

## CLINICAL PRACTICE GUIDELINES

# 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American College of Clinical Pharmacy, American College of Emergency Physicians, American College of Chest Physicians, Society for Cardiovascular Angiography & Interventions, Society of Hospital Medicine, Society of Interventional Radiology, Society for Vascular Medicine, and the Society of Vascular Nursing



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**AIM:** The “2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults” is a de novo guideline that provides comprehensive recommendations for the evaluation, management, and follow-up of adult patients (≥18 years of age) with acute pulmonary embolism (PE). A key feature of this guideline is the introduction of the AHA/ACC Acute Pulmonary Embolism Clinical Categories, which enhance the precision of severity classification, prognosis assessment, and evidence-based therapeutic decision-making.

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information. †ACC/AHA Joint Committee on Clinical Practice Guidelines liaison. ‡American College of Clinical Pharmacy representative. §AHA Patient representative. ||Society of Hospital Medicine representative. ¶AHA/ACC Joint Committee on Performance Measures liaison. #Society for Cardiovascular Angiography and Interventions representative. \*\*American College of Chest Physicians representative. ††Society of Vascular Nursing representative. ‡‡Society of Interventional Radiology representative. §§Society of Vascular Medicine representative. |||American College of Emergency Physicians representative.

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The American Heart Association requests that this document be cited as follows: Creager MA, Barnes GD, Giri J, Mukherjee D, Jones WS, Burnett AE, Carman T, Casanegra AI, Castellucci LA, Clark SM, Cushman M, de Wit K, Eaves JM, Fang MC, Goldberg JB, Henkin S, Johnston-Cox H, Kadavath S, Kadian-Dodov D, Keeling WB, Klein AJP, Li J, McDaniel MC, Moores LK, Piazza G, Prenger KS, Pugliese SC, Ranade M, Rosovsky RP, Russo F, Secemsky EA, Sista AK, Tefera L, Weinberg I, Westafer LM, Young MN. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN guideline for the evaluation and management of acute pulmonary embolism in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153:e00000000001415. doi: 10.1161/CIR.000000000001415

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**METHODS:** A comprehensive literature search was conducted from February 2024 to October 2024 to identify clinical studies, reviews, and other evidence conducted on human subjects that were published in English from MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Select key studies published until April 2025 were added by the guideline writing committee as appropriate.

**STRUCTURE:** The focus of this clinical practice guideline is an evidence-based and patient-centered approach for acute PE evaluation and management of the adult patient. This guideline encompasses the period from the onset of symptoms through clinical follow-up, focusing on risk outcomes assessment, clinical diagnosis of acute PE, appropriate use of adjunctive cardiovascular testing, and management in both the acute and early post-acute phases of PE. It addresses evidence-based diagnostic and management strategies (including pharmacological therapies, advanced interventional therapies, and in-hospital support) for acute PE and associated outcomes.

**Key Words:** AHA Scientific Statements ■ acute disease ■ acute pulmonary embolism ■ anticoagulant ■ diagnosis

■ chronic thromboembolic pulmonary hypertension ■ diagnostic imaging ■ direct acting oral anticoagulant ■ heparin  
 ■ hypertension, pulmonary ■ imaging ■ kidney disease ■ kidney insufficiency ■ multimodal imaging ■ oral anticoagulants ■ perfusion imaging  
 ■ pulmonary embolism ■ risk assessment ■ risk factors ■ risk stratification ■ thrombectomy ■ thromboembolism ■ thrombolytic therapy  
 ■ tomography ■ venous thromboembolism

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## TOP TAKE-HOME MESSAGES

1. A new clinical classification scheme is presented, entitled "Acute Pulmonary Embolism Clinical Categories," with 5 categories (A-E) and subcategories, ranging from low to high risk for adverse outcomes, in order to enhance the precision of severity classification, prognosis assessment, and evidence-based therapeutic decision-making for patients presenting with acute pulmonary embolism (PE).
2. Patients with acute PE who are asymptomatic (AHA/ACC PE Category A) can safely be discharged home from the emergency room and do not need to be hospitalized.
3. Early hospital discharge is generally recommended for patients with acute PE who are symptomatic but have a low clinical severity score (AHA/ACC PE Category B).
4. Symptomatic patients with acute PE and an elevated clinical severity score, including those with elevated biomarkers and/or right ventricular dysfunction (AHA/ACC PE Category C), incipient cardiopulmonary failure (AHA/ACC PE Category D), and those with cardiopulmonary failure characterized by persistent hypotension (AHA/ACC PE Category E) should be hospitalized to optimize treatment strategies.
5. Advanced therapies, including systemic thrombolysis, catheter-based thrombolysis, mechanical thrombectomy, and surgical embolectomy are reasonable for patients with acute PE in AHA/ACC PE Category E1 and can be considered for patients with acute PE in AHA/ACC PE Category D1-2.
6. PE response teams (PERTs) are recommended to improve timeliness of care.
7. In patients with acute PE who require initial parenteral anticoagulant therapy, low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin (UFH).
8. In patients with acute PE who are eligible for oral anticoagulation, direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists (VKAs), unless contraindicated, to prevent recurrent venous thromboembolism (VTE) and reduce major bleeding.
9. In patients with a first acute PE without a major reversible risk factor and in those with a persistent risk factor, continuing anticoagulation beyond the initial treatment phase (3-6 months) into the extended phase is recommended.
10. Patients who have had acute PE should be asked about PE-related symptoms and functional limitations at every visit for at least 1 year to screen for chronic thromboembolic pulmonary disease (CTEPD) or other causes of dyspnea and functional limitation.

## PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a foundation for delivering high-quality cardiovascular care. When applicable, the guidelines also provide economic value statements that apply cost-effectiveness analyses. The methodology for these economic value statements can be found in the AHA/ACC Statement on Cost Value Methodology publication.<sup>1</sup> The ACC/AHA Guideline Core Principles and Development Process publication describes best practices for cardiology clinicians and additional background on the methodology used in the creation of guidelines.<sup>2</sup> Details about the alignment between the US Food and Drug Administration approval processes for drugs and devices and AHA/ACC guideline methodology can be found in the Guidance for Incorporating FDA Processes.<sup>3</sup>

Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are the official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

*Catherine M. Otto, MD, FAHA, FACC  
Chair, ACC/AHA Joint Committee on  
Clinical Practice Guidelines*

## 1. INTRODUCTION

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from February 2024 to October 2024. Select key studies published until April 2025 were added by the guideline writing committee as appropriate. The final evidence tables are available online and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present guideline are not all-inclusive.

### 1.2. Organization of the Writing Committee

The writing committee consisted of general cardiologists, interventional cardiologists, cardiac imaging experts,

critical care physicians, internal medicine hospitalists, cardiothoracic surgeons, advance practice nurses, clinical pharmacists, vascular medicine physicians, vascular interventionalists, hematologists, pulmonologists, emergency medicine physicians, and patient representatives. The writing committee included representatives from the ACC and AHA, American College of Clinical Pharmacology, American College of Emergency Physicians, American College of Chest Physicians, Society for Cardiovascular Angiography & Interventions, Society of Hospital Medicine, Society of Interventional Radiology, Society for Vascular Medicine, and the Society of Vascular Nursing.

### 1.3. Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found [online](#). Appendix 1 of the guideline lists committee members' comprehensive and relevant RWI.

### 1.4. Peer Review Committee

The Joint Committee appointed a peer review committee to review the guideline. The peer review committee comprised individuals nominated by the ACC, AHA, and the collaborating organizations. Reviewers' RWI information was distributed to the writing committee and is published in the guideline ([Appendix 2](#)).

### 1.5. Scope of the Guideline

The focus of this clinical practice guideline is the evaluation and management of acute pulmonary embolism (PE) in the adult patient ( $\geq 18$  years of age). The guideline addresses the clinical assessment of the patient presenting with symptoms and signs of acute PE, initial laboratory testing (specifically D-dimer), and the appropriate use of imaging to diagnose acute PE. This guideline introduces an Acute Pulmonary Embolism Clinical Category system to classify severity, assess prognosis, and enable more effective evidence-based therapeutic decisions to improve patient outcomes more precisely. The categories build on previous risk schemes by incorporating clinical, hemodynamic, and respiratory factors, along with biomarkers and assessment of right ventricular size and function. Care of the patient with acute PE is uniquely multidisciplinary and crosses emergency department, inpatient settings and outpatient clinics. Accordingly, the guideline includes recommendations on the preferred care setting, including which patients can be discharged from the emergency department and managed as outpatients, which patients require hospitalization, and which patients should

**Table 1. AHA and ACC Associated Publications**

Title	Organization	Publication Year (Reference)
<b>Guidelines</b>		
Evaluation and diagnosis of chest pain	AHA/ACC/ASE/ CHEST/SAEM/ SCCT/SCMR	2021 <sup>1</sup>
<b>Other Relevant Documents</b>		
Management of massive and submassive PE	AHA	2011 <sup>2</sup>
Interventional therapies for acute PE	AHA	2019 <sup>3</sup>
Expert consensus statement on anticoagulant and antiplatelet therapy for Afib/VTE	ACC	2020 <sup>4</sup>
Surgical therapy and MCS for acute PE	AHA	2023 <sup>5</sup>
Balloon pulmonary angioplasty for CTEPH & CTEPD	AHA	2024 <sup>6</sup>

ACC indicates American College of Cardiology; Afib, atrial fibrillation; AHA, American Heart Association; ASE, American Society of Echocardiography; CHEST, American College of Chest Physicians; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; MCS, mechanical circulatory support; PE, pulmonary embolism; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; and VTE, venous thromboembolism.

be placed in a critical care or intermediate level of care setting. Local implementation of these recommendations requires adaptation to the resources available, such as immediate specialty consultation, urgent echocardiography, and outpatient appointment scheduling from the emergency department, and advanced interventions. The guideline also makes recommendations about which patients require interhospital transfer to more resourced facilities and when to use a multidisciplinary PE response team care delivery model. Sections of this guideline address evidence-based management strategies, such as anticoagulant therapy, the role of inferior vena cava filters, and the use of advanced therapies, including systemic thrombolysis, catheter-directed thrombolysis, mechanical thrombectomy, and surgical thrombectomy. There are also recommendations regarding sedation, ventilation, mechanical circulatory support, and other hemodynamic support for critically ill patients with acute PE. Finally, the guideline provides recommendations on follow-up management, including patient education, activity after an acute PE, indications for long-term anticoagulation, and assessment of the patient with persistent symptoms and postacute PE functional impairment.

This guideline focuses on acute PE. It does not include recommendations about prophylactic treatment for primary prevention of venous thromboembolism. Recommendations for evaluation and treatment of deep vein thrombosis (DVT), except when considered in conjunction with acute PE, are outside the scope of these guidelines. Lastly, although the initial evaluation of chronic

**Table 2. Applying the American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated December 2024)**

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<p><b>Class 1 (STRONG) Benefit &gt;&gt;&gt; Risk</b></p> <p><b>Suggested phrases for writing recommendations:</b></p> <ul style="list-style-type: none"> <li>• Is recommended</li> <li>• Is indicated/useful/effective/beneficial</li> <li>• Should be performed/administered/other</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>- Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>- Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<p><b>Level A</b></p> <ul style="list-style-type: none"> <li>• High-quality evidence‡ from more than 1 RCT</li> <li>• Meta-analyses of high-quality RCTs</li> <li>• One or more RCTs corroborated by high-quality registry studies</li> </ul>
<p><b>Class 2a (MODERATE) Benefit &gt;&gt; Risk</b></p> <p><b>Suggested phrases for writing recommendations:</b></p> <ul style="list-style-type: none"> <li>• Is reasonable</li> <li>• Can be useful/effective/beneficial</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>- Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>- It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<p><b>Level B-R (Randomized)</b></p> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more RCTs</li> <li>• Meta-analyses of moderate-quality RCTs</li> </ul>
<p><b>Class 2b (WEAK) Benefit ≥ Risk</b></p> <p><b>Suggested phrases for writing recommendations:</b></p> <ul style="list-style-type: none"> <li>• May/might be reasonable</li> <li>• May/might be considered</li> <li>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li> </ul>	<p><b>Level B-NR (Nonrandomized)</b></p> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>• Meta-analyses of such studies</li> </ul>
<p><b>Class 3: No Benefit (MODERATE) Benefit = Risk (Generally, LOE A or B use only)</b></p> <p><b>Suggested phrases for writing recommendations:</b></p> <ul style="list-style-type: none"> <li>• Is not recommended</li> <li>• Is not indicated/useful/effective/beneficial</li> <li>• Should not be performed/administered/other</li> </ul>	<p><b>Level C-LD (Limited Data)</b></p> <ul style="list-style-type: none"> <li>• Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>• Meta-analyses of such studies</li> <li>• Physiological or mechanistic studies in human subjects</li> </ul>
<p><b>Class 3: HARM (STRONG) Risk &gt; Benefit</b></p> <p><b>Suggested phrases for writing recommendations:</b></p> <ul style="list-style-type: none"> <li>• Potentially harmful</li> <li>• Causes harm</li> <li>• Associated with excess morbidity/mortality</li> <li>• Should not be performed/administered/other</li> </ul>	<p><b>Level C-EO (Expert Opinion)</b></p> <ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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thromboembolic pulmonary disease (CTEPD) after acute PE is discussed in this guideline, the management of patients with established CTEPD, with and without pulmonary hypertension, is outside the scope of this document. In developing this guideline, the writing committee reviewed previously published AHA/ACC guidelines and related scientific statements. Table 1 contains a list of these publications deemed pertinent to this writing effort.

## 1.6. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation and encompasses estimated benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention based on the type, quantity, and consistency of data from clinical trials and other sources (Table 2).

## 2. DEFINITIONS AND CLASSIFICATIONS

### 2.1. Definitions

Guideline-directed medical therapy: the term guideline-directed medical therapy encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

The ACC/AHA Acute PE Clinical Categories comprise a system designed to categorize the severity and prognosis of PE through the integration of various clinical, laboratory, and imaging parameters.

*Initial Treatment Phase* describes the first 3 to 6 months of anticoagulation therapy after an acute PE. *Extended Treatment Phase* designates more than 6 months of anticoagulation therapy after an acute PE.

### 2.2. Abbreviations

Abbreviation	Meaning/Phrase
APS	antiphospholipid syndrome
AUB	abnormal uterine bleeding
BMI	body mass index
BNP	brain natriuretic protein
BPA	balloon pulmonary angioplasty
CDL	catheter-directed thrombolysis
CKD	chronic kidney disease

(Continued)

Abbreviation	Meaning/Phrase
CPET	cardiopulmonary exercise testing
CPR	cardiopulmonary resuscitation
CT	computed tomography
CTEPD	chronic thromboembolic pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiography
CTV	computed tomography venography
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
ED	emergency department
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
HFNC	high-flow nasal cannula
ICH	intracranial hemorrhage
ICU	intensive care unit
IVC	inferior vena cava
LMWH	low molecular weight heparin
LV	left ventricle
MAP	mean arterial pressure
MRA	magnetic resonance angiography
MT	mechanical thrombectomy
NE	norepinephrine
NEWS	national early warning score
NIV	noninvasive mechanical ventilation
PA	pulmonary artery
PE	pulmonary embolism
PESI	pulmonary embolism severity index
PH	pulmonary hypertension
PTE	pulmonary thromboendarterectomy
PVFR	pulmonary venous flow reduction
PVR	pulmonary vascular resistance
RCT	randomized controlled trial
RPVO	residual pulmonary vascular obstruction
RV	right ventricle
SPECT	single-photon emission computed tomography
SVR	systemic vascular resistance
TAPSE	tricuspid annular plane systolic excursion
TTE	transthoracic echocardiogram
UFH	unfractionated heparin
VD/VT	alveolar dead space
VE/VCO <sub>2</sub>	ventilatory efficiency
VKA	vitamin K antagonist
V/Q	ventilation/perfusion
VTE	venous thromboembolism

## 3. EVALUATION AND DIAGNOSIS

### 3.1. Evaluation

#### 3.1.1. Clinical Assessment

Recommendations for Clinical Assessment Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	A	1. In patients presenting with symptoms suggestive of acute PE, a targeted history and comprehensive physical examination is recommended to assist in determining the clinical pretest probability of acute PE. <sup>1,2</sup>
2a	B-R	2. In adult patients undergoing evaluation for PE and who have a low or intermediate clinical probability of PE (<50%) by risk assessment, an age-adjusted D-dimer value below the threshold (age × 10 µg/L for fibrinogen equivalent units assays) effectively excludes PE and the need for imaging. <sup>2-5</sup>
2a	B-R	3. In adult patients with suspected PE, the YEARS algorithm* can be useful to identify which patients do not need imaging to rule out a PE. <sup>2,3,6,7</sup>
2b	B-NR	4. In pregnant adults, it may be reasonable to use pregnancy-adapted YEARS criteria to identify patients who do not need imaging for PE. <sup>8-10</sup>

\*YEARS algorithm: A D-dimer threshold of 500 µg/L in patients who have ≥1 of the following: 1) clinical signs of DVT; 2) hemoptysis; and/or 3) PE as the most likely diagnosis. A D-dimer threshold of 1000 µg/L is used for patients who have no YEARS criteria.

### Synopsis

Prompt diagnosis of acute PE requires recognition of a patient's predisposing risk factors for venous thromboembolism (VTE). The evaluation of patients with suspected PE integrates the clinical history with physical examination findings, laboratory testing, and diagnostic imaging.<sup>11</sup> Many symptoms of acute PE are non-specific.<sup>12-18</sup> The most common symptoms of PE are pleuritic chest pain and dyspnea. Hemoptysis, syncