlikely to have PE?

3.1A. Unlikely to have PE

3.1B. Likely to have PE

PART 2 - What would you do next?

3.2A. Perform imaging to rule out PE

3.2B. Perform D dimer to rule out PE

3.2C. Use the PERC tool to determine if she is at such low risk of PE that further investigation is not needed

3.2D. None of the above

Note: more about PERC later!

CORRECT ANSWERS:

PART 1 - She is:

3.1A. Unlikely to have PE

FEEDBACK: In a previously healthy younger person, a diagnosis such as bronchitis or influenza is more likely than PE given this clinical information. Her score is 0, the Wells Score tells us that PE is unlikely in this woman.

PART 2 - What would you do next?

3.2C. Use the PERC tool to determine if she is at such low risk of PE that further investigation is not needed

FEEDBACK: As shown in the diagnostic process above (page 7), you should use the PERC tool to determine if she is at such low risk of PE that further investigation is not needed. More information about the PERC tool will be provided later.

THE SIMPLIFIED WELLS SCORE

Summary Statement:

This is a large study based on the Wells Score.³ It creates a simplified version of the Wells rule that is easier to follow and should be easier to apply in clinical situations. It is also a larger external validation of the Wells Score. It may be applied in adult inpatient and outpatients with confidence. The study found that using the Simplified Wells Score, a patient with a score of ≤ 1 and a negative D dimer has an extremely low probability of PE and an alternative diagnosis should be sought.

In addition, the PERC rule may be used with patients with a score of ≤ 1 to determine who should have a D dimer and who require no further testing for PE.

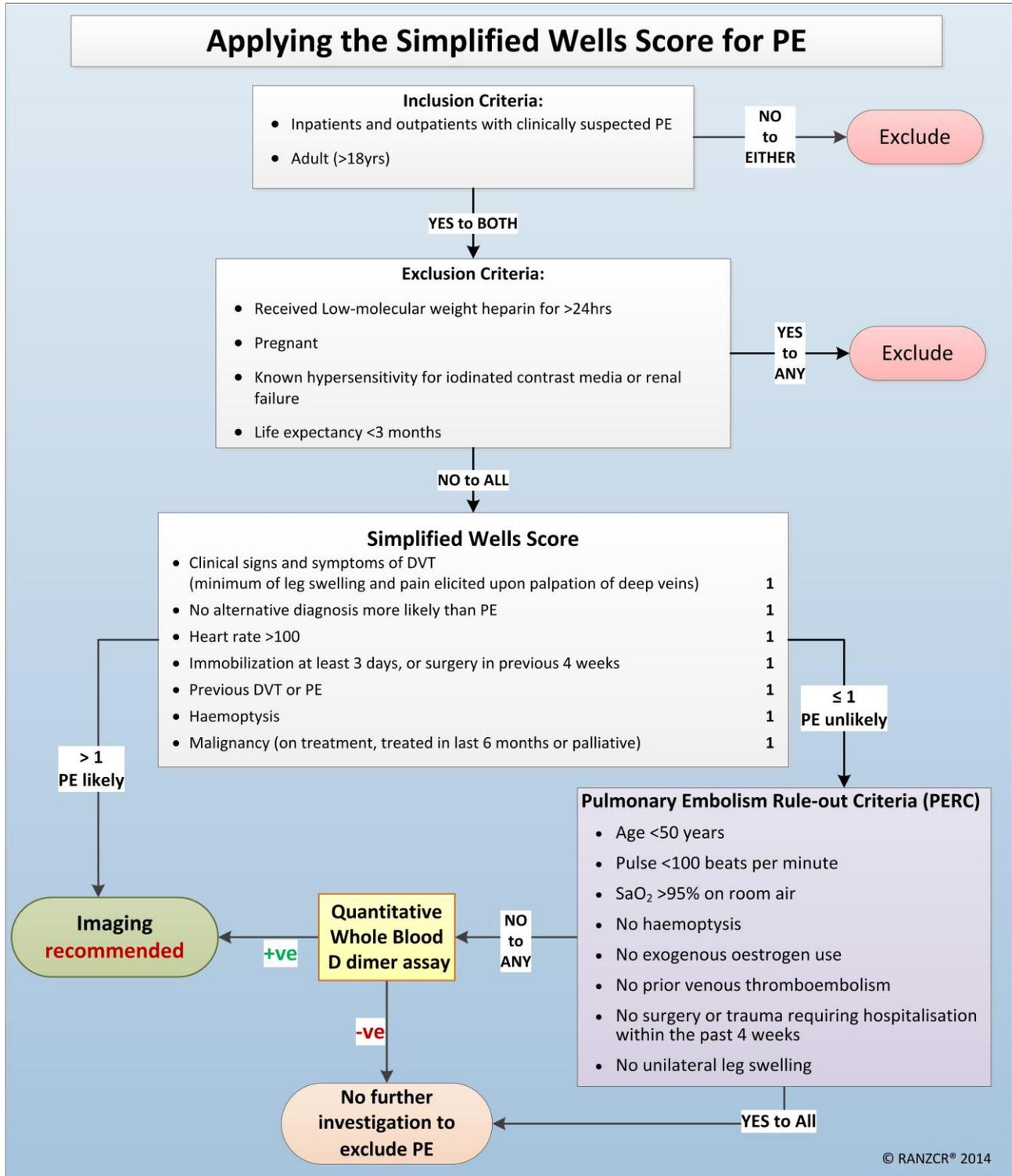


FIGURE 2: THE SIMPLIFIED WELLS SCORE.

THE REVISED GENEVA AND SIMPLIFIED REVISED GENEVA SCORES

These scoring systems were developed for use in the emergency department in patients with chest pain and/or new onset or worsening shortness of breath. As with the Wells Score, the original **Geneva Score**⁴ gave different weightings to the elements of the CDR and the **Simplified Revised Geneva Score (SRGS)**⁵ was an attempt to make this easier to use and remember.

The Revised Geneva Score allocated various scores to a number of clinical variables and summation of the scores resulted in patients being classified as low (<4), intermediate (4-10), or high (> or = 11) probability for PE.

The Simplified Revised Geneva Score (SRGS) resulted from two changes, based on reanalysis of the original data collected for the derivation of the Geneva Score. These changes were to allocate each decision rule item 1 point and to dichotomize the outcome, as for Wells Score, as low (score 0-2, PE unlikely, suitable for D dimer) or high (score more than 2, requires imaging for exclusion of PE).

EXERCISE

Compare the elements of the Simplified Revised Geneva Score and the Simplified Wells Score
What things are the same? Which ones are different?

THE REVISED GENEVA SCORE

Summary statement:

The Revised Geneva Score (RGS) developed by Le Gal et al⁴, has undergone limited validation for use in patients (age limitation not specified) admitted to an emergency department with possible pulmonary embolism (PE) (defined as new or worsening shortness of breath or chest pain without any other obvious cause). It allows classification of patients into 3 categories (low, intermediate and high) corresponding to an increasing pre-test probability of PE.

It has not been derived or validated for use in patients in the following situations:

- On anticoagulant treatment
- Who have a contraindication to contrast administration for CTPA (known allergy to iodinated contrast agents or risk for allergic reaction or very poor renal function)
- Pregnancy

Le Gal et al demonstrated that patients classified into the low-probability category had a 9.3% and 7.8% probability of having PE when applying the score in the derivation and validation populations, respectively. The NPV for PE of the combination of “low risk” defined in this way and negative D dimer was approximately 99%.

The Revised Geneva Score*	
Variable	Points
Risk Factors	
Age >65 y	1
Previous DVT or PE	3
Surgery (under general anaesthesia) or fracture (of the lower limbs) within 1 month	2
Active malignant condition (solid or haematologic malignant condition, currently active or considered cured <1 y)	2
Symptoms	
Unilateral lower-limb pain	3
Haemoptysis	2
Clinical Signs	
Heart rate, beats/min	
75-94	3
≥95	5
Pain on lower-limb deep venous palpation and unilateral edema	4
Clinical Probability	
Low	0-3 total
Intermediate	4-10 total
High	≥11 total
* DVT = deep venous thrombosis; PE = pulmonary embolism	

TABLE 2: THE REVISED GENEVA SCORE

Inclusions:

- Patients (age limitation not specified) admitted to the emergency department, in whom pulmonary embolism (PE) is suspected (new or worsening shortness of breath or chest pain without any other obvious cause).

Exclusions:

- Ongoing anticoagulant treatment; or
- Contraindication to CT (known allergy to iodinated contrast agents or risk for allergic reaction, creatinine clearance <0.5 mL/s (<30 mL/min)); or
- Pregnancy; or
- Suspected massive PE with shock; or
- Estimated life expectancy less than 3 months.

SIMPLIFIED REVISED GENEVA SCORE:

Scoring of the 8 Variables in the Simplified Revised Geneva Score	
Variable	Simplified
Age >65 y	1
Previous DVT or PE	1
Surgery (under general anaesthesia) or fracture (of lower limbs) within 1 month	1
Active malignant condition (Solid or haematologic, currently active or considered cured <1 y)	1
Unilateral lower-limb pain	1
Haemoptysis	1
Heart rate, beats/min	
75-94	1
≥ 95	1
Pain on lower-limb deep venous palpation and unilateral oedema	1
Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism	

TABLE 3: THE SIMPLIFIED REVISED GENEVA SCORE

Summary statement:

The Simplified Revised Geneva Score (SRGS) developed by Klok⁵ and colleagues by pooling data from two cohort studies, has undergone limited validation for use in patients (age limitation not specified) admitted to an emergency department with suspected PE (new or worsening shortness of breath or chest pain without any other obvious cause).

It has not been validated for use in patients on anticoagulant treatment, or who have a contraindication to CT (known allergy to iodinated contrast agents or risk for allergic reaction, creatinine clearance <0.5 mL/s (<30 mL/min)) or in pregnancy.

The only published external validation study of the SRGS, is a prospective cohort study by Douma, et al⁶ which demonstrated high sensitivity (99.5%) and LR- (0.016) of the SRGS when the low risk group is combined with a negative D dimer. This study found that the SRGS was less specific than the Wells Score when used in the same group of patients.

