CDI QUALITY INSTITUTE

Provider Led Entity

CDI Quality Institute PLE
Chest / Pulmonary Embolus AUC
2019 Update

09/10/2019

Appropriateness of advanced imaging procedures* in patients with suspected or known pulmonary embolus and the following clinical presentations:

*including CT pulmonary angiography (CTPA) , CT chest with IV contrast, CT chest without IV contrast, CT venography lower extremities, MRA chest, MRI chest, Tc-99m ventilation/perfusion lung scan (V/Q), V/Q SPECT, VQ SPECT/CT, and Tc-99m perfusion scan.

Abbreviation list:

AAFP	American Academy of Family Physicians
ACEP	American College of Emergency Physicians
ACP	American College of Physicians
ACR	American College of Radiology
AHA	American Heart Association
AUC	Appropriate Use Criteria
BTS	British Thoracic Society
CT	Computed tomography
CTA	CT angiography
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
CTS	Canadian Thoracic Society
DVT	Deep vein thrombosis
ESC	European Society of Cardiology
IPAH	Idiopathic pulmonary arterial hypertension
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
PE	Pulmonary embolism / embolus
PERC	Pulmonary embolism rule-out criteria
PLE	Provider Led Entity
SEPAR	Spanish Society of Pneumology and Thoracic Surgery
SPECT	Single-photon emission computed tomography
THANZ	Thrombosis and Haemostasis Society of Australia and New Zealand
V/Q	Ventilation/perfusion scanning Ventilation/perfusion imaging
VTE	Venous thromboembolism

Low pretest probability or low clinical suspicion for pulmonary embolus (PE) based on a validated clinical prediction rule in patients who meet all of the Pulmonary Embolism Rule-Out Criteria (PERC):

- **Green** –
- **Yellow** –
- **Orange** –
- **Red** – CTPA; CT chest; MRA chest; MRI chest; V/Q scan; V/Q SPECT; V/Q SPECT/CT; Perfusion scan; CT venography of the lower extremities

Level of Evidence: High

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Clinicians should use validated clinical prediction rules to estimate the pretest probability in patients with suspected PE (Raja et al., *[ACP]* 2015; Streiff et al., 2016; Qaseem et al., [*ACP/AAFP*] 2007).

The Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to all patients with a low pretest probability of PE, and the D-dimer test should not be obtained in low-risk patients who meet all of the criteria (Fesmire et al., [*ACEP*] 2011)/Level B recommendation; Raja et al., [*ACP*] 2015).

Clinicians should not obtain imaging studies in patients with a low pretest probability of PE and who meet all Pulmonary Embolism Rule-Out Criteria (Raja et al., [*ACP*] 2015).

Clinicians should not use imaging studies as the initial test in patients with low or intermediate pretest probability of PE (Raja et al., [*ACP*] 2015).

PE can be excluded without D-dimer or radiological testing in selected patients if the PE rule-out criteria (negative PERC rule) are met (Tran et al., [*THANZ*] 2019*, strong recommendation/moderate level of evidence).

* This guideline did not pass the AGREE II cutoff of 90. It was included, however, because of its direct relevance to this scenario.

Clinical notes:

- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2015; Kirsch et al., [*ACR*] 2017).
- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al., [*ACP*] 2015).
- PERC has a sensitivity for PE of 97% and a specificity of 22% - the risk of missing a PE by using PERC was only 0.3%. (Raja et al., [*ACP*] 2015).
- D-dimer testing should not be ordered on patients with very little or no risk for PE as false-positive D-dimer results may increase the harms associated with unnecessary advanced imaging (Fesmire et al., [*ACEP*] 2011).

Evidence update (2014-present):
There were no new studies that affected the conclusions and recommendations from the guidelines noted above.

Normal plasma high sensitivity D-dimer test with:

- **Low pretest probability or low clinical suspicion for PE based on a validated clinical prediction rule in patients who do not meet all the PERC; or**
- **Intermediate pretest probability or intermediate clinical suspicion for PE based on a validated clinical prediction rule.**

- **Green** –
- **Yellow** –
- **Orange** –
- **Red** – CTPA; CT chest; MRA chest; MRI chest; V/Q scan; V/Q SPECT; V/Q SPECT/CT; Perfusion scan; CT venography of the lower extremities

Level of Evidence: High

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Clinicians should use validated clinical prediction rules to estimate the pretest probability in patients with suspected PE (Raja et al., [*ACP*] 2015; Streiff et al., 2016; Qaseem et al., [*ACP/AAFP*] 2007; Uresandi et al., [*SEPAR*] 2013*).

The Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to all patients with a low pretest probability of PE (Fesmire et al., [*ACEP*] 2011/Level B recommendation; Raja et al., [*ACP*] 2015).

Clinicians should obtain high sensitivity D-dimer testing in patients with a low pretest probability of PE who do not meet all of the PERC, and in patients with intermediate pretest probability or intermediate clinical suspicion for PE (Raja et al., [*ACP*] 2015).

In emergency department patients with symptoms concerning for pulmonary embolism, the logical first step is to assess risk with a validated clinical prediction tool and if not PERC negative, obtain a D-dimer. This strategy allows PE to be ruled out in approximately 30% of patients, with a subsequent incidence of CTE in less than 1% of untreated patients (Konstantinides et al., [*ESC*] 2014).

Clinicians should not obtain any imaging studies in patients with a low or intermediate pretest probability of PE with a normal D-dimer level or D-dimer level below the age-adjusted cutoff (Kirsch et al., [*ACR*] 2017*; Raja et al., [*ACP*] 2015).

In patients with a low pretest probability for PE, a negative [normal] quantitative D-dimer assay result can be safely used to exclude PE (Fesmire et al., [*ACEP*] 2011/Level A recommendation).

In patients with an intermediate pretest probability for PE, a negative [normal] quantitative D-dimer assay result may be used to exclude for PE (Fesmire et al., [*ACEP*] 2011/Level C recommendation).

A non-high pre-test probability (Wells or Geneva score) combined with a negative D-dimer result safely excludes VTE without imaging (Tran et al., [*THANZ*] 2019*, strong recommendation/high level of evidence).

Clinicians should not use imaging studies as the initial test in patients with low or intermediate pretest probability of PE (Raja et al., [*ACP*] 2015).

In patients with the clinical scenario: *PE unlikely, D-dimer negative*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 1 (rarely appropriate) to V/Q imaging.

* This guideline did not pass the AGREE II cutoff of 90. It was included, however, because of its direct relevance to this scenario.

Clinical notes:

- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2015; Kirsch et al., [*ACR*] 2017).
- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al., [*ACP*] 2015).
- The PERC should be applied to all patients with a low pretest probability of PE, and the D-dimer test should be obtained in low-risk patients who do not meet one or more of the criteria (Fesmire et al., [*ACEP*] 2011/Level B recommendation; Raja et al., [*ACP*] 2015).
- PERC should not be applied to patients at intermediate/high risk for PE (Raja et al., [*ACP*] 2015).
- PERC has a sensitivity for PE of 97% and a specificity of 22%. The risk of missing a PE by using PERC is 0.3% (Raja et al., [*ACP*] 2015).
- A generally accepted cutoff value for many D-dimer assays is 500 ng/ml, however, reference ranges and cutoff values for D-dimer may vary by performing laboratory (Parry et al., 2018; Riley et al., 2016).
- Clinicians should use age-adjusted D-dimer thresholds (e.g. age x 10 ng/ml versus 500 ng/ml) when possible (Raja et al., [*ACP*] 2015). The use of age-adjusted thresholds maintains the sensitivity for PE at or above 97% while increasing the specificity (van Es et al., 2016; Konstantinides et al., [*ESC*] 2014; Woller et al., 2014; Wilts et al., 2017; Parry et al 2018).
- D-dimer testing is 99.5-100% sensitive for excluding PE on CTPA in patients with intermediate clinical probability of PE (Kirsch et al., [*ACR*] 2017).
- These recommendations pertain to the use of a highly sensitive (> 95%) D-dimer assay (e.g. ELISA, ELFA, immunoturbidimetric or other immunoassays) (Raja et al., [*ACP*] 2015; Konstantinides et al., [*ESC*] 2014; Riley et al., 2016; Uresandi et al., [*SEPAR*] 2013).
- Since D-dimer levels are elevated in any significant thrombotic process their [ability] to predict the presence of pulmonary embolism and/or deep venous thrombosis is [decreased] in patients with recent surgery, significant trauma, cancer, or renal failure (Konstantinides et al., [*ESC*] 2014, Lindner et al., 2014).

Evidence update (2014-present):

Crawford et al. (2016), in a meta-analysis, concluded that a negative D-dimer test is valuable in ruling out PE in patients presenting to the emergency setting with a low pre-test probability (high level of evidence). They note high levels of false-positive results, especially among those > age 65, with estimates of specificity from 23% to 63%. No empirical evidence was available, however, to support an

increase in the diagnostic threshold of interpretation of D-dimer results for those over the age of 65 years (high level of evidence).

Bates et al. (2016), in a multicenter prospective cohort management study of 808 consecutive patients with suspected PE, evaluated whether PE can be safely excluded in patients with a negative D-dimer test without incorporating clinical probability assessment. Ninety-nine (12%) were diagnosed with VTE at presentation. Four hundred and twenty (52%) had a negative D-dimer level at presentation and were treated without anticoagulation; of these, one had VTE during follow-up. The negative predictive value of D-dimer testing for PE was 99.8% (95% CI, 98.7 – 99.9) (high level of evidence).

van Es et al. (2016), in a systematic review and meta-analysis, concluded that age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients with suspected PE in whom imaging can be safely withheld compared with fixed D-dimer testing (high level of evidence).

Woller et al. (2014), in a retrospective study of 923 patients who underwent CTPA, compared the safety of age-adjusted D-dimer thresholds in the work-up of patients for suspected PE. The authors report that the use of an age-adjusted D-dimer threshold among patients considered unlikely to have PE was associated with a low 90-day rate of failure to diagnose PE, although using an age-adjusted D-dimer threshold did result in missing more cases of PE. Among 104 patients with a negative conventional D-dimer test result and a Revised Geneva Score (RGS) ≤ 10, no PE was observed within 90 days (false-negative rate, 0%; 95% CI, 0%-2.8%). Among 273 patients with a negative age-adjusted D-dimer result and an RGS ≤ 10, four PEs were observed within 90 days (false-negative rate, 1.5%; 95% CI, 0.4%-3.7%). We observed an 18.3% (95% CI, 15.9%-21.0%) absolute reduction in the proportion of patients aged > 50 years who would merit CTPA by using age-adjusted D-dimer thresholds (low level of evidence).

Lindner et al. (2014) conducted a retrospective study of 1305 patients presenting to an academic emergency department and had CTPA and D-dimer to work-up potential PE. The objective was to determine the diagnostic accuracy of D-dimer to rule out PE in patients with renal insufficiency, in which D-dimer can be elevated. Sensitivity of D-dimer for patients with an eGFR > 60 mL/min was 96% (95% CI: 0.93 – 0.99) and 100% (95% CI: 100-100%) for those with 30-60 mL/min eGFR, though specificity decreased significantly with impaired renal function. The authors concluded that D-dimer levels were elevated in patients with eGFR < 60 mL/min, though were still highly sensitive for exclusion of PE. Because almost all patients with impaired renal function had elevated D-dimer irrespective of the presence of PE, the authors posit that future studies should be performed to determine renal function-adjusted D-dimer cutoffs for PE (low level of evidence).

Wilts et al. (2017), in a prospective study of 3,324 patients, found that the use of age-adjusted D-dimer cutoff (vs. a conventional cutoff) doubles the proportion of patients with cancer in whom PE can be safely excluded by clinical decision rule and D-dimer without imaging (moderate level of evidence).

Polo Friz et al. (2014), in a retrospective cohort study of 481 patients evaluated in the emergency department (ED), sought to evaluate whether using a higher cutoff value for D-dimer could increase the test specificity without reducing its sensitivity for ruling out PE in elderly and very elderly patients presenting to the ED. The authors concluded that in elderly subjects with clinically suspected PE, the application of a fixed higher D-dimer cutoff (1000ng/ml) increases the specificity of D-dimer assay for excluding PE without reducing test sensitivity (low level of evidence).

Sharp et al. (2016), in a retrospective study of 31,094 ED patients > 50 years, sought to determine the

accuracy of age-adjusted D-dimer threshold to detect PE. Over a 6-year study period, the expected number of missed or delayed PE diagnoses because of false-negative D-dimer test results would have been 36 with the age-adjusted threshold, 10 with the threshold of 500 ng/dL, and 80 with the threshold of 1,000 ng/dL. The authors concluded that their data supports the use of D-dimer and age adjustment to further aid ability to exclude acute PE (low level of evidence).

Parry et al. (2018), in a multicenter (n =24) cross-sectional study of 3,837 consecutive ED patients, evaluated characteristics of an automated INNOVANCE D-dimer assay for exclusion of PE and DVT using both standard and age-adjusted cut-offs. All patients had low or intermediate Wells score, and < 500 ng/ml was used as a standard negative D-dimer result. The diagnostic standard was imaging (CTPA or V/Q for PE, and venous U/S or contrast venography for DVT) demonstrating PE or DVT within 3 months. Mean age of patients evaluated for PE (n=1834) was 48 +/- 16 years and for DVT (n=1752) was 53 +/- 16 years. D-dimer test characteristics for PE were: sensitivity 98.0%, specificity 55.4%, negative predictive value (NPV) 99.8%, positive predictive value (PPV) 11.4%, and for DVT were: sensitivity 92.0%, specificity 44.8%, NPV 98.8%, PPV 10.3%. Age adjustment [age (years) * 10] increased specificity (59.6% [PE], 51.1% [DVT]). The authors conclude that D-dimer testing is highly sensitive and can be used to exclude PE and first event of proximal DVT in ED patients with low- and intermediate- pre-test probability. Age adjustment increases specificity without increasing false negatives (moderate level of evidence).

Elevated plasma high sensitivity D-dimer test with:

- **Low pretest probability or low clinical suspicion for PE based on a validated clinical prediction rule in patients who do not meet all the PERC; or**
- **Intermediate pretest probability or intermediate clinical suspicion for PE based on a validated clinical prediction rule.**

- **Green** – CTPA or CT chest with IV contrast
- **Yellow** – V/Q SPECT or V/Q SPECT/CT
- **Yellow** – V/Q scanning in patients unable to undergo CTPA or CT chest with IV contrast
- **Yellow** - V/Q scanning if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Yellow** – Perfusion scan in patients in clinical distress who are unable to undergo CTPA, CT chest with IV contrast, or V/Q scanning
- **Yellow** – Pulmonary MRA in patients unable to undergo CTPA or CT chest with IV contrast, or if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Orange** – CT venography of the lower extremities, except when ultrasound is not available
- **Red** – CT chest without IV contrast; CT chest without and with IV contrast; MRI chest

Level of Evidence: High

Notes concerning applicability and/or patient preferences:
V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al., 2016; Kan et al., 2015; Phillips et al., 2015; Stubbs et al., 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al., 2017; Squizzato et al., 2017; and Pasin et al., 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al. review, and 18.89% in the Zhou et al. 2015 study. The use of MRI is also limited by the presence of claustrophobia in a significant number of patients and by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA if to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
Clinicians should not use imaging studies as the initial test in patients with low or intermediate pretest probability of PE (Raja et al., [*ACP*] 2015).

Clinicians should use validated clinical prediction rules to estimate the pretest probability in patients with suspected PE (Raja et al., [*ACP*] 2015; Streiff et al., 2016; Qaseem et al., [*ACP/AAFP*] 2007; Uresandi et al., [*SEPAR*] 2013*).

The Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to all patients with a low pretest probability of PE (Fesmire et al., [*ACEP*] 2011/Level B recommendation; Raja et al., [*ACP*] 2015).

Clinicians should obtain high sensitivity D-dimer testing in patients with a low pretest probability of PE who do not meet all of the PERC, and in patients with intermediate pretest probability or intermediate clinical suspicion for PE (Raja et al., [*ACP*] 2015).

In patients with an elevated D-dimer level, imaging should be obtained (Raja et al., [*ACP*] 2015; *NICE* 2015). A positive D-dimer result alone is not diagnostic of VTE and requires further radiological investigation (Tran et al., [*THANZ*] 2019*).

CTPA is the procedure of choice to evaluate for PE in patients with positive D-dimer tests or in patients with clinical suspicion for PE in whom D-dimer testing is not available (Raja et al., [*ACP*] 2015; Kirsch et al., [*ACR*] 2017*; Fesmire et al., [*ACEP*] 2011/Level B recommendation; Konstantinides et al., [*ESC*] 2014; *NICE* 2015). Normal CT angiography safely excludes PE in patients with low or intermediate clinical probability (Konstantinides et al., [*ESC*] 2014/Level A recommendation).

In the evaluation of acute PE, clinicians should reserve V/Q scanning for patients who have a contraindication to CTPA or for instances in which CTPA is not available (Raja et al., [*ACP*] 2015; Konstatinides et al., [*ESC*] 2014; *NICE* 2015).

The *ACR* gives CTPA and optimized CT chest with IV contrast a score of 9, Tc-99m V/Q scan 7, MRA chest 6, and CTA chest with CT venography 5 in patients with a positive plasma D-dimer test (Kirsch et al., [*ACR*] 2017*).

CTPA and V/Q scanning are generally not indicated in patients with suspected PE and a known or recently diagnosed [proximal] deep venous thrombosis or pelvic vein thrombosis undergoing current treatment, as the results will not eliminate the need for anticoagulation therapy (Raja et al., [*ACP*] 2015; Fesmire et al., [*ACEP*] 2011/Level B recommendation; Konstantinides et al., [*ESC*] 2014/Level B recommendation).

Computed tomography pulmonary angiography (CTPA) is the preferred imaging modality for suspected PE due to its accuracy (Tran et al., [*THANZ*] 2019, GRADE: Strong; Evidence, High). A negative technically adequate CTPA excludes PE and anticoagulation can be safely withheld (Tran et al., [*THANZ*] 2019*, strong recommendation/high level of evidence).

Ventilation–perfusion (VQ) scanning does not require radiocontrast, and so is suitable for patients with renal impairment (Tran et al., [THANZ] 2019, GRADE: Strong; Evidence, High). A normal VQ scan excludes PE and anticoagulation can be safely withheld (Tran et al., [*THANZ*] 2019*, strong recommendation/high level of evidence).

MRI and pulmonary MRA should not be done as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014; Uresandi et al., [*SEPAR*] 2013*). A

new systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism (Chen et al., 2017).

In patients with the clinical scenario: *PE unlikely, D-dimer positive*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 8 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE unlikely, ultrasound of lower extremity with clot*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 5 (may be appropriate) to V/Q imaging.

For patients with an intermediate pretest probability for PE and a negative CTPA for whom clinical suspicion for PE persists, imaging of the lower extremity may be performed to exclude DVT (Fesmire et al., *ACEP* 2011/Level C recommendation).

Because CT uses ionizing radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014).

It is recommended not to perform CT venography routinely to increase the diagnostic yield of CTPA (Uresandi et al., [*SEPAR*] 2013*).

* This guideline did not pass the AGREE II cutoff of 90. It was included, however, because of its direct relevance to this scenario.

Clinical notes:

- Patients with suspected PE should, where reasonably practical, undergo investigation on the same day of presentation to exclude a diagnosis of PE (Howard et al., [*BTS*] 2018).
- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2015; Kirsch et al., [*ACR*] 2017).
- The PERC are not a screening tool and were developed to guide physicians in the care of patients with a real clinical concern for PE who have a low pretest probability based on validated clinical prediction rules (Raja et al., [*ACP*] 2015).
- The Pulmonary Embolism Rule-Out Criteria (PERC) should be applied to all patients with a low pretest probability of PE, and the D-dimer test should be obtained in low-risk patients who do not meet one or more of the [PERC] criteria (Fesmire et al., [*ACEP*] 2011/Level B recommendation; Raja et al., [*ACP*] 2015).
- PERC should not be applied to patients at intermediate or high risk for PE (Raja et al., [*ACP*] 2015).
- A generally accepted cutoff value for many D-dimer assays is 500 ng/ml, however, reference ranges and cutoff values for D-dimer may vary by performing laboratory (Riley et al., 2016).
- Clinicians should use age-adjusted D-dimer thresholds (e.g. age x 10 ng/ml versus 500 ng/ml) when possible (Raja et al., [*ACP*] 2015; Konstantinides et al., [*ESC*] 2014). The use of age-adjusted thresholds maintains the sensitivity for PE at or above 97% while increasing the specificity (van Es et al., 2016; Konstantinides et al., [*ESC*] 2014; Parry et al 2018).
- These recommendations pertain to the use of a highly sensitive (>95%) D-dimer assay (e.g. ELISA, ELFA, immunoturbidimetric or other immunoassays) (Raja et al., [*ACP*] 2015; Konstantinides et al., [*ESC*] 2014; Riley et al., 2016; Uresandi et al., [*SEPAR*] 2013).

- Since D-dimer levels are elevated in any significant thrombotic process, their [ability] to predict the presence of pulmonary embolism and/or deep venous thrombosis is [decreased] in patients with recent surgery, significant trauma, cancer, or renal failure (Konstantinides et al., [*ESC*] 2014).
- CTPA has a sensitivity and specificity of 95-100% for PE in patients with low or intermediate pretest probability (Raja et al., [*ACP*] 2015).
- The sensitivity of V/Q scanning for PE is 50-98% and the specificity 20-60% (Raja et al., [*ACP*] 2015).
- With an increasing clinical consensus that not all PEs should be treated, it is clear that PE imaging is best evaluated on the basis of outcomes rather than accuracy. In a prospective study comparing V/Q and CTPA, Anderson et al. (2007) showed that the outcomes (based on a 3-mo follow-up of negative cases) were similar (false-negative rate, ≤1%) despite the fact that more PEs were detected with CTPA than with V/Q scans (17.7% for CTPA and 11.7% for V/Q) (Waxman et al., [*SNMMI*] 2017).
- Lower extremity ultrasound may be beneficial in:
    - Patients with symptoms of acute PE and DVT (Raja et al., [*ACP*] 2015; Fesmire et al., [*ACEP*] 2011/Level B recommendation; Konstantinides et al., [*ESC*] 2014/Level B recommendation);
    - Patients being evaluated for acute PE who have indeterminate or nondiagnostic CTPA or V/Q scans (Fesmire et al., [*ACEP*] 2011/Level C recommendation); or
    - Patients for whom CTPA is unable to rule out a PE in the main, lobar or segmental PA (PLE expert panel consensus opinion).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al., [*THANZ*] 2019).
- It is recommended not to perform CT venography routinely to increase the diagnostic yield of CTPA (Uresandi et al., [*SEPAR*] 2013).
- Pulmonary angiography is not free of risk, and is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy (Konstantinides et al., [*ESC*] 2014). Pulmonary angiography is invasive and should only be used in patients in whom the diagnosis is uncertain after V/Q scanning [and ultrasound or the lower extremity], or [if CTPA is inadequate to rule out a PE in the main or lobar artery] (Raja et al., [*ACP*] 2015; PLE expert panel consensus opinion).

<u>Technical notes:</u>

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al., [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al., [*ACR*] 2017).

<u>Evidence update (2014-present):</u>

Hess et al. (2016), in a systematic review and meta-analysis, reported the diagnostic performance of single-photon emission computed tomography (V/Q SPECT) with or without additional low-dose CT (SPECT/CT) and CT angiography (CTA). Eight articles met inclusion criteria. The authors concluded that V/Q SPECT, V/Q SPECT/CT, and CTA are all viable options, but consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance. Pooled sensitivities of V/Q SPECT/CT vs. CTA was (97.6 vs. 82.0%), specificities (95.9 vs. 94.9%), positive predictive values (93.0 vs. 93.8%), negative predictive values (98.6 vs. 84.7%), and accuracies (96.5 vs. 88.6%) (high level of evidence).

Kan et al. (2015), in a systematic review/meta-analysis, concluded that V/Q SPECT is an accurate method in acute PE patients with high sensitivity and high specificity in the diagnosis of PE. Nine studies met the inclusion criteria. The pooled sensitivity and specificity of V/Q SPECT in the diagnosis of acute PE patients, calculated on a per-patient-based analysis, was 96% (95% confidence interval 95-97%), and 97% (95% CI, 96-98%) respectively. The pooled negative LR, positive LR of V/Q SPECT in acute PE patients was 0.06 (range, 0.02-0.19) and 16.64 (range, 9.78-31.54). The area under the ROC curve of V/Q SPECT in the diagnosis of acute PE patients was 0.99 (high level of evidence).

Phillips et al. (2015), in a systematic review and meta-analysis of 19 studies (n = 5923 patients), showed no performance difference between V/Q SPECT and CTPA; planar V/Q is inferior. CTPA is clearly the most cost effective technique. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is inappropriate (high level of evidence for diagnostic accuracy).

Stubbs et al. (2017), in a retrospective study of 1300 consecutive V/Q exams, found that indeterminate scans were decreased from 72/589 (12.2%) in the planar group ($P < 0.05$) to 42/542 (7.7%) in the SPECT group. The authors concluded that V/Q SPECT has greater diagnostic certainty of PE with a reduction in an indeterminate scan frequency compared with planar scintigraphy (moderate level of evidence).

Sun et al. (2014), in a retrospective cohort study of 90 consecutive noncontrast CT exams, concluded that non-contrast chest CT is neither sensitive nor specific enough to accurately detect central PE (low level of evidence).

Li et al. (2016), in a systematic review/meta-analysis, concluded that MRA can be used for the diagnosis of acute PE, however, due to limited sensitivity, cannot be used as a stand-alone test to exclude acute PE. Five studies were included in the meta-analysis. The pooled sensitivity 0.83 (0.78-0.88) and specificity 0.99 (0.98-1.00) demonstrated that MRA diagnosis had limited sensitivity and high specificity in the detection of acute PE (moderate level of evidence).

Zhou et al. (2015) conducted a systematic review and meta-analysis of 15 studies for patient accuracy and 9 studies for vessel accuracy on MRI. The authors concluded that MRI exhibits a high diagnostic capability with proximal arteries, but lacks sensitivity for peripheral embolism. The patient-based analysis yielded an overall sensitivity of 0.75 (0.70-0.79) and 0.84 (0.80-0.87) for all patients and patients with technically adequate images, respectively. The overall specificity was 0.80 (0.77-0.83) and 0.97 (0.96-0.98). On average, MRI was technically inadequate in 18.89% of patients (range, 2.10%-27.70%) (low level of evidence).

Bates et al. (2016), in a multicenter prospective cohort management study of 808 consecutive patients with suspected PE, evaluated whether PE can be safely excluded in patients with a negative D-dimer without incorporating clinical probability assessment. Ninety-nine (12%) were diagnosed with VTE at presentation. Four hundred and twenty (52%) had a negative D-dimer level at presentation and were treated without anticoagulation; of these, one had VTE during follow-up. The negative predictive value of D-dimer testing for PE was 99.8% (95% CI, 98.7 – 99.9) (high level of evidence).

van Es et al. (2016), in a systematic review and meta-analysis, concluded that age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients with suspected PE in whom imaging can be safely withheld compared with fixed D-dimer testing (high level of evidence).

Woller et al. (2014), in a retrospective study of 923 patients who underwent CTPA, compared the safety of age-adjusted D-dimer thresholds in the work-up of patients for suspected PE. The authors report that the use of an age-adjusted D-dimer threshold among patients considered unlikely to have PE was associated with a low 90-day rate of failure to diagnose PE, although using an age-adjusted D-dimer threshold did result in missing more cases of PE. Among 104 patients with a negative conventional D-dimer test result and a Revised Geneva Score (RGS) ≤10, no PE was observed within 90 days (false-negative rate, 0%; 95% CI, 0%-2.8%). Among 273 patients with a negative age-adjusted D-dimer result and an RGS ≤10, four PEs were observed within 90 days (false-negative rate, 1.5%; 95% CI, 0.4%-3.7%). We observed an 18.3% (95% CI, 15.9%-21.0%) absolute reduction in the proportion of patients aged >50 years who would merit CTPA by using age-adjusted D-dimer thresholds (low level of evidence).

Lindner et al. (2014) conducted a retrospective study of 1305 patients who presented to an academic emergency department and who had CTPA and D-dimer to work-up potential pulmonary embolism. The objective of the study was to determine the diagnostic accuracy of D-dimer to rule out PE in patients with renal insufficiency, in which D-dimer can be elevated due to inherent renal pathology. The authors found that sensitivity of D-dimer for patients with an eGFR > 60 mL/min was 96% (95% CI: 0.93 – 0.99) and 100% (95% CI: 100-100%) for those with 30-60 mL/min eGFR, though specificity decreased significantly with impaired renal function. The authors concluded that D-dimer levels were elevated in patients with an eGFR < 60 mL/min, though were still highly sensitive for exclusion of PE. Additionally, because almost all patients with impaired renal function had elevated D-dimer irrespective of the presence of PE, the authors posit that future studies should be performed to determine renal function-adjusted D-dimer cutoffs for PE (low level of evidence).

Wilts et al. (2017), in a prospective study of 3,324 patients, found that the use of age-adjusted D-dimer cutoff versus a conventional cutoff doubles the proportion of patients with cancer in whom PE can be safely excluded by clinical decision rule and D-dimer without imaging (moderate level of evidence).

Polo Friz et al. (2014), in a retrospective cohort study of 481 patients, evaluated in the ED, sought to evaluate whether using a higher cutoff value for D-dimer could increase the test specificity without reducing its sensitivity for ruling out PE in elderly and very elderly patients presenting to the Emergency Department (ED). The authors concluded that in elderly subjects with clinically suspected PE, the application of a fixed higher D-dimer cutoff (1000ng/ml) increases the specificity of D-dimer assay for excluding PE without reducing test sensitivity (low level of evidence).

Sharp et al. (2016), in a retrospective study of 31,094 ED patients > 50 years, sought to determine the accuracy of age-adjusted D-dimer threshold to detect PE. Over a 6-year study period, the expected number of missed or delayed PE diagnoses because of false-negative D-dimer test results would have been 36 with the age-adjusted threshold, 10 with the threshold of 500 ng/dL, and 80 with the threshold of 1,000 ng/dL. The authors concluded that their data supports the use of D-dimer and age adjustment to further aid ability to exclude acute PE (low level of evidence).

Aleva et al. (2017) conducted a systematic review and meta-analysis of seven studies to determine the prevalence, embolus localization, clinical relevance, and clinical markers of PE in unexplained acute exacerbations of COPD (AE-COPD). The pooled prevalence of PE in unexplained AE-COPD was found to be 16.1% (95% CI, 8.3%-25.8%). A total of 68% of the emboli found were located in the main pulmonary arteries, lobar arteries, or interlobar arteries. Mortality and length of hospital admission seemed to increase in those with unexplained AE-COPD and PE. The authors conclude that PE is frequently seen in unexplained AE-COPD, and two-thirds of emboli are found at locations that have a clear indication for

anticoagulant treatment. PE should receive increased awareness in those with unexplained AE-COPD (moderate level of evidence).

Squizzato et al. (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI (moderate level of evidence).

Chen et al. (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE (low level of evidence).

Pasin et al. (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for pulmonary embolism in 93 patients with CTPA as the gold standard. PE prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected (low level of evidence).

Parry et al. (2018), in a multicenter (n =24) cross-sectional study of 3,837 consecutive ED patients, evaluated characteristics of an automated INNOVANCE D-dimer assay for exclusion of PE and DVT using both standard and age-adjusted cut-offs. All patients had low or intermediate Wells score, and < 500 ng/ml was used as a standard negative D-dimer result. The diagnostic standard was imaging (CTPA or V/Q for PE, and venous U/S or contrast venography for DVT) demonstrating PE or DVT within 3 months. Mean age of patients evaluated for PE (n=1834) was 48 +/- 16 years and for DVT (n=1752) was 53 +/- 16 years. D-dimer test characteristics for PE were: sensitivity 98.0%, specificity 55.4%, negative predictive value (NPV) 99.8%, positive predictive value (PPV) 11.4%, and for DVT were: sensitivity 92.0%, specificity 44.8%, NPV 98.8%, PPV 10.3%. Age adjustment [age (years) * 10] increased specificity (59.6% [PE], 51.1% [DVT]). The authors conclude that D-dimer testing is highly sensitive and can be used to exclude PE and first event of proximal DVT in ED patients with low- and intermediate- pre-test probability. Age adjustment increases specificity without increasing false negatives (moderate level of evidence).

High clinical suspicion and/or high pretest probability for pulmonary embolus based on a validated clinical prediction rule:

- **Green** – CTPA or CT chest with IV contrast
- **Yellow** – V/Q SPECT or V/Q SPECT/CT
- **Yellow** – V/Q scanning in patients unable to undergo CTPA or CT chest with IV contrast
- **Yellow** – V/Q scanning if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Yellow** – Perfusion scan in patients in clinical distress who are unable to undergo CTPA, CT chest with IV contrast, or V/Q scanning
- **Yellow** – Pulmonary MRA in patients unable to undergo CTPA or CT chest with IV contrast, or if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Orange** – CT venography of the lower extremities, except when ultrasound is not available
- **Red** – CT chest without IV contrast; CT chest without and with IV contrast; MRI chest

Level of Evidence: High

Notes concerning applicability and/or patient preferences: V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al., 2016; Kan et al., 2015; Phillips et al., 2015; Stubbs et al., 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al., 2017; Squizzato et al., 2017; and Pasin et al., 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al. review, and 18.89% in the Zhou et al. 2015 study. The use of MRI is also limited by the presence of claustrophobia in a significant number of patients and by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA if to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
Clinicians should use validated clinical prediction rules to estimate the pretest probability in patients with suspected PE (Raja et al., [*ACP*] 2015; Streiff et al., 2016; Qaseem et al., [*ACP/AAFP*] 2007).

In patients with a high pretest probability or high clinical suspicion for PE, CTPA is the preferred method of diagnosis when available and the patient has no contraindications to contrast (Raja et al., [*ACP*] 2015; Konstantinides et al., [*ESC*] 2014; *NICE* 2015).

In the evaluation for acute PE, clinicians should reserve V/Q scanning for patients who have a contraindication to CTPA or if CTPA is not available (Raja et al., [*ACP*] 2015; Konstantinides et al., [*ESC*] 2014; *NICE* 2015).

The *ACR* gives CTPA and optimized CT chest with IV contrast a score of 9, Tc-99m V/Q scan 7, MRA chest 6, and CTA chest with CT venography 5 in patients with a high pretest probability (Kirsch et al., [*ACR*] 2017*).

CTPA and V/Q scanning are not generally indicated in patients with suspected PE and a known or recently diagnosed [proximal] deep venous thrombosis or pelvic vein thrombosis currently undergoing treatment, as the results will not eliminate the need for anticoagulation therapy (Raja et al., [*ACP*] 2015; Fesmire et al., [*ACEP*] 2011/Level B recommendation; Konstantinides et al., [*ESC*] 2014/Level B recommendation).

Computed tomography pulmonary angiography (CTPA) is the preferred imaging modality for suspected PE due to its accuracy (Tran et al., [*THANZ*] 2019, GRADE: Strong; Evidence, High). A negative technically adequate CTPA excludes PE and anticoagulation can be safely withheld (Tran et al., [*THANZ*] 2019*, strong recommendation/high level of evidence).

Ventilation–perfusion (VQ) scanning does not require radiocontrast, and so is suitable for patients with renal impairment (Tran et al., [THANZ] 2019, GRADE: Strong; Evidence, High). A normal VQ scan excludes PE and anticoagulation can be safely withheld (Tran et al., [*THANZ*] 2019*, strong recommendation/high level of evidence).

MRI and pulmonary MRA should not be done as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014; Uresandi et al., [*SEPAR*] 2013*). A new systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism (Chen et al. 2017).

In patients with the clinical scenario: *PE likely, D-dimer negative*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 8 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, male or nonpregnant female with normal or mild abnormality chest radiograph*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *suspected PE, male or nonpregnant female with significant abnormal chest radiograph*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 5 (may be appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, patient with abnormal renal function*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, patient at risk for contrast complication*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, patient who cannot cooperate for ventilation imaging,*

perfusion only, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 5 (may be appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, CTPA inconclusive or discordant with clinical probability*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

In patients with the clinical scenario: *PE likely, ultrasound of lower extremity with clot*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging. *The PLE expert panel thought that V/Q scanning would not be indicated in this patient populations unless it changes therapy, as patients may undergo anticoagulation therapy for the DVT.*

Because CT uses ionizing radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014).

It is recommended not to perform CT venography routinely to increase the diagnostic yield of CTPA (Uresandi et al., [*SEPAR*] 2013*).

* This guideline did not pass the AGREE II cutoff of 90. It was included, however, because of its direct relevance to this scenario.

Clinical notes:

- Patients with suspected PE should, where reasonably practical, undergo investigation on the same day of presentation to exclude a diagnosis of PE (Howard et al., [*BTS*] 2018).
- Chest radiographs should be obtained in all patients with pulmonary symptoms to exclude other causes for the patient's symptoms and signs (*NICE* 2015).
- PERC should not be applied to patients at intermediate or high risk for PE (Raja et al., [*ACP*] 2015).
- D-dimer testing should not be obtained in patients with a high clinical suspicion of PE or in patients with a high pretest probability of PE as the results will not eliminate the need for anticoagulation therapy (Raja et al., [*ACP*] 2015; Uresandi et al., [*SEPAR*] 2013). A normal value does not exclude PE in patients with a high pretest probability (Konstantinides et al., [*ESC*] 2014).
- CT angiography has a sensitivity of 85-95% in patients with a high pretest probability of PE (Raja et al., [*ACP*] 2015).
- The sensitivity of V/Q scanning for acute PE is 50-98% and the specificity 20-60% (Raja et al., [*ACP*] 2015).
- With an increasing clinical consensus that not all PEs should be treated, it is clear that PE imaging is best evaluated on the basis of outcomes rather than accuracy. In a prospective study comparing V/Q and CTPA, Anderson et al. (2007) showed that the outcomes (based on a 3-mo follow-up of negative cases) were similar (false-negative rate, ≤1%) despite the fact that more PEs were detected with CTPA than with V/Q scans (17.7% for CTPA and 11.7% for V/Q) (Waxman et al., [*SNMMI*] 2017).
- Additional testing should be considered in patients with a high clinical suspicion for PE and a negative CTPA (Uresandi et al., [*SEPAR*] 2013; Moores et al., 2016).
- Lower extremity ultrasound may be beneficial in:

    - Patients with symptoms of acute PE and DVT (Raja et al., [*ACP*] 2015; Fesmire et al., [*ACEP*] 2011/Level B recommendation; Konstantinides et al., [*ESC*] 2014/Level B recommendation);
    - Patients with a high pretest probability for PE be who have negative, indeterminate or nondiagnostic CTPA or V/Q scans (Fesmire et al., [*ACEP*] 2011/Level C recommendation); or
    - Patients for whom CTPA is unable to rule out a PE in the main, lobar or segmental PA (PLE expert panel consensus opinion).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al., [*THANZ*] 2019).
- Pulmonary angiography is not free of risk, and is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy (Konstantinides et al., [*ESC*] 2014). Pulmonary angiography is invasive and should only be used in patients in whom the diagnosis is uncertain after V/Q scanning [and ultrasound or the lower extremity], or [if CTPA is inadequate to rule out a PE in the main or lobar artery] (Raja et al., [*ACP*] 2015; PLE expert panel consensus opinion).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al., [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al., [*ACR*] 2017).

Evidence update (2014-present):

Moores et al. (2016) conducted a prospective study of 498 patients with high probability of PE and a completed CTPA study. CTPA excluded PE in 134 patients; in these patients, the pooled incidence of VTE was 5.2% (seven of 134 patients; 95% confidence interval [CI] 1.5–9.0). None of the patients had a fatal PE during follow-up. The authors concluded that "a negative multi-detector CTPA result alone may not safely exclude PE in patients with a high clinical retest probability" (moderate level of evidence).

Hess et al. (2016), in a systematic review and meta-analysis, reported the diagnostic performance of single-photon emission computed tomography (V/Q SPECT) with or without additional low-dose CT (SPECT/CT) and CT angiography (CTA). Eight articles met inclusion criteria. The authors concluded that V/Q SPECT, V/Q SPECT/CT, and CTA are all viable options, but consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance. Pooled sensitivities of V/Q SPECT/CT vs. CTA was (97.6 vs. 82.0%), specificities (95.9 vs. 94.9%), positive predictive values (93.0 vs. 93.8%), negative predictive values (98.6 vs. 84.7%), and accuracies (96.5 vs. 88.6%) (high level of evidence).

Kan et al. (2015), in a systematic review/meta-analysis, concluded that V/Q SPECT is an accurate method in acute PE patients with high sensitivity and high specificity in the diagnosis of PE. Nine studies met the inclusion criteria. The pooled sensitivity and specificity of V/Q SPECT in the diagnosis of acute PE patients, calculated on a per-patient-based analysis, was 96% (95% confidence interval 95-97%), and 97% (95% CI, 96-98%) respectively. The pooled negative LR, positive LR of V/Q SPECT in acute PE patients was 0.06 (range, 0.02-0.19) and 16.64 (range, 9.78-31.54). The area under the ROC curve of V/Q SPECT in the diagnosis of acute PE patients was 0.99 (high level of evidence).

Phillips et al. (2015), in a systematic review and meta-analysis of 19 studies (n = 5,923 patients), showed no performance difference between V/Q SPECT and CTPA; planar V/Q is inferior. CTPA is clearly the

most cost effective technique. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is inappropriate (high level of evidence for diagnostic accuracy).

Stubbs et al. (2017), in a retrospective study of 1300 consecutive V/Q exams, found that indeterminate scans were decreased from 72/589 (12.2%) in the planar group ($P < 0.05$) to 42/542 (7.7%) in the SPECT group. The authors concluded that V/Q SPECT has greater diagnostic certainty of PE with a reduction in an indeterminate scan frequency compared with planar scintigraphy (moderate level of evidence).

Sun et al. (2014), in a retrospective cohort study of 90 consecutive noncontrast CT exams, concluded that non-contrast chest CT is neither sensitive nor specific enough to accurately detect central PE (low level of evidence).

Li et al. (2016), in a systematic review/meta-analysis, concluded that MRA can be used for the diagnosis of acute PE, however, due to limited sensitivity, cannot be used as a stand-alone test to exclude acute PE. Five studies were included in the meta-analysis. The pooled sensitivity 0.83 (0.78-0.88) and specificity 0.99 (0.98-1.00) demonstrated that MRA diagnosis had limited sensitivity and high specificity in the detection of acute PE (moderate level of evidence).

Zhou et al. (2015) conducted a systematic review and meta-analysis of 15 studies for patient accuracy and 9 studies for vessel accuracy on MRI. The authors concluded that MRI exhibits a high diagnostic capability with proximal arteries, but lacks sensitivity for peripheral embolism. The patient-based analysis yielded an overall sensitivity of 0.75 (0.70-0.79) and 0.84 (0.80-0.87) for all patients and patients with technically adequate images, respectively. The overall specificity was 0.80 (0.77-0.83) and 0.97 (0.96-0.98). On average, MRI was technically inadequate in 18.89% of patients (range, 2.10%-27.70%) (low level of evidence).

Squizzato et al. (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI (moderate level of evidence).

Chen et al. (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE (low level of evidence).

Pasin et al. (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for pulmonary embolism in 93 patients with CTPA as the gold standard. PE

prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected (low level of evidence).

Suspected chronic thromboembolic pulmonary hypertension (CTEPH) in a patient with newly diagnosed pulmonary hypertension:

- **Green** – V/Q scanning to screen/diagnose CTEPH
- **Green** – CTPA to confirm CTEPH and/or to assess the anatomical extent of surgically accessible embolism in patients with CTEPH
- **Yellow** – CTPA and/or CT chest with IV contrast to screen for the diagnosis of CTEPH*
- **Red** – MRI chest; MRA chest; CT chest without IV contrast; CT chest without and with IV contrast; perfusion scan

*If CTPA is used to differentiate CTEPH from IPAH, then the exam should be performed in a center of excellence with 40- or 64- row MDCT technology and subspecialty radiologic expertise (PLE expert panel consensus opinion).

Level of Evidence: Low

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
V/Q scanning is recommended in all patients with unexplained PH to assess for CTEPH (Sirajuddin et al., [*ACR*] 2017; Jaff et al., 2011; Galiè et al., [*ESC*] 2015).

V/Q scanning is the procedure of choice in evaluating for CTEPH and differentiating CTEPH from other causes of PH (Sirajuddin et al., [*ACR*] 2017; Konstantinides et al., [*ESC*] 2014).

V/Q lung scanning is recommended instead of CT pulmonary angiography as a screening test to rule out the possibility of CTEPH in patients diagnosed with PH. A normal [or low probability] V/Q scan effectively rules out the possibility of CTEPH (Mehta et al., [*CTS*] 2010/Grade 1C).

In patients with prior PE who have ongoing symptoms (e.g., decreased exercise tolerance, dyspnea), perform a VQ scan and [echocardiography] to assess for residual pulmonary obstruction and screen for pulmonary hypertension (Tran et al., [*THANZ*] 2019, Low; Evidence moderate).

Routine follow-up imaging (echocardiography, V/Q, CT or MR) is not recommended as a screening tool for CTEPH in asymptomatic patients following an acute VTE event (Mehta et al., [*CTS*] 2010/Grade 2C; Galiè et al., [*ESC*] 2015).

CT pulmonary angiogram is recommended to assess the anatomical extent of surgically accessible embolism in CTEPH. V/Q lung scanning should not be used to assess the anatomical extent of potentially surgically accessible CTEPH (Mehta et al., [*CTS*] 2010/Grade 1C).

The *ACR* states that CTPA is useful to evaluate patients with unexplained PH and gives both V/Q scanning and CTPA values of 8 (Sirajuddin et al., [*ACR*] 2017).

MR pulmonary angiography is not recommended for the preoperative assessment of patients with CTEPH (Mehta et al., [*CTS*] 2010/Grade 2C).

Clinical notes:

- Subspecialty pulmonologist consultation should be considered in the evaluation of patients with suspected CTEPH (Tran et al., [*THANZ*] 2019; PLE expert panel consensus opinion).
- Patients with unexplained dyspnea, exercise intolerance or clinical evidence of right-sided heart failure, with or without prior history of symptomatic VTE, should be evaluated for CTEPH (Jaff et al., [*AHA*] 2011/ Class I recommendation, level C evidence).
- 25% of patients with CTEPH have no known history of pulmonary embolism (Pepke-Zaba et al., 2011).
- V/Q scanning has a sensitivity of 90-100% and specificity of 90-100% for the differentiation of CTEPH and IPAH (Jaff et al., [*AHA*] 2011; Sirajuddin et al., [*ACR*] 2017; Galiè et al., [*ESC*] 2015).
- A normal or low probability V/Q scan effectively excludes the diagnosis of CTEPH with a sensitivity of 90–100% and a specificity of 94–100% (Jaff et al., [*AHA*] 2011; Sirajuddin et al., [*ACR*] 2017; Tunariu et al., 2007).
- A relatively normal CTPA can be observed in CTEPH despite substantial V/Q scan abnormalities (Jaff et al., [*AHA*] 2011).
- Initial studies found that V/Q imaging was more sensitive for CTEPH compared to CTPA at 96-97.4% versus 51%. Subsequent studies with 40- or 64-row scanners have suggested that CTPA may be accurate for the detection of CTEPH in expert hands (Sirajuddin et al., [*ACR*] 2017; Galiè et al., [*ESC*] 2015). If CTPA is used to differentiate CTEPH from IPAH then 40- or 64- row MDCT technology is recommended at a center with local expertise (PLE expert panel consensus opinion).
- A negative CTPA does not effectively rule out the presence of surgically accessible embolism in CTEPH, which is better assessed by contrast pulmonary angiography (Mehta et al., [*CTS*] 2010).
- CTPA chest has better sensitivity for CTEPH than does MRA with and without IV contrast (Sirajuddin et al., [*ACR*] 2017).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al., [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al., [*ACR*] 2017).

Evidence update (2014-present):

Dong et al. (2015), in a systematic review and meta-analysis of 11 articles (n = 712), found CT as a favorable method to rule in CTEPH and to rule out pulmonary endarterectomy (PEA) patients for proximal branches. The patient-based analysis demonstrated a pooled sensitivity of 76% (95% confidence interval [CI]: 69% to 82%), and a pooled specificity of 96% (95% CI: 93%to 98%). This resulted in a pooled diagnostic odds ratio (DOR) of 191 (95% CI: 75 to 486) (moderate level of evidence).

Masy et al (2018), in a retrospective study, compared concordance rates between dual-energy CT (DECT) perfusion and V/Q scanning in diagnosing CTEPH among 80 consecutive patients with pulmonary hypertension. Final diagnosis (36 with CTEPH, 44 with non-CTEPH) was established by multidisciplinary expert review (gold standard) according to recommended guidelines and standard CT angiographic information. Imaging criteria for diagnosing CTEPH relied on $\geq$ 1 segmental triangular perfusion defect on DECT perfusion studies and V/Q mismatch on scintigraphy examinations. On DECT perfusion studies, there were 35 true positives, 6 false positives and 1 false negative (sensitivity 0.97, specificity 0.86, PPV

0.85, NPV 0.97). On V/Q scans, there were 35 true positives and 1 false negative (sensitivity 0.97, specificity 1, PPV 1, NPV 0.98). There was excellent agreement between CT perfusion and scintigraphy in diagnosing CTEPH (kappa value 0.80). Combined information from DECT perfusion and CT angiographic images enabled correct reclassification of the DECT perfusion studies (low level of evidence). *The expert panel noted that DECT perfusion scan is an emerging technology and has limited availability in the community outpatient setting* (PLE expert panel consensus opinion).

Evaluation for new or recurrent pulmonary embolism (PE) in patients with a history of treated thromboembolic disease and a high or likely clinical probability of PE or an elevated D-dimer test result:

- **Green** – CTPA or CT chest with IV contrast
- **Yellow** – V/Q SPECT or V/Q SPECT/CT
- **Yellow** – V/Q scanning in patients unable to undergo CTPA or CT chest with IV contrast
- **Yellow** – V/Q scanning if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Yellow** – Perfusion scan in patients in clinical distress who are unable to undergo CTPA, CT chest with IV contrast, or V/Q scanning
- **Yellow** – Pulmonary MRA in patients unable to undergo CTPA or CT chest with IV contrast, or if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Orange** – CT venography to evaluate for progressive or recurrent DVT, except when ultrasound is not available
- **Red** – CT chest without IV contrast; CT chest without and with IV contrast; Pulmonary MRA; MRI chest

Level of Evidence: Low

Notes concerning applicability and/or patient preferences: V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al., 2016; Kan et al., 2015; Phillips et al., 2015; Stubbs et al., 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al., 2017; Squizzato et al., 2017; and Pasin et al., 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al. review, and 18.89% in the Zhou et al. 2015 study. The use of MRI is also limited by the presence of claustrophobia in a significant number of patients and by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA if to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
In patients with the clinical scenario: *recent/prior documentation of PE with CTPA, suspected new PE*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 2 (rarely appropriate) to V/Q imaging.

In patients with the clinical scenario: *recent/prior documentation of PE with V/Q scan, suspected new PE*,

the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

MRI and pulmonary MRA should not be done as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014). *A new systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism* (Chen et al., 2017).

Imaging of the lower extremity may be performed to exclude new or recurrent DVT. Because of the additional radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014).

It is recommended not to perform CT venography routinely to increase the diagnostic yield of CTPA (Uresandi et al., [*SEPAR*] 2013*).

* This guideline did not pass the AGREE II cutoff of 90. It was included, however, because of its direct relevance to this scenario.

Clinical notes:

- Patients with suspected PE should, where reasonably practical, undergo investigation on the same day of presentation to exclude a diagnosis of PE (Howard et al., [*BTS*] 2018).
- The standard diagnostic algorithms outlined above apply in patients with a history of treated PE although they are less efficient with CTPA avoided in only 15% of patients with this history (Fabiá Valls et al., 2015).
- Residual defects may complicate the interpretation of CTPA and V/Q in patients with recurrent PE (Choi et al., 2016; den Exter et al., 2015).
- An ultrasound at 3-6 months is useful as a baseline for comparison with future ultrasound for suspected recurrent DVT (Tran et al., [*THANZ*] 2019).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al., [*THANZ*] 2019).

Technical notes:

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al., [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al., [*ACR*] 2017).

Evidence update (2014-present):

Fabiá Valls et al. (2015) reported on a meta-analysis of four prospective studies evaluating a diagnostic algorithm using clinical prediction rules, D-dimer testing and CTPA in consecutive patients with clinically suspected PE and a history of VTE. Four studies concerning 1,286 patients were included with a pooled baseline PE prevalence of 36% (95% confidence interval [CI] 30–42). In only 217 patients (15%; 95% CI 11–20) PE could be excluded without CTPA. The three-month VTE incidence rate was 0.8% (95% CI 0.06–2.4) in patients managed without CTPA, 1.6% (95% CI 0.3–4.0) in patients in whom PE was excluded by CTPA and 1.4% (95% CI 0.6–2.7) overall. In the pooled studies, PE was safely excluded in patients with a history of VTE based on a CPR followed by a D-dimer test and/or CTPA, although the efficiency of the

algorithm is relatively low compared to patients without a history of VTE (high level of evidence). One of these studies explicitly excluded patients with ongoing anticoagulation therapy. Two studies excluded patients on vitamin K antagonists. It is assumed that the final study also excluded patients with long term anticoagulant therapy as anticoagulant therapy was withheld in patients with low probability and normal D-dimer levels (high level of evidence).

Mos et al. (2014) conducted a prospective multicenter study of 512 patients with clinically suspected acute recurrent PE. 17% of patients had an unlikely clinical probability (Well's score ≤4) and negative D-dimer and were not imaged with CTPA. None of these patients developed a recurrent PE (0%; 95% CI 0.0-3.4%) during the 3-month follow-up period. CTPA was performed in the remaining patients and was positive for PE in 33%. During the follow-up period, seven out of 253 patients with a negative CTPA had recurrent VTE, of which one was fatal (moderate level of evidence).

Squizzato et al. (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI (moderate level of evidence).

Chen et al. (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE (low level of evidence).

Pasin et al. (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for pulmonary embolism in 93 patients with CTPA as the gold standard. PE prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected (low level of evidence).

Evaluation for new or recurrent PE in patients on therapy for thromboembolic disease (DVT or PE):

- **Green** – CTPA or CT chest with IV contrast
- **Yellow** – V/Q SPECT or V/Q SPECT/CT
- **Yellow** – V/Q scanning in patients unable to undergo CTPA or CT chest with IV contrast
- **Yellow** – V/Q scanning if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Yellow** – Perfusion scan in patients in clinical distress who are unable to undergo CTPA, CT chest with IV contrast, or V/Q scanning
- **Yellow** – Pulmonary MRA in patients unable to undergo CTPA or CT chest with IV contrast, or if CTPA or CT chest with IV contrast is unable to rule out a PE in the main, lobar, and segmental arteries
- **Orange** – CT venography to evaluate for progressive or recurrent DVT, except when ultrasound is not available
- **Red** – CT chest without IV contrast; CT chest without and with IV contrast; Pulmonary MRA; MRI chest

Level of Evidence: Panel consensus opinion

Notes concerning applicability and/or patient preferences: V/Q SPECT and V/Q SPECT/CT were downgraded from green to yellow despite favorable accuracy in recent reports (Hess et al., 2016; Kan et al., 2015; Phillips et al., 2015; Stubbs et al., 2017) because of concern surrounding the applicability and availability of this evolving technology in the community outpatient setting (PLE expert panel consensus opinion).

Pulmonary MRA was downgraded from green to yellow despite favorable accuracy reported in the recent studies (Chen et al., 2017; Squizzato et al., 2017; and Pasin et al., 2017) because of concerns about the applicability, expertise and availability of emergent pulmonary MRA in an outpatient setting. Pulmonary MRA was also downgraded because of concerns over the rate of nondiagnostic MRI studies which was reported to be 6.3-30.3% in three of the studies in the Squizzato et al. review, and 18.89% in the Zhou et al. 2015 study. The use of MRI is also limited by the presence of claustrophobia in a significant number of patients and by concerns over the need to exclude electrical implants, metallic implants and foreign bodies in patients undergoing emergent imaging. The expert panel thought that if pulmonary MRA if to be performed to exclude PE, it should only be done in MRI centers with high field strength MRI systems, experience, and appropriate clinical expertise in pulmonary imaging (PLE expert panel consensus opinion).

Guideline and PLE expert panel consensus summary:
Preventing frequent use of repeated CT requires thoughtful planning. Clinicians should educate patients about the risk of radiation from multiple CTs. When such patients develop symptoms, providers should review them in the context of their prior symptoms and discuss testing strategies with the patients and their primary care providers (Raja et al., [*ACP*] 2015).

In patients with recurrent VTE despite anticoagulation, it is important for providers to assess adherence to therapy and identify clinical conditions associated with anticoagulation failure including cancer,

antiphospholipid syndrome, heparin-induced thrombocytopenia and vascular compression syndromes (Streiff et al., 2016).

CTPA or V/Q scanning should only be obtained if documentation of recurrent PE will change therapy (PLE expert panel consensus opinion).

In patients with the clinical scenario: *recent documentation of PE by CTPA, patient now on anticoagulation; imaging to document disease status when clinically indicated*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 2 (rarely appropriate) to V/Q imaging.

In patients with the clinical scenario: *recent documentation of PE by V/Q scan, patient now on anticoagulation; imaging to document disease status when clinically indicated*, the *Society of Nuclear Medicine and Molecular Imaging* (Waxman et al., [*SNMMI*] 2017) assigns a score of 9 (appropriate) to V/Q imaging.

MRI and pulmonary MRA should not be done as it has not been found to have the sensitivity or specificity required to detect segmental or subsegmental PEs and has a high proportion of inconclusive scans (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014). *A new systematic review/meta-analysis indicates that pulmonary MRA using newer techniques has a similar accuracy for large vessel pulmonary embolism, and may have a higher sensitivity for subsegmental pulmonary embolism* (Chen et al. 2017).

Imaging of the lower extremity may be performed to exclude new or recurrent DVT. Because of the additional radiation, compression ultrasound should be used instead of CT venography when indicated to exclude the presence of DVT (Kirsch et al., [*ACR*] 2017*; Konstantinides et al., [*ESC*] 2014).

It is recommended not to perform CT venography routinely to increase the diagnostic yield of CTPA (Uresandi et al., [*SEPAR*] 2013*).

<u>Clinical notes:</u>

- The standard diagnostic algorithms outlined above apply in patients with a history of treated PE, although they are less efficient, with CTPA avoided in only 15% of patients with this history (Fabiá Valls et al., 2015).
- Residual defects may complicate the interpretation of CTPA and V/Q in patients with recurrent PE (Choi et al., 2016; den Exter et al., 2015).
- An ultrasound at 3-6 months is useful as a baseline for comparison with future ultrasound for suspected recurrent DVT (Tran et al., [*THANZ*] 2019).
- In general, a negative whole leg ultrasound is sufficient to exclude DVT (Tran et al., [*THANZ*] 2019).

<u>Technical notes:</u>

- CTPA and chest CT with IV contrast should be optimized for pulmonary artery enhancement (Kirsch et al., [*ACR*] 2017).
- Chest CT with IV contrast, if performed, should include sagittal and coronal high resolution reconstructions. CTPA and optimized Chest CT IV contrast exams differ only in the inclusion of 3D rendering with CTPA (Kirsch et al., [*ACR*] 2017).

Evidence update (2014-present):
Squizzato et al. (2017) conducted a systematic review and meta-analysis of 13 studies (total n = 1170) to systematically assess the diagnostic accuracy of MRI for PE diagnosis. 11/13 studies used MR contrast. Only 3 (23.1%) studies reported rate of inconclusive MRI results, ranging from 6.3 to 30.3% (mean prevalence of 19%) of all performed MRI. All 3 studies required imaging down to subsegmental arteries to exclude PE. After exclusion of technical inadequate results, MRI bivariate weighted mean sensitivity was 80.9% (95% CI, 68.2-89.4%) with a bivariate weighted mean specificity of 96.4% (95% CI, 92.4-98.3%). The authors conclude that MRI has high specificity but limited sensitivity for the diagnosis of PE. Inconclusive results are a major limitation to the practical application of MRI (moderate level of evidence).

Chen et al. (2017) conducted a meta-analysis of 10 studies (590 total cases) to compare the effects of MRI and CT in the assessment of PE. The MRI technique and the use of MR contrast in each study was not stated in the meta-analysis. In addition, the article does not provide information on the number of inconclusive or nondiagnostic MRI exams in the studies. The pooled sensitivity of CT was 0.90 (95% CI, 0.85-0.93) and pooled specificity of CT was 0.88 (95% CI, 0.77-0.95). The pooled sensitivity of MRI was 0.92 (95% CI, 0.89-0.94) and pooled specificity of MRI was 0.91 (95% CI, 0.77-0.97). The SROC curve areas under the curve of CT and MRI were 0.94 (95% CI, 0.91-0.96) and 0.93 (95% CI, 0.91-0.95), respectively. The authors conclude that this meta-analysis demonstrates that MRI has better sensitivity and specificity in detecting subsegmental artery PE (low level of evidence).

Pasin et al. (2017) performed a prospective evaluation of the accuracy of a free breathing True-FISP MRI (without contrast) for pulmonary embolism in 93 patients with CTPA as the gold standard. PE prevalence was 22%. During the 1-year follow-up period, eight patients died, and PE was responsible for death in 12.5% of cases. Of the patients who developed PE, only 5% died due to this condition. There were no differences between MR and CT embolism detection in these subjects. MR sequences had a sensitivity of 85%, specificity was 98.6% and accuracy was 95.6%. Agreement between readers was high (κ= 0.87). The authors concluded that compared with contrast-enhanced CT, unenhanced MR sequences demonstrate good accuracy and no differences in the mortality rates in 1 year were detected (low level of evidence).

Surveillance of established pulmonary embolism prior to stopping anticoagulation

- **Green** –
- **Yellow** –
- **Orange** –
- **Red** – CTPA; CT chest; MRA chest; MRI chest; V/Q scan; V/Q SPECT, V/Q SPECT/CT, Perfusion scan; CT venography of the lower extremities

Level of Evidence: PLE expert panel consensus opinion

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
In patients with a history of PE, it is recommended not to use thoracic imaging tests to evaluate the persistence of residual thrombosis or reperfusion of the initial defects (Uresandi et al., [*SEPAR*] 2013*).

Routine performance of imaging in the presence of a low PE severity index or a simplified PE severity index of zero is not considered necessary as it has not been shown to have therapeutic implications (Konstantinides et al., [*ESC*] 2014).

Clinical notes:

- The presence of residual defects on CTPA at 6 months is not predictive of recurrent VTE (den Exter et al., 2015).

Evidence update (2014-present):
Choi et al. (2016) conducted a retrospective observational study of 764 hospitalized patients with PE diagnosed by MDCT who underwent serial CT scans for follow-up of PE. They found that the rates of clot resolution were 24% within one week, 47% after 1–3 weeks, and 78% after three weeks to three months. The authors conclude that pulmonary emboli undergo the process of resolution at a rate of approximately 25% within one week, 50% after 1–3 weeks, and 80% after three weeks to three months. The study is primarily limited by its retrospective nature and specific patient population (hospitalized patients at a tertiary care center) (low level of evidence).

den Exter et al. (2015) conducted a prospective multi-center cohort study of 157 patients with acute PE diagnosed by CT pulmonary angiography (CTPA) who underwent follow-up CTPA-imaging after six months of anticoagulant treatment. After six months of treatment, complete PE resolution had occurred in 84.1% of the patients (95% confidence interval (CI): 77.4–89.4%). During follow-up, 16 (10.2%) patients experienced recurrent VTE. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2–4.1). The authors conclude "These findings, combined with the absence of a correlation between residual thrombotic obstruction and recurrent VTE, do not support the routine use of follow-up CTPA-imaging in patients treated for acute PE" (moderate level of evidence).

Begic et al. (2015) conducted a prospective observational study of 269 patients with suspected PE and no history of PE who underwent V/Q SPECT at index with follow-up at three and six months. They found

that of the 100 patients with PE, 71% (48/67) had a normal V/Q scan at three months. Of the 35 patients with a normal V/Q scan (without risk factors) who stopped anticoagulation at three months, none developed a recurrent PE. The authors conclude that normalization of perfusion at three months was a reliable indicator that therapy could be withdrawn (low level of evidence).

Guideline exclusions:

- Measurement of right ventricular (RV):left ventricular (LV) ratio
- Assessment of ventricular dysfunction (e.g., dilatation, hypokinesis, paradoxical septal motion, McConnell's sign, tricuspid regurgitation)
- Detection of PE in patients during pregnancy
- Pediatric patients
- PET imaging
- Subsegmental defects on CTPA or V/Q examinations.

AUC Revision History:

Revision Date:	New AUC Clinical Scenario(s):	Posting Date:	Approved By:
09/10/2019	n/a	09/19/2019	CDI Quality Institute's Multidisciplinary Committee

Information on our evidence development process, including our conflicts of interest policy is available on our website at **https://www.mycdi.com/ple**