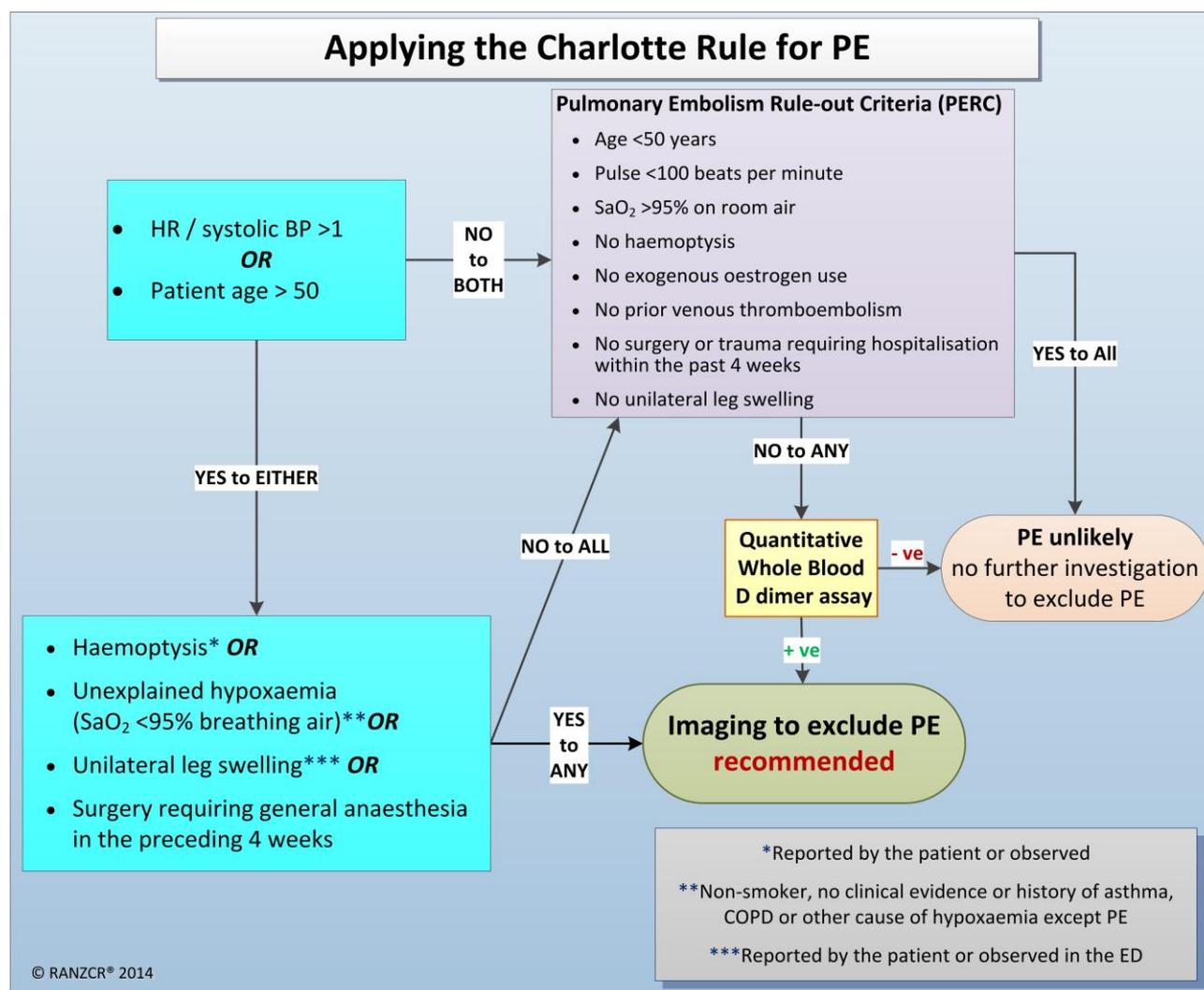
Inclusions:

- Patients (age limitation not specified) admitted to the emergency department, in whom pulmonary embolism (PE) is suspected (new or worsening shortness of breath or chest pain without any other obvious cause).

Exclusions:

- Ongoing anticoagulant treatment; or
- Contraindication to CT (known allergy to contrast iodine agents or risk for allergic reaction, creatinine clearance <0.5 mL/s (<30 mL/min), calculated by the Cockcroft-Gault formula; or
- Pregnancy; or
- Suspected massive PE with shock; or
- Estimated life expectancy less than 3 months.

THE CHARLOTTE RULE

FIGURE 3 APPLYING THE CHARLOTTE RULE ⁷**Summary Statement:**

This decision tool by Kline et al, 2002⁷ is for patients presenting to the emergency department in whom a board-certified emergency physician has enough suspicion for PE, to order a pulmonary vascular imaging study (either a contrast-enhanced CT scan of the chest or a ventilation-perfusion lung scan [V/Q scan]).

The rule has been extensively validated and safely rules out PE in patients classified as “Safe” or “Low probability” in the presence of a negative result using a sensitive whole blood D dimer assay (sensitivity of at least 90%)⁸. Its disadvantage in practice is that use of the Charlotte Rule may result in more patients over age 50 being triaged to imaging rather than D dimer due to the way the rule works than would be the case if the Wells Score were used. This may lead to more imaging in this particular age group than if the Simplified Wells Score was used but the Charlotte Rule has the advantage of potentially more reproducible rule criteria and does not require the user to make a subjective judgement about whether PE is more likely than another diagnosis.

Patients who are classified as “unlikely” for PE with the Charlotte Rule, who also have a negative result on a sensitive whole blood D dimer assay, have a probability of PE of 2% or less and thus require no further investigation, such as imaging, to exclude PE.

In addition, the PERC rule may be used with patients identified as “unlikely” to determine those who should have a D dimer test and those who require no further testing for PE.

THE PULMONARY EMBOLISM RULE-OUT CRITERIA (PERC) RULE

The stimulus for development of this rule by Kline et al⁹ was the frequent “false positive” D dimer results in patients assessed as low risk using the Wells or Geneva Score who then had D dimer assay performed in preference to imaging. When D dimer is positive in this situation, clinicians are obliged to rule out PE using imaging, but 50% or fewer patients with low risk and positive D dimer end up having PE.

The PERC CDR helps you to decide whether you need to do any investigation for PE, including D dimer. Some studies have shown that a “gestalt” (or overall clinical impression) of low risk of PE prior to applying the PERC rule is just as good as undertaking a formal risk assessment using the Simplified Wells, Simplified Revised Geneva, or Charlotte CDRs.¹⁰ However, it is probably safer to establish a low pre-test risk with one of these tools prior to using the PERC tool to determine if no further investigation needs to occur.

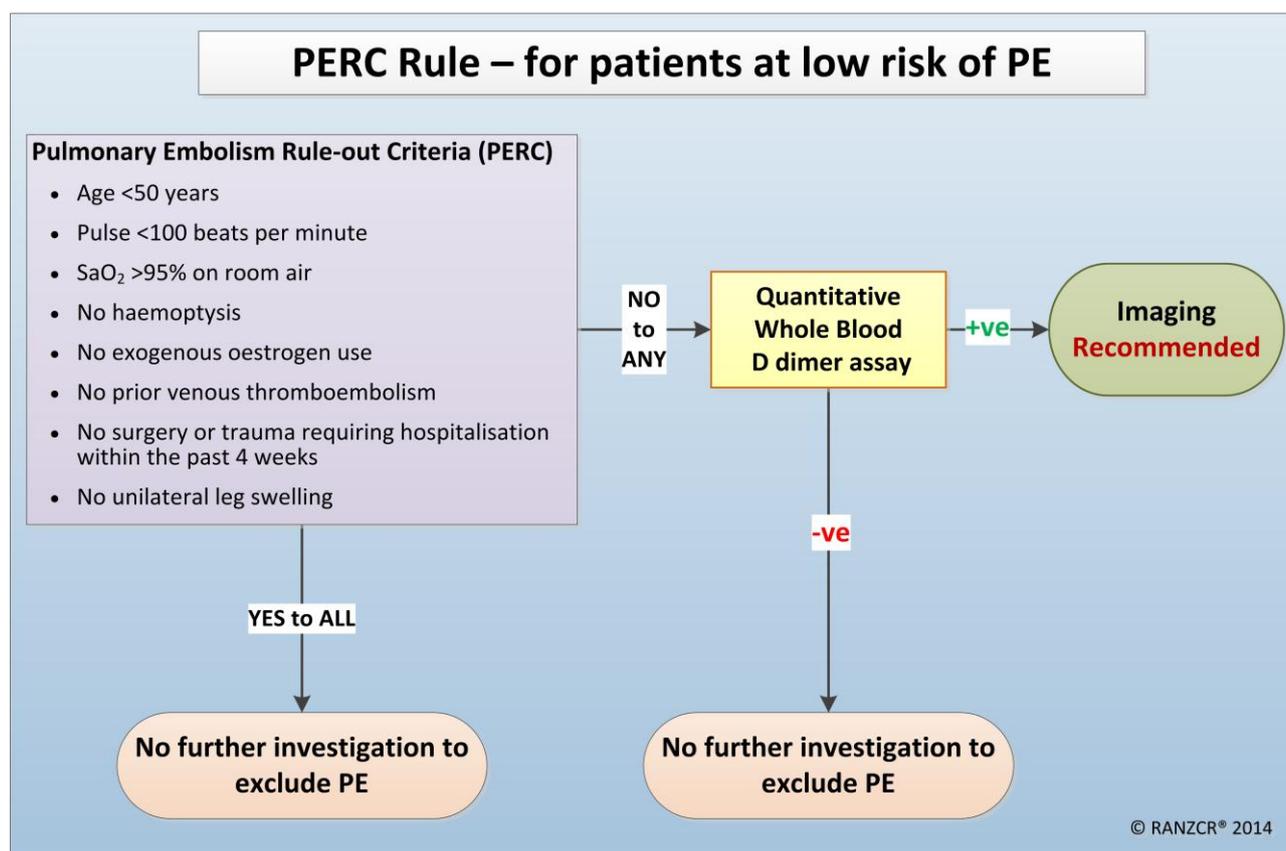


FIGURE 4: THE PERC RULE

Patients at low or very-low risk of PE (the population for whom the rule is intended), who meet the rule criteria (i.e. answer YES to the 8 clinical variables), are deemed PERC negative.

The authors found that PERC negative patients have a probability of PE <1.8%, and hence, are safe to have PE excluded without further diagnostic testing, since the post-test probability of PE after a negative VQ scan is greater than 1.8%

Summary Statement:

The Pulmonary Embolism Rule-out Criteria (PERC) score has undergone extensive validation and can be used for adult patients presenting to the emergency department with a sole or primary complaint of shortness of breath and low clinical suspicion of PE. When all 8 predictors that comprise the rule are **positive**, further diagnostic testing for PE is not required since the post-test probability of PE is below the test threshold of 1.8%. In PERC(-) patients, the rule has a sensitivity of 96% (90-99%), specificity of 27% (25-30%), false negative rate of 1.4% (0.5-3.0%) and a LR- of 0.015. In a very low risk PERC(-) population, the rule performs better still; with sensitivity 100% (96-97.5%), specificity of 15% (11-18%) and LR- of 0.067. It has not been validated, and therefore should not be used in patients with high or intermediate probability of PE.

The PERC rule has been externally validated in a number of studies, including a systematic review and meta-analysis. The systematic review and meta-analysis by Singh et al¹¹, concluded that their pooled analysis strongly corroborates

the safety of using PERC to avoid D dimer testing, reflected in the results of existing literature suggesting consistently high sensitivity and low but acceptable specificity of the PERC rule. However, an impact analysis by Kline et al⁷ suggests that while just over one fifth of surveyed clinicians are electing to use the rule in eligible patients in clinical practice, only 5% of these document the rule without missing any components. **This underlines the importance of referring to an electronic or hard copy when you use a CDR to remind you of the elements and the inclusion/exclusion criteria.**

Inclusions:

- Patients presenting to the ED with clinical suspicion of PE (board- certified emergency physician felt a formal evaluation for pulmonary embolism was necessary).

Exclusions:

- No clear exclusion criteria described

QUESTION 4.

A 28 year old woman presented to the emergency department with a 2 day history of shortness of breath associated with right sided pleuritic chest pain. She had an uncomplicated vaginal delivery of a healthy male infant 3 months ago. She reports two days of cough but no sputum production. She is a non-smoker and is not on oral contraceptive pills. She has no other relevant medical history. On examination, her chest is clear, heart rate 81 bpm, SaO₂ 96% breathing room air (by pulse oximeter) and she has no swelling in her lower limbs.

Use the links to the Wells Score calculator to determine if PE is likely or unlikely in this patient.

<http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/>

Part 1 - Her chest X-ray reveals no abnormality. Is this patient likely or unlikely to have pulmonary embolism?

4.1A. PE is likely

4.1B. PE is unlikely

Part 2 - Now use the Charlotte Rule to determine if PE is likely or unlikely (the Charlotte rule calls this “safe for D dimer testing” when PE is unlikely and “unsafe for D dimer testing” when PE is likely). Do you get the same result as for the Wells Score?

4.2A. Yes

4.2B. No

Part 3 - Use the PERC calculator; is it safe to manage this patient without performing D dimer to screen for PE? <http://www.mdcalc.com/perc-rule-for-pulmonary-embolism/>

4.3A. Yes

4.3B. No

CORRECT ANSWERS:

Part 1. Her chest X-ray reveals no abnormality. Which one of the following statements is correct?

4.1B. PE is unlikely

Part 2. Using the Charlotte Rule, do you get the same result as for the Wells’ score?

4.2A. Yes

FEEDBACK: PE is unlikely

Part 3. Use the PERC calculator; is it safe to manage this patient without performing D dimer to screen for PE?

4.3A. Yes

FEEDBACK: according to the PERC score it is safe to manage this patient without using D dimer to screen for PE.

SUSPECTED PE IN THE PREGNANT/POSTPARTUM PATIENT:

Background/Introduction:

Pulmonary embolism in pregnancy and the postpartum period is an important cause of preventable maternal morbidity and mortality. Failure to investigate symptoms suggestive of PE is a consistent finding in maternal death enquiries, and clinical symptoms should not be relied on to exclude or diagnose VTE.

- When a woman becomes pregnant, her risk of venous thromboembolism (VTE) increases by two- to five-fold compared with the non-pregnant population of the same age with an overall absolute incidence of 0.5 to 2 per 1000 pregnancies¹².
- Her risk of fatal PE is 0.79 to 1.94 per 100 000 pregnancies^{13, 14}
- During pregnancy, there are physiological changes that can increase the thrombotic tendency. These include changes in hormonal levels such as an increase in the plasma oestrogen level, a reduction in naturally occurring anticoagulants (antithrombin and Protein C and Protein S levels) and physical changes such as compression of pelvic veins by the gravid uterus, as well as increasing venous capacitance that results in reduced blood flow.
- There is consistent epidemiological evidence that **the post-partum period is the period of highest VTE risk per day in pregnancy**, estimated to be increased by 15- to 30-fold when compared with age-matched non-pregnant control¹⁵.

PRINCIPLES GUIDING THE DIAGNOSTIC EVALUATION OF POSSIBLE PULMONARY EMBOLISM IN PREGNANCY

1. **Risk assessment strategies that are used for non-pregnant patients are not suitable for use in pregnancy** because they have not been validated in this patient group.
2. **D dimer becomes physiologically elevated in most patients after the first trimester.** Normal values for each trimester have yet to be validated in a large patient population to enable them to be used to screen for the possibility of pulmonary embolism during pregnancy in routine clinical practice. Therefore, D dimer is generally not used to screen pregnant women for suspected PE, particularly during the second and third trimester when it is physiologically elevated.
3. **If PE is suspected in a pregnant woman, a chest radiograph should be performed to:**
 - a. Rule out other causes of the symptoms, such as pneumonia
 - b. Determine if VQ or CTPA should be performed as the diagnostic test to diagnose PE
4. **If the chest radiograph is clear, VQ scan using a lower dose technique is recommended** as it is associated with a lower breast dose than CTPA and a comparably small dose to the fetus.
5. **Lower limb venous ultrasound is negative in more than 90% of pregnant women with PE. Lower limb venous ultrasound is not recommended as a first line investigation unless there are clinical symptoms of DVT (e.g. unilateral leg swelling, calf tenderness).** This is because of the very low rate of lower limb deep venous thrombosis in pregnant women with PE. Almost no VQ scans or CTPAs would be avoided in pregnant women with possible PE by performing ultrasound first because ultrasound is almost invariably negative in this situation when there are no specific symptoms of DVT. Therefore, the reduction in radiation exposure to the population of women with possible PE and their fetuses that would result from an “ultrasound first” strategy is negligible.

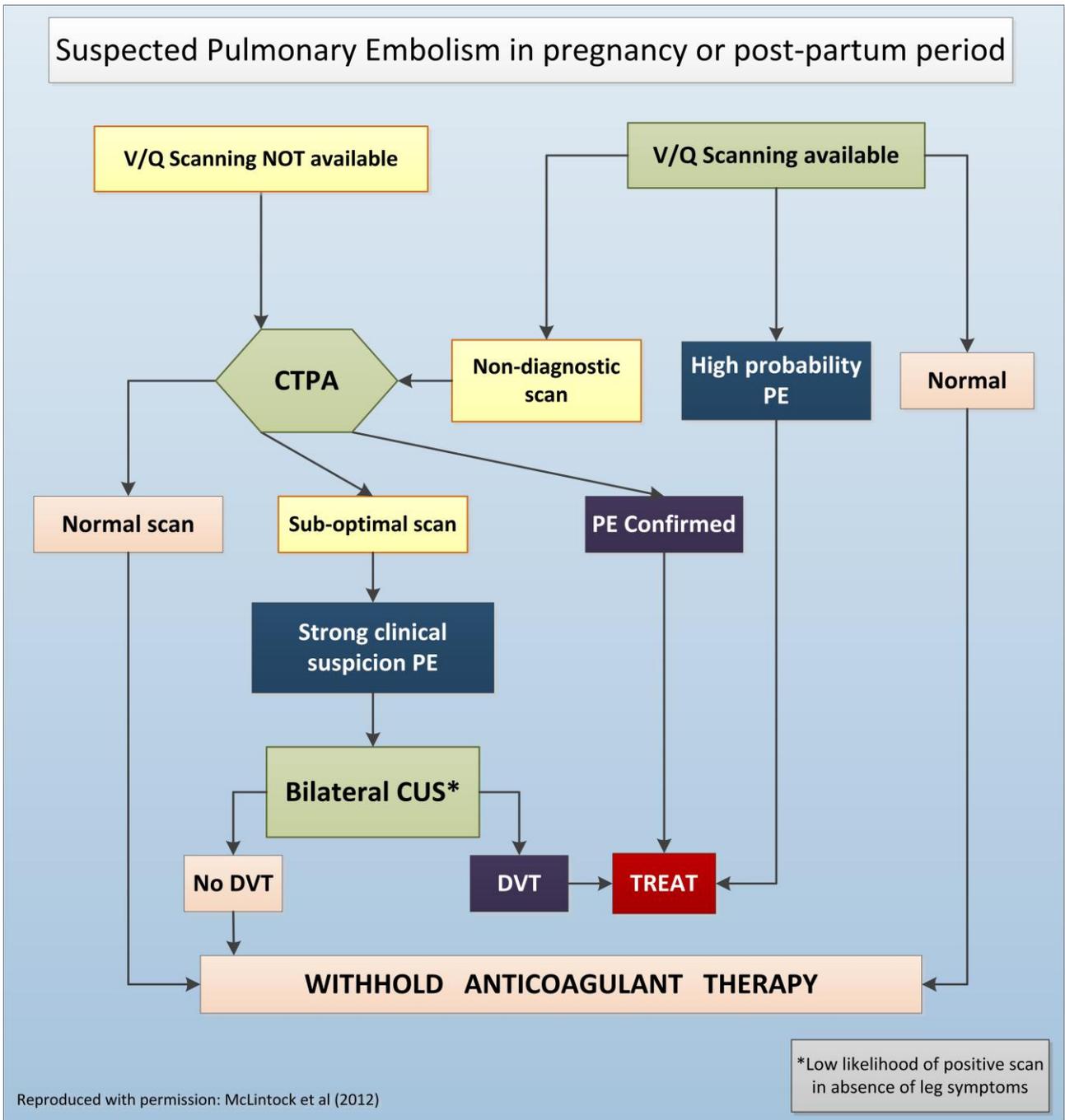


FIGURE 5: DIAGNOSTIC PATHWAY FOR SUSPECTED PULMONARY EMBOLISM IN PREGNANCY. FLOW DIAGRAM FROM MCLINTOCK ET AL 2012¹⁶

QUESTION 5.

Which of the following are true of suspected pulmonary embolism in a pregnant woman? Select all possible answers.

- 5A. The prevalence in most clinical series is < 10%
- 5B. Ventilation perfusion (VQ) scanning confers a lower radiation dose to the breast than does CT pulmonary angiography (CTPA)
- 5C. D dimer is useful for screening pregnant women at low risk for PE in order to avoid the need for imaging
- 5D. Lower limb compression ultrasound shows evidence of DVT in about 35% of pregnant women with PE
- 5E. The radiation dose conferred to the fetus is substantially lower for CTPA than for VQ

CORRECT ANSWER:

The following are true:

- 5A. The prevalence in most clinical series is < 10%
- 5B. Ventilation perfusion (VQ) scanning confers a lower radiation dose to the breast than does CT pulmonary angiography (CTPA)

FEEDBACK: D dimer is physiologically elevated in mid to late pregnancy when most women present with suspected/actual PE). The fetal dose from conventional VQ scanning and CTPA is comparable. Demonstrated lower limb DVT on duplex compression ultrasound is uncommon in pregnant women with PE.

QUESTION 6.

A 35 year old woman who is 13 weeks pregnant presents with suspected pulmonary embolism. She has a normal chest X-ray. What is the most appropriate investigation to exclude or confirm PE?

- 6A. CT pulmonary angiogram
- 6B. Duplex Doppler and Compression Ultrasound of the lower limbs
- 6C. Pulmonary Angiography via femoral route
- 6D. Ventilation-Perfusion Lung scan (V/Q)
- 6E. Magnetic Resonance Imaging (MRI)

CORRECT ANSWER:

The most appropriate investigation to exclude or confirm PE:

- 6D. Ventilation-Perfusion Lung scan (V/Q)

QUESTION 7.

Which of the following best describes the utility of the Wells Score for patients presenting with suspected PE? Select all possible answers.

- 7A. It should be applied to all patients during pregnancy only
- 7B. It should be applied to all patients in the post-partum period only
- 7C. It should be applied to all patients during pregnancy and the post-partum period
- 7D. It has not been validated for use in pregnancy
- 7E. It should be used when the CXR is normal

CORRECT ANSWER:

The following best describes the utility of the Wells Score:

- 7D. It has not been validated for use in pregnancy

QUESTION 8.

Which of the following best describes the utility of the D dimer for patients with suspected PE? Select all possible answers

- 8A. It is equally useful for both inpatients and outpatients
- 8B. It is equally useful in pregnant and non-pregnant patients
- 8C. It need not be measured in patients with a high pre-test probability score for PE
- 8D. A negative D dimer result in patients with a “PE likely” score means that further imaging is unnecessary.
- 8E. A positive D dimer result in patients with a “PE unlikely” score means that further imaging is unnecessary.

CORRECT ANSWER:

The following best describes the utility of the D dimer for patients with suspected PE:

- 8A. It is equally useful for both inpatients and outpatients
- 8C. It need not be measured in patients with a high pre-test probability score for PE

3. WHAT ELSE DO YOU NEED TO THINK ABOUT, OTHER THAN PRE-TEST PROBABILITY OF PULMONARY EMBOLISM, WHEN YOU ARE CONSIDERING PERFORMING DIAGNOSTIC IMAGING IN A PATIENT WITH SUSPECTED PE?

URGENCY:

Once you have risk assessed a patient with clinical features that might be attributable to PE and they are either:

- a. Classified as “likely” to have PE (depending on the CDR you use, this generally equates to a pre-test risk of more than 13%); OR
- b. Classified as unlikely but they have a positive D dimer.

It is generally considered urgent (within a few hours if they are stable, or within minutes if they are haemodynamically unstable) to obtain imaging to rule out this diagnosis. Patients with evidence of hypotension/tachycardia/severe hypoxia in this situation generally need to have a CTPA urgently and are best managed in an emergency department.

IS IMAGING THE BEST TEST?

Imaging should be performed in ALL patients in either of the two situations described above. Positive D dimer does not equate to a diagnosis of PE or deep venous thrombosis as it is non-specific. The diagnosis of PE can only be made with certainty using imaging. This certainty is generally important because of the risks associated with several weeks of anticoagulation used to treat patients with PE.

D dimer assay on a sample of peripheral blood is used to exclude PE in low risk individuals because when it is negative in this setting, imaging is not required.

IS THERE A GENERALLY ACCEPTED FIRST LINE IMAGING TEST FOR PULMONARY EMBOLISM, AND IF SO WHAT IS IT? DOES THIS DEPEND ON THE PRESENCE OF MARKERS OF POTENTIALLY MORE SERIOUS PATHOLOGY?

The best test to perform in the setting of suspected PE depends on:

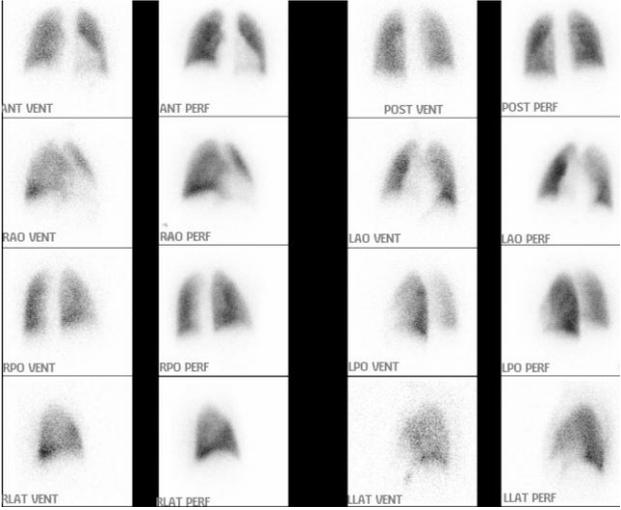
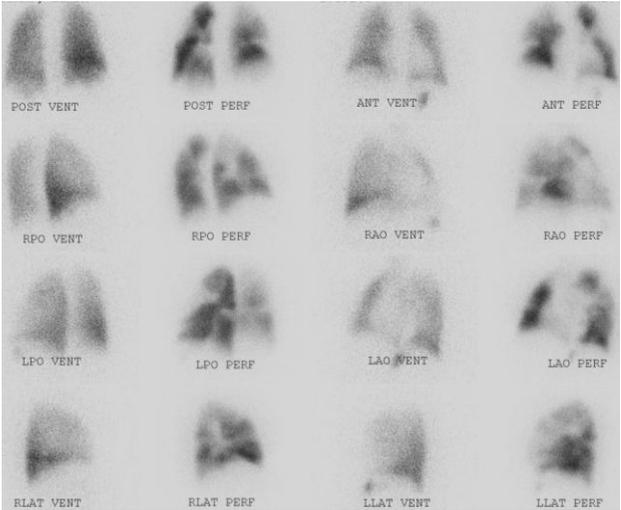
- a. Pre-test probability of PE;
- b. Whether the chest radiograph is normal; and
- c. Whether you are considering other causes for the clinical presentation such as aortic dissection, pneumothorax, lung cancer, pneumonia or a pleural collection (such as fluid or empyema).

RADIATION DOSE:

The dose to the breast is much lower for VQ scanning than for CTPA and thus it is the preferred test in women in the reproductive age group with:

- a. A clear chest radiograph; or
- b. No significant clinical suspicion of another diagnosis.

MODALITY TABLE

MODALITY	STRENGTHS	WEAKNESSES	COMMENTS
<p>V/Q scan</p> <p>Link - http://www.insideradiology.com.au/pages/view.php?id=65</p>	<ul style="list-style-type: none"> Significantly lower radiation dose when compared to CTPA More sensitive in diagnosing peripheral pulmonary embolus. Less prone to suboptimal image quality due to either poor contrast opacification of pulmonary vessels or respiratory motion artefact as might be seen in up to 6% of all CTPA studies. Safe to be performed in the following patients in whom CTPA is relatively or absolutely contraindicated: <ol style="list-style-type: none"> Iodinated contrast hypersensitivity Patients with severe renal impairment (eGFR <40) or with higher eGFR but acutely declining function due to the theoretical risk of iodinated contrast inducing further deterioration in renal function Premenopausal women, in whom the radiosensitive breast tissues will receive only a very small fraction of breast radiation when compared to CTPA. Pregnancy (the fetal dose for CTPA and VQ is extremely small and comparable but the breast dose from VQ is much lower) 	<ul style="list-style-type: none"> V/Q scan cannot diagnose other potentially fatal conditions such as aortic dissection to account for patient’s symptoms when pulmonary embolism is excluded. It does not offer clues to the aetiology for patients with pulmonary embolism such as the presence of previously undetected malignancy. Not useful for patients who are haemodynamically unstable (e.g. due to massive PE) and / or in cardiac failure OR uncooperative for any reason. V/Q scan requires up to 30 minutes to complete, if only planar ventilation and perfusion images were performed, and will require even longer period to complete if SPECT (Single Photon Emission Computer Tomography) images are considered. Therefore, the patient must be relatively co-operative and be able to lay relatively flat and still for the test. Diagnostic accuracy may be compromised if the baseline CXR is abnormal, especially if only planar images were performed. Hence patients with chest radiograph abnormalities such as a mass, pneumonia, or a pleural effusion are better imaged with CTPA. 	 <p>Figure 4: Planar Ventilation and Perfusion Images – Normal study</p>  <p>Figure 5: Planar Ventilation and Perfusion Images – Bilateral multiple pulmonary emboli</p>

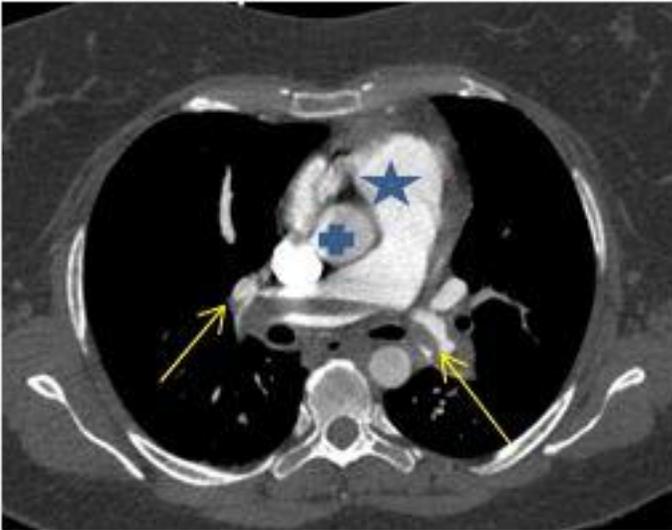
MODALITY	STRENGTHS	WEAKNESSES	COMMENTS
CT Pulmonary Angiogram	<ul style="list-style-type: none"> CT is widely available 24 / 7 where an emergency department is located CTPA takes < 15 minutes to perform from arrival of the patient and requires the patient to remain still for only a few seconds. Shows emboli in the main, right, left, lobar, and segmental pulmonary arteries Can demonstrate other causes of the same presentation e.g. pneumonia, aortic dissection, lung cancer 	<ul style="list-style-type: none"> Known iodinated contrast allergy is an absolute contraindication. Premedication with steroids takes over 24 hours to complete but emergency premedication protocols are available if the patient is suspected to have massive PE or cannot have V/Q (see disadvantages of V/Q above) Radiation dose to the breast substantially higher than for V/Q particularly when the breast is most radiosensitive (prior to menopause, pregnancy, lactation). Radiation dose to the fetus comparable to V/Q (Ref: http://www.insideradiology.com.au/pages/view.php?T_id=96) Iodinated contrast can theoretically further impair renal function in patients with acutely declining function or stable severe chronic renal impairment (eGFR<40) (Ref: http://www.insideradiology.com.au/pages/view.php?T_id=21&ref_info) 	 <p>Figure 6: CT pulmonary angiogram in a young woman with profound hypotension noted in the recovery room following a minor surgical procedure. The arrows indicate emboli in the right and left main pulmonary arteries and a “saddle” embolus connecting the two. The star shows a dilated main pulmonary artery (larger than the diameter of the ascending aorta, which is indicated with a cross) indicative of pulmonary hypertension due to massive embolism.</p>

TABLE 4: IMAGING MODALITIES FOR PULMONARY EMBOLISM

QUESTION 9.

A 55 year old male sales executive returned from an overseas business trip to Brussels one week ago. He now presents to an emergency department in Sydney with acute onset of left sided chest pain, worse with inspiration and associated with shortness of breath at rest. He has no cough or sputum production and is a lifelong non-smoker. His other relevant medical history is that he is a type II diabetic with normal renal function and is currently well controlled on metformin. On examination, he is afebrile, has sinus tachycardia (115bpm), tachypnoea (22 breaths per min), and is haemodynamically stable. On auscultation, his lungs are clear. He has a normal CXR.

Links to relevant clinical decision rules are provided below:

<http://www.mdcalc.com/perc-rule-for-pulmonary-embolism/>

<http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/>

PART 1 – Which one of the following investigations should be performed next?

- 9.1A. He should be investigated with CTPA immediately because he has a high pre-test probability for pulmonary embolism.
- 9.1B. He should be investigated with V/Q scan immediately because he has a high pre-test probability for pulmonary embolism
- 9.1C. He should have D dimer performed because the pre-test probability of PE is low
- 9.1D. Either A) or B) is appropriate depending upon availability of emergency VQ scanning and whether or not other causes of the clinical presentation are considered possible, such as lung cancer or aortic dissection
- 9.1E. He should have a formal blood gases analysis to confirm the presence of hypoxia

CORRECT ANSWERS:

Part 1. Which one of the following investigations should be performed next?

9.1D. Either A) or B) is appropriate depending upon availability of emergency VQ scanning and whether or not other causes of the clinical presentation are considered possible, such as lung cancer or aortic dissection.

REFERENCES:

1. Lucassen W, Geersing GJ, Erkens PM, Reitsma JB, Moons KG, Buller H, et al. Clinical decision rules for excluding pulmonary embolism: A meta-analysis. *Ann Intern Med.* 2011; 155(7): 448-60.
2. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. 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; 83(3): 416-20. Stuttgart.
3. Gibson NS, Sohne M, Kruip MJ, Tick LW, Gerdes VE, Bossuyt PM, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. *Thromb Haemost.* 2008; 99(1): 229-34.
4. Le Gal G, Righini M, Roy P, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: The Revised Geneva Score. *Ann Intern Med.* 2006; 144(3): 165-71.
5. Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, et al. Simplification of the Revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med.* 2008; 168(19): 2131-6.
6. Douma RA, Gibson NS, Gerdes VE, Buller HR, Wells PS, Perrier A, et al. Validity and clinical utility of the Simplified Wells rule for assessing clinical probability for the exclusion of pulmonary embolism. *Thromb Haemost.* 2009; 101(1): 197-200.
7. Kline JA, Nelson RD, Jackson RE, Courtney DM. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: A multicenter US study. *Ann Emerg Med.* 2002; 39(2): 144-52.
8. Ceriani E, Combescure C, Le Gal G, Nendaz M, Perneger T, Bounameaux H, et al. Clinical prediction rules for pulmonary embolism: A systematic review and meta-analysis. *J Thromb Haemost.* 2010; 8(5): 957-70.
9. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost.* 2004; 2(8): 1247-55.
10. Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the Pulmonary Embolism Rule-out Criteria. *J Thromb Haemost.* 2008; 6(5): 772-80.
11. Singh B, Parsaik AK, Agarwal D, Surana A, Mascarenhas SS, Chandra S. Diagnostic accuracy of Pulmonary Embolism Rule-out Criteria: A systematic review and meta-analysis. *Ann Emerg Med.* 2012; 59(6): 517-20.e4.
12. Chunilal SD, Bates SM. Venous thromboembolism in pregnancy: Diagnosis, management and prevention. *J Thromb Haemost.* 2009; 101(3): 428-38.
13. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006–2008. *BJOG.* 2011; 118: 1-203.
14. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al. American Thoracic Society documents: An official American Thoracic Society / Society of Thoracic Radiology: Clinical Practice Guideline — Evaluation of suspected pulmonary embolism in pregnancy. *Radiology.* 2012; 262(2): 635-46.
15. Rodger M. Evidence base for the management of venous thromboembolism in pregnancy. *Hematology Am Soc Hematol Educ Program.* 2010; 2010: 174-80.
16. McLintock C, Brighton T, Chunilal S, Dekker G, McDonnell N, McRae S, et al. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. *Aust N Z J Obstet Gynaecol.* 2012; 52(1): 14-22.
17. Douma RA, Mos IC, Erkens PM, Nizet TAC, Durian MF, Hovens MM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism - A prospective cohort study. *Ann Intern Med.* 2011; 154(11): 709-18.
18. Wolf SJ, McCubbin TR, Nordenholz KE, Naviaux NW, Haukoos JS. Assessment of the Pulmonary Embolism Rule-out Criteria rule for evaluation of suspected pulmonary embolism in the emergency department. *Am J Emerg Med.* 2008; 26(2): 181-5.
19. Kline JA, Peterson CE, Steuerwald MT. Prospective evaluation of real time use of the Pulmonary Embolism Rule-out Criteria in an academic emergency department. *Acad Emerg Med.* 2010; 17(9): 1016-9.
20. Penalzoza A, Verschuren F, Dambrine S, Zech F, Thys F, Roy P-M. Performance of the Pulmonary Embolism Rule-out Criteria (the PERC rule) combined with low clinical probability in high prevalence population. *Thromb Res.* 2012; 129(5): e189-93.

APPENDIX ONE: EVIDENCE SUMMARY TABLE

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Primary Derivation Studies of CDR for Suspected PE									
Wells, et al 2000 ²	“Wells Score” Using “Low risk of PE” (<2)	Derivation	1211 Patients included in study. 491 patients in “low risk (<2)” group. 392 in derivation. 99 in validation. 1) Inpatients and outpatients 2) Suspected PE 3) Symptoms lasted <30 days	1) Suspected upper extremity DVT as source of PE 2) No symptoms of PE for more than 3 days before presentation 3) Use of anticoagulation for more than 72hrs 4) Expected survival <3 months (introduced halfway through study due to higher mortality than expected due to causes other than PE) 5) Contraindication to contrast media 6) Pregnancy 7) Geographical inability for follow-up 8) <18 years 9) Informed consent not obtained	Sens: 62.5% (35.47-84.71)	Spec: 72.21% (67.95-76.20) PPV: 7.04% (3.43-12.57) NPV: 98.28% (96.29-99.36)	LR-: 0.52 (0.28-0.98)	N	
Wells, et al. 2000 ²	“Wells Score” Using “PE Unlikely” (≤4)	Derivation	1211 patients included in study. 867 patients in “PE unlikely (≤4)” category. 689 in derivation. 178 in validation. Inclusion criteria as above	As above	Sens: 80 (95% CI: 69.09-89.74)	Spec: 68% (65.58-72.09) PPV: 16.94% (12.88-21.67) NPV: 97.88 (96.33-98.90)	LR-: 0.28 (0.17-0.46)	N	

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Lucassen et al 2011 ¹	Systematic review Aim: To compare the test characteristics of gestalt (a physician's unstructured estimate) and clinical decision rules for evaluating adults with suspected PE and assess the failure rate of gestalt and rules when used in combination with D-dimer testing	"Gestalt" physician estimate of risk of PE (no CDR) compared with Wells Score < or =4, simplified Wells (<2), Geneva rule, and the simplified revised Geneva rule	Studies had to estimate the probability of PE by using gestalt or a decision rule and verify the diagnosis by using an appropriate reference standard		Failure rate for "low risk" defined by any strategy including gestalt when combined with sensitive D dimer assay was acceptable for clinical use except for the combination of Wells Score <or = to 4 combined with qualitative (less sensitive) D dimer (this was due to lower sensitivity of Wells Score using < or = 4 cut-off compared with other strategies	Specificity of gestalt and both versions of Geneva lower than Wells' score using either < or = 4 (original) scoring system or the simplified system (using <2 as the cut-off) See Table extracted from paper below for details	n/a	n/a	n/a
Gibson. et al 2008 ³	Performance of the Wells Score was compared to Modified and "Simplified Wells Score"	Validation	3306 patients included in study. 2701 outpatients. 605 inpatients. 1) Inpatients and outpatients with clinically suspected PE 2) Adult (>18yrs)	1) Received Low-molecular weight heparin for >24hrs 2) <18 years of age 3) Pregnant 4) Known hypersensitivity for iodinated contrast fluid or renal failure 5) Life expectancy <3 months 6) Geographic inability for follow-up 7) Informed consent not obtained	Failure rate of combination of low risk (defined as Wells Score <or = 4) incidence at three months in patients with a Wells Score < or = 4 and a normal D dimer was 0.5%, 0.3% with a modified rule and 0.5% with a simplified rule. The proportion of patients safely excluded for PE was 32%, versus 31% and 30%, respectively.	n/a	n/a		

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Le Gal, G., et al. 2006 ⁴	Prediction of pulmonary embolism in the emergency department: Revised Geneva Score (RGS)	Primary derivation and validation study	Patients (age limitation not specified) admitted to the emergency department, in whom pulmonary embolism (PE) is suspected (new or worsening shortness of breath or chest pain without any other obvious cause). Total study patients: • Derivation: 965 patients, 221 had PE (23.1%) • Validation: 749 patients, 192 had PE (25.6%)	<ul style="list-style-type: none"> • Ongoing anticoagulant treatment, or • Contraindication to CT (known allergy to contrast iodine agents or risk for allergic reaction, creatinine clearance <0.5 mL/s (<30mL/min), calculated by the Cockcroft-Gault formula or • Pregnancy or • Massive PE with shock, or • Estimated life expectancy less than 3 months. 	Derivation: 85.5 <i>NB: The authors did not combine the low risk group with negative D-dimer. Had this been the case, we would expect a higher NPV.</i>	Derivation: 43.8	Derivation: 0.331	Derivation: N	Level III-IV
					Validation: 89.6	Validation: 37.8	Validation: 0.275	Validation: N	
Klok, F.A., et al. 2008 ⁵	Simplification of the Revised Geneva Score for Assessing Clinical Probability of Pulmonary Embolism	Primary derivation and validation Study <i>NB: This study is the first to “derive” the SRGS by changing the weighting assigned to the variables of the RGS (no variable derivation takes place) Hence, the authors call both studies validation studies.</i>	Patients (age limitation not specified) admitted to the emergency department, in whom pulmonary embolism (PE) is suspected (new or worsening shortness of breath or chest pain without any other obvious cause). n=1049 patients, 241 (23%) had PE	<ul style="list-style-type: none"> • Ongoing anticoagulant treatment, or • Contraindication to CT (known allergy to contrast iodine agents or risk for allergic reaction, creatinine clearance <0.5 mL/s (<30mL/min), calculated by the Cockcroft-Gault formula)or • Pregnancy, • Massive PE with shock, or • Estimated life expectancy less than 3 months. 	Three-level SRGS: 88.0 NPV = 92.3% 7.7% probability of PE	Three-level SRGS: 43.2	Three-level SRGS: 0.277	N	Level III-IV
					Two-level SRGS: 33.8 NPV = 77% 23% probability of PE	Two-level SRGS: 64.8	Two-level SRGS: 1.0		

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Kline, J.A., et al. 2002 ⁷	Criteria for the Safe Use of D Dimer Testing in Emergency Department Patients With Suspected Pulmonary Embolism (The Charlotte Rule)	Primary Derivation and Validation study	Patients (age limitation not specified) were eligible for enrolment when a board-certified emergency physician had enough suspicion for PE to order a pulmonary vascular imaging study (either a contrast-enhanced CT scan of the chest or a ventilation-perfusion lung scan [V/Q scan]) n=934 patients, 181 (19.4%) had PE	Patients were excluded from the study on the basis of: <ul style="list-style-type: none"> patient inability or unwillingness to provide written informed consent. failure to complete pulmonary vascular imaging, or presence of conditions (e.g., cardiac arrest) that precluded data collection. 	45.9 Patients classified as low risk had 13% probability of PE Combined with negative D dimer assay, patients in this study classified as low risk or “safe” for exclusion of PE with negative D dimer had a 1.1% probability of PE	84.9 NPV 86.7	0.637	Y	Level II
Kline, J., et al. 2004 ⁹	Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. (The PERC rule)	Primary Derivation and Validation study	Derivation: Patients presenting to the ED with clinical suspicion of PE (board- certified emergency physician felt a formal evaluation for pulmonary embolism was necessary). n= 3148 patients, 348 (11%) had VTE Validation (Low-Risk): Same as above, except that clinicians believed that patients were at low enough risk to justify exclusion of pulmonary embolism on the basis of a negative D dimer. n=1427 patients, 114 (8%) had VTE.	Derivation and Validation Study No clear exclusion criteria described	Low risk population: 96% (90–99%)	Low risk population: 27% (25–30%)	Low risk population: 0.15	Low risk population: N	Level II-III

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
			<p>Validation (Very-Low Risk):</p> <p>Dyspnea was the primary presenting complaint and an ED physician believed PE was not the most likely Dx.</p> <p>n= 328 patients, 9 (2%) had VTE</p>		<p>Very-low risk population: 100%, (59–97.5%)</p>	<p>Very-low risk population: 15% (11–18%).</p>	<p>Very-low risk population: 0.067</p>	<p>Very-low risk population: Y</p>	
Validation Studies of CDR for Suspected PE									
Douma 2009 ⁶	Simplified Wells Score	Retrospective Validation	<p>Adults outpatients presenting to ED with clinically suspicious PE</p> <p>n=965 Patients</p>	<ol style="list-style-type: none"> 1) Receiving ongoing anticoagulation therapy 2) Contraindication to CT scan (known hypersensitivity for iodinated contrast fluid or renal failure) 3) Suspected massive PE with shock 4) Life expectancy <3 months 5) Geographic inability for follow-up <p>Informed consent not obtained</p>	<p><u>Original Wells Score (< or = 4):</u> 100 % (95%CI: 98.5-100%)</p> <p><u>Simplified Wells Score (<2):</u> 100% (95%CI: 98.4-100%)</p>	<p><u>Original Wells Score (< or = 4):</u> 56% (95%CI: 49-63%)</p> <p><u>Simplified Wells Score (<2):</u> 47% (95%: 41-53%)</p> <p><i>NB original Wells Score more specific and therefore may lead to lower rates of imaging due to fewer patients without PE being misclassified as "PE likely"</i></p>			

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Douma RA, Mos IC, Erkens PM, et al; Prometheus Study Group. (2011) ¹⁷	Performance of 4 clinical decision rules (<i>Wells, Revised Wells, Revised Geneva and Simplified Geneva Scores</i>) in the diagnostic management of acute pulmonary embolism: a prospective cohort study	Validation of Revised Geneva Score(RGS) and Simplified Revised Geneva Score(SRGS) In the form of a prospective cohort study comparing the RGS and SRGS, combined with a high-sensitivity D dimer test	<ul style="list-style-type: none"> Patients ≥18 years of age, with clinically suspected acute PE (sudden onset of dyspnoea, increase in existing dyspnoea, or sudden onset of pleuritic chest pain). n=807 patients, 186 (23%) had PE	Previous: <ul style="list-style-type: none"> PE, Treatment with therapeutic heparin initiated ≥ 24 hours before eligibility assessment, Treatment with vitamin K antagonists, Pregnancy, and contraindication to computed tomography (CT). 	RGS 99.5% (97 to 100)	RGS 30% (27 to 34)	RGS 0.017	RGS Y (Although CI's for LR-not reported)	N/A
					SRGS 99.5% (97 to 100)	SRGS 31% (28 to 34)	SRGS 0.016	SRGS Y (Although CI's for LR-not reported)	
Wolf et al (2008) ¹⁸	Assessment of the pulmonary embolism rule-out criteria rule for evaluation of suspected pulmonary embolism in the emergency department	Single centre Validation study with results derived from a secondary analysis of a prospective database	Patients presenting to the ED (to a single residency-affiliated community-based Denver ED), with clinical suspicion of PE after history, physical examination, chest X-ray study, and electrocardiogram were obtained. n=134 patients, 16 (12%) had PE	Eligible subjects were excluded if: <ul style="list-style-type: none"> they did not speak English, were pregnant within the preceding 6 months, weighed more than 350 pounds, had a pre-established diagnosis of thrombophilia, were younger than 18 years or older than 85 years, were critically ill or unable to consent, or were known to have a recently elevated or normal D dimer assay. 	Unable to calculate from reported data	Unable to calculate from reported data	0 (95% CI not reported) - Applies to the group identified by the rule as very low risk)		N/A

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Kline JA, Courtney DM, Kabrhel C, et al (2008) ¹⁰	Prospective multicenter evaluation of the pulmonary embolism rule-out criteria (PERC) rule.	Multicentre prospective observational validation trial across the US and NZ	<p>Patients presenting to the ED (12 hospitals in the USA and one in Christchurch, New Zealand), with suspected PE defined as patients in whom a board-certified emergency physician was concerned enough about PE to order an objective test (CT, V/Q, or D dimer) after the initial history and physical examination were obtained.</p> <p>n= 8138 patients, 561 (6.9%) had VTE</p>	<p>Subjects were excluded for any of the following reasons:</p> <ul style="list-style-type: none"> • clinician knowledge of a positive PE imaging study in the preceding 7 days; • the enrollment hospital was not the patient’s hospital-of-choice for follow-up; or any circumstance that might compromise follow-up (e.g., homelessness or lack of a telephone) 	<p>Low suspicion and PERC(-):</p> <p>97.4% (95.8–98.5%)</p>	<p>Low suspicion and PERC(-):</p> <p>21.9% (21.0–22.9%)</p>	<p>Low suspicion and PERC(-):</p> <p>0.17 (95% CI 0.11– 0.25)</p>	<p>Low suspicion and PERC(-):</p> <p>N</p>	N/A
Kline, MD, Courtney E. Peterson, and Michael T. Steuerwald , MD. (2010) ¹⁹	Prospective Evaluation of Real-time Use of the Pulmonary Embolism Rule-out Criteria in an Academic Emergency Department	Single centre prospective pilot study of physician use of the PERC criteria for ruling out PE (impact analysis of PERC)	<p>Patients over age of 17 years with one or more of the following chief complaints entered by the triage nurse:</p> <ul style="list-style-type: none"> • chest pain, shortness of breath, • respiratory distress, syncope, hypotension, palpitations, • cough, • altered mental status, or • clinical notes indicating that the patient was sent from an outside facility for PE evaluation. <p>n=526 patients</p>	<p>- Clinicians indicated that PE was on their active differential diagnosis list in 183 of 526 (35%) and their intent to use the PERC rule in 115 of 526 (22%) of cases. Clinicians ultimately documented PERC negative or “PERC(-)” in 65 of 115 patients.</p> <p>- Of these, 62 (95%) patients had records in which the physician had not recorded one or more element of the rule. Hence the rule criteria were recorded in full in only 3 patients (5%).</p>					

Author and date	Name of CDR	Derivation or validation	Inclusion	Exclusion	Sensitivity (95%ci)	Specificity (95% ci)	LR- (95%CI)	High performance (y/n)*	Hierarchy**
Penaloza, A., et al. 2012 ²⁰	Performance of the Pulmonary Embolism Rule-out Criteria (the PERC rule) Combined with low clinical probability in high prevalence population.	Multicentre prospective cohort validation study	Patients presenting to the emergency department with suspected PE. The authors note that their population had a higher overall prevalence of PE compared to other populations on which the rule was studied since they claimed that European populations have a higher overall PE prevalence (more than 20%). n=959 patients, 286 (29.8%) had PE	Patients were excluded if; 1) the diagnosis of thromboembolic disease was documented before admission; 2) PE was suspected during a hospital stay of more than 2 days' duration; or 3) diagnostic testing was cancelled for ethical reasons, because of rapid death, or because the patient decided to leave the hospital against medical advice or declined testing.	<u>PERC- alone</u> 98.6 (97.2-100) <u>PERC- with RGS low pretest probability</u> 98.6 (97.2-100) <u>PERC- with low gestalt pretest probability</u> 100 (99-100)	<u>PERC- alone</u> 10 (8-13) <u>PERC- with RGS low pretest probability</u> 9 (7-11) <u>PERC- with low gestalt pretest probability</u> 9 (6-11)	<u>PERC- alone</u> 0.13 (0.05-0.36) <u>PERC- with RGS low pretest probability</u> 0.15 (0.06-0.42) <u>PERC- with low gestalt pretest probability</u> 0 (no 95% CI reported)	<u>PERC- alone</u> N <u>PERC- with RGS low pretest probability</u> N <u>PERC- with low gestalt pretest probability</u> Y	N/A
Singh B, Parsaik AK, Agarwal D, et al (2012) ¹¹	Diagnostic Accuracy of Pulmonary Embolism Rule-Out Criteria: A Systematic Review and Meta-analysis	Validation	- Please refer to the original paper for the inclusion criteria of the various studies.	- Please refer to the original paper for the exclusion criteria of the various studies.	<u>Pooled sensitivity</u> 0.97 (95% confidence interval [CI] 0.96 to 0.98)	<u>Pooled specificity</u> 0.23 (95% CI 0.22 to 0.24) <i>Significant heterogeneity was observed in specificity (I²=97.2%)</i>	<u>Pooled LR+</u> 1.24 (95% CI 1.18 to 1.30) <i>NB: Sig heterogeneity was observed in LR+ (I²=84.2%).</i> <u>Pooled LR-</u> 0.17 (95% CI 0.13 to 0.23)	N (LR- > than 0.1)	The authors conclude that existing literature suggests consistently high sensitivity and low but acceptable specificity of the PERC to rule out PE in patients with low pretest probability

*High performance (Y/N) for the derivation study defined as:

- Sens > 0.95 AND
- Lower limit of 95%CI for sensitivity >0.95 AND
- LR-<0.1 AND
- Upper limit of LR-95% CI < 0.1
- Likelihood ratio for negative test result = $\frac{\text{proportion of patients WITH disease who have a negative test result (1 - SENSITIVITY)}}{\text{proportion of patients WITHOUT disease who have a negative test result (SPECIFICITY)}} = \frac{(1 - \text{SENSITIVITY})}{(\text{SPECIFICITY})}$

**Hierarchy (see reference I. below)

Level I: can be used in a variety of clinical settings and includes at least one validation study (external) and at least one impact analysis showing favourable change in clinician behaviour when the CDR is used/implemented

Level II: can be used in various setting with confidence about accuracy (1 prospective validation in heterogeneous population or several smaller ones)

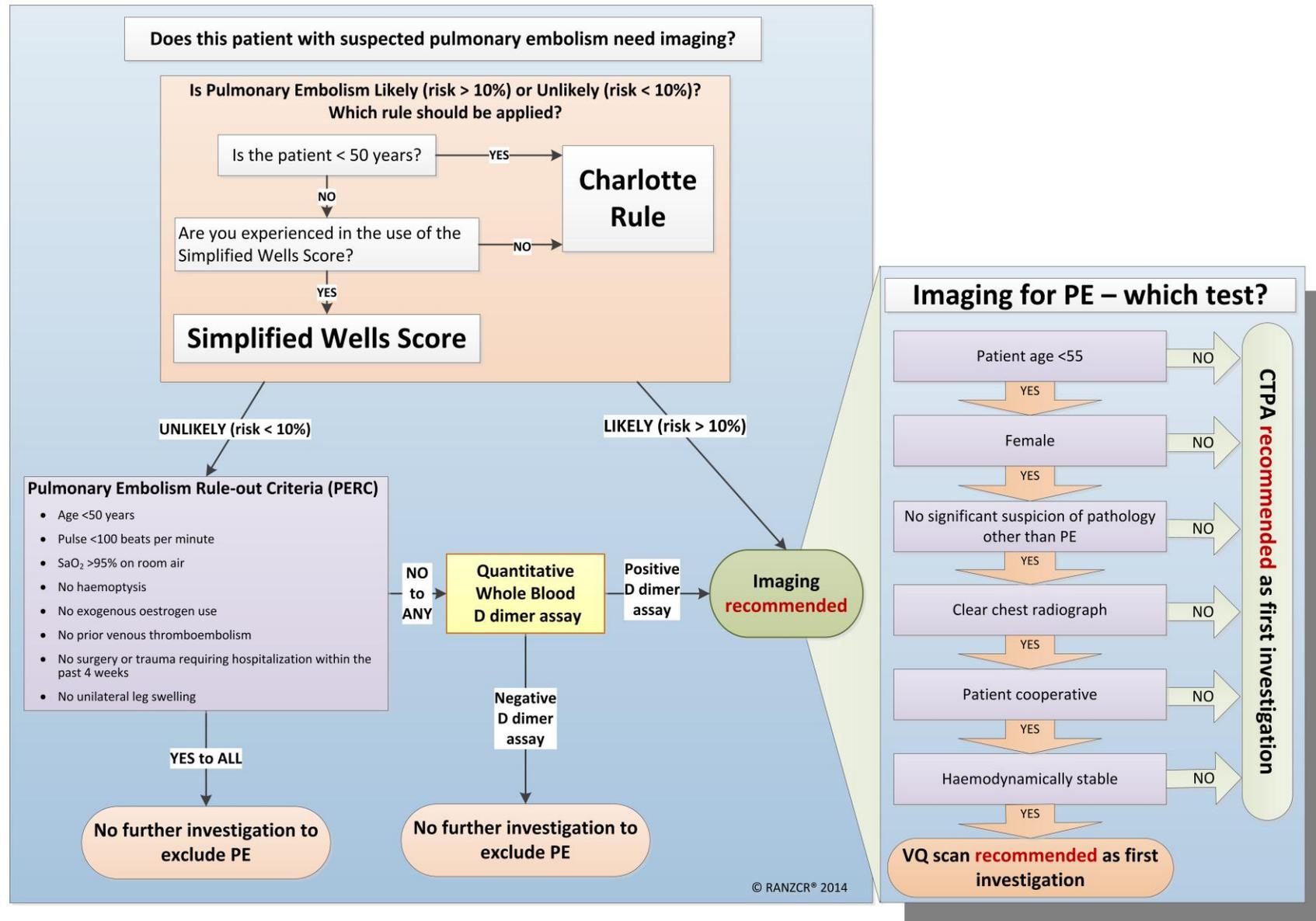
Level III: use with caution in narrowly defined group of patients (validated in one narrow prospective sample)

Level IV: CDRs requiring more evaluation before they are implemented (no validation or only validated with statistical techniques or retrospective databases, or split samples)

APPRAISAL TABLE REFERENCES:

- I. McGinn T, Guyatt G, Wyer P, Naylor C, Stiell I, Richardson W. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. *JAMA*. 2000; 284(1): 79-84.
- II. Pickering A, Harnan S, Fitzgerald P, Pandor A, Goodacre S. Clinical decision rules for children with minor head injury: A systematic review. *Arch Dis Child*. 2011; 96(5): 414-21.

APPENDIX TWO: USING CDRs FOR SUSPECTED PE AND SELECTING THE INVESTIGATIVE PATHWAY



APPENDIX THREE: WELLS SCORE

Predictor	Score
Clinical Signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)	+3
An alternative diagnosis is less likely than PE	+3
Heart rate greater than 100	+1.5
Immobilisation at least 3 days or surgery in previous 4 weeks	+1.5
Previous DVT/PE	+1.5
Hemoptysis	+1
Malignancy	+1
Total	/12.5

Risk of PE	Associated Score
Low (3% risk of PE)	<2
Moderate (28%)	2-6
High (78%)	>6

Risk of PE	Associated Score
Unlikely (5.1-7.8% rate of PE)	≤4
Likely (~40%)	>4

Inclusion Criteria:

(Unless ALL are satisfied, the Wells Score cannot be applied to assess the pre-test probability of PE)

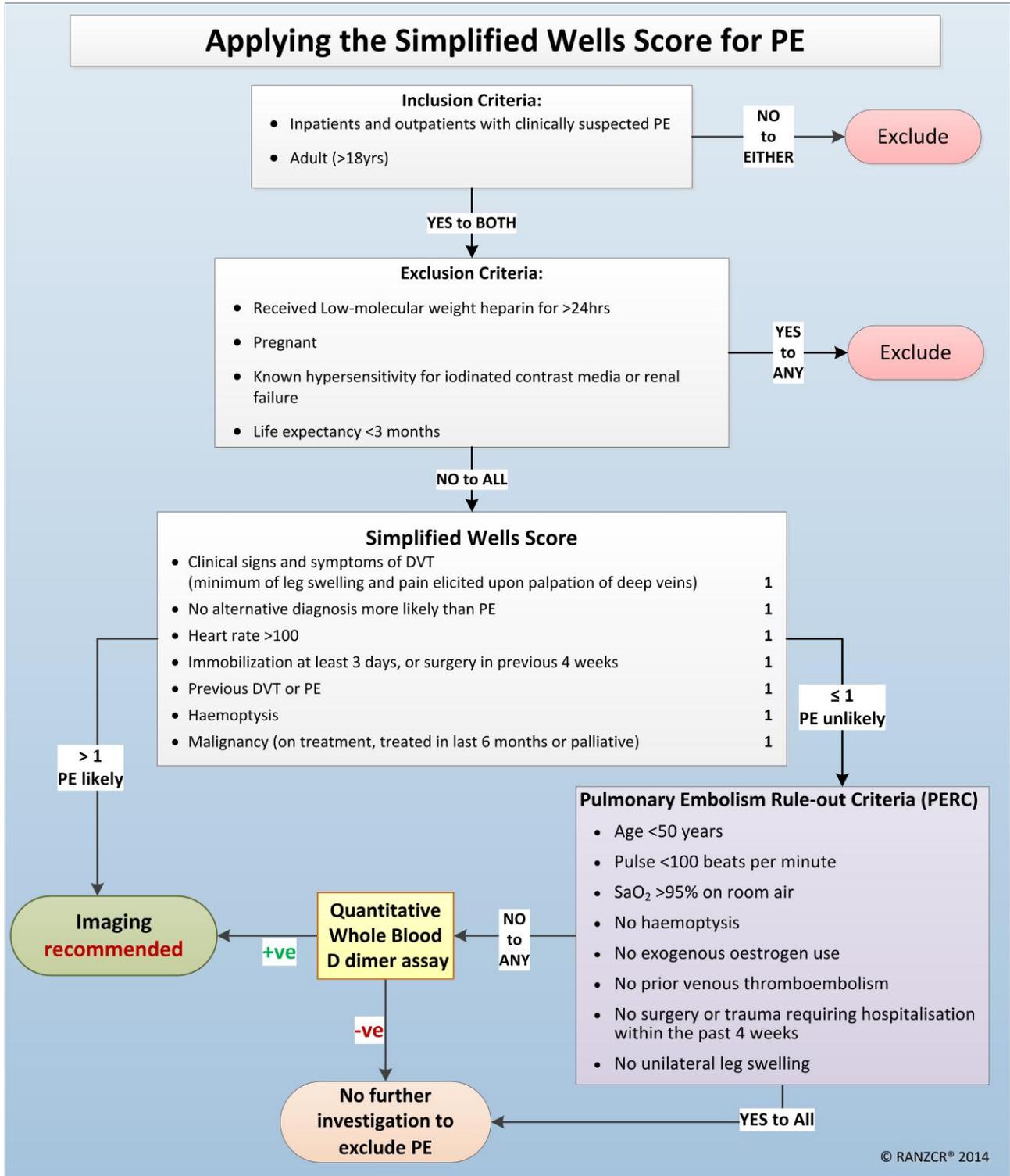
- Inpatients or outpatients with clinical suspicion for PE
- Symptoms for < 30 days

Exclusion Criteria:

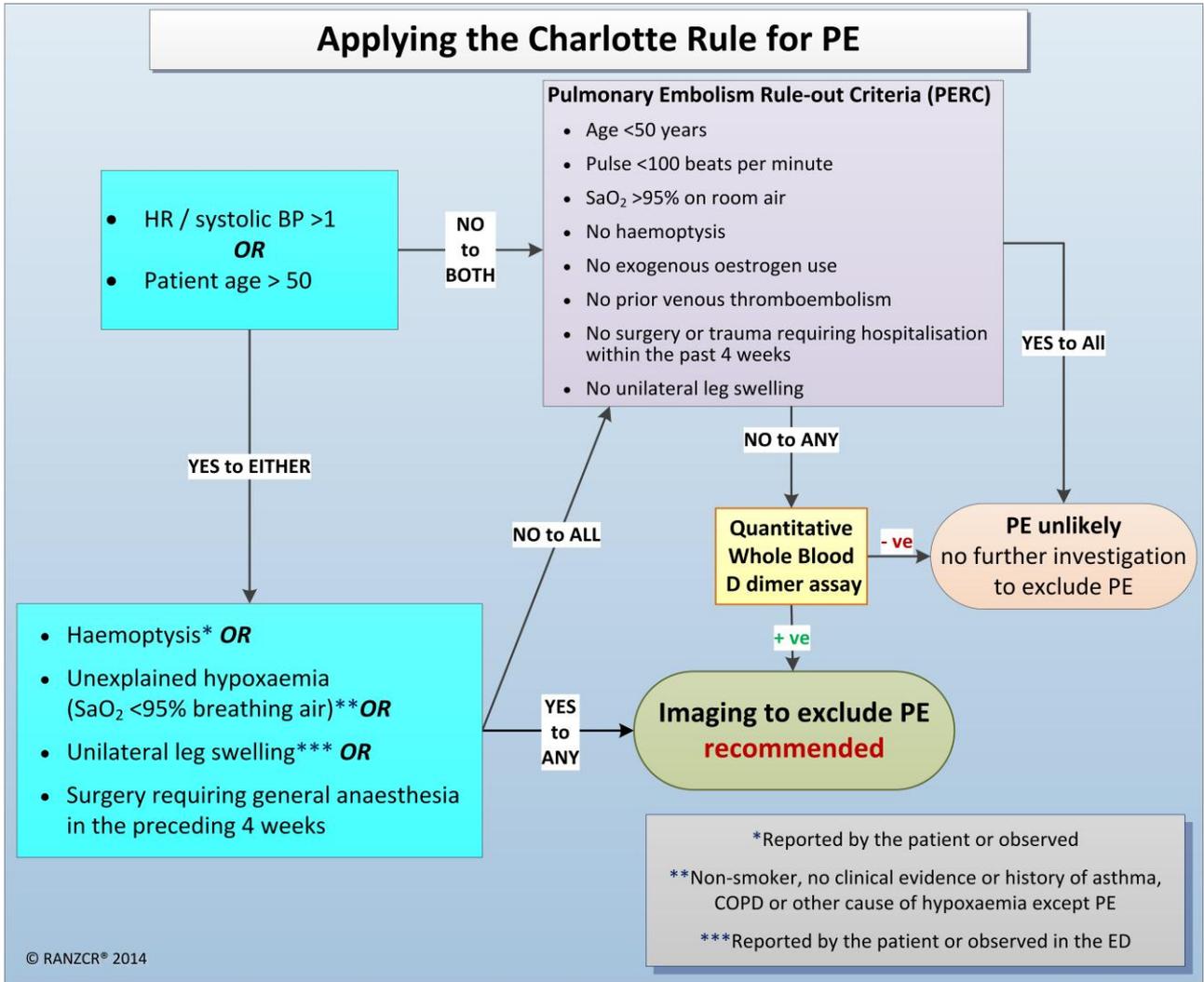
(If ANY these are satisfied, the Wells Score cannot be applied to assess the pre-test probability of PE)

- Suspected upper extremity DVT as source of PE
- No symptoms of PE for more than 3 days before presentation
- Use of anticoagulation for more than 72hrs
- Expected survival <3 months
- Contraindication to contrast media
- Pregnancy

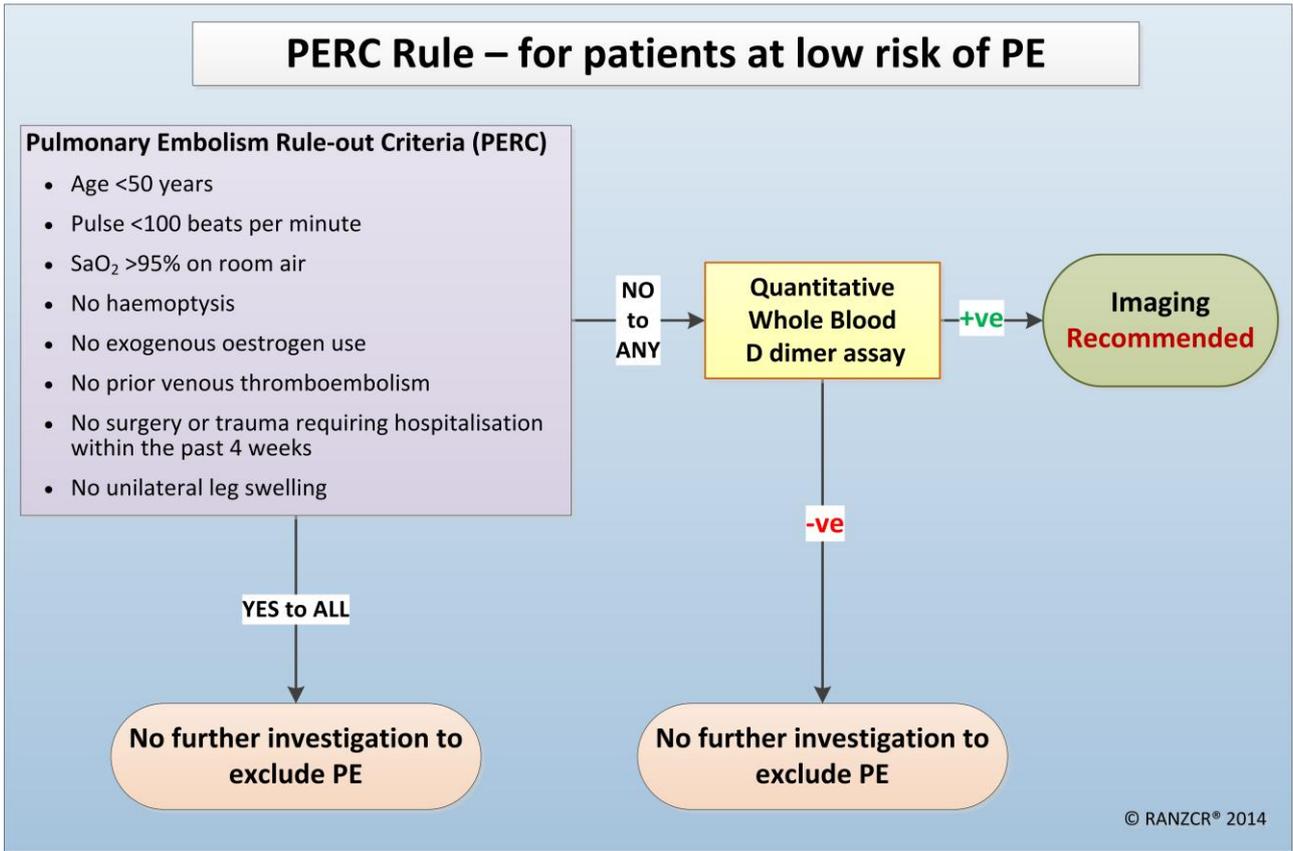
APPENDIX FOUR: SIMPLIFIED WELLS SCORE



APPENDIX FIVE: THE CHARLOTTE RULE



APPENDIX SIX: THE PERC RULE



Patients at low or very-low risk of PE (the population for whom the rule is intended), who meet the rule criteria (i.e. answer YES to the 8 clinical variables), are deemed PERC negative.

The authors found that PERC negative patients have a probability of PE <1.8%, and hence, are safe to have PE excluded without further diagnostic testing, since the post-test probability of PE after a negative VQ scan is greater than 1.8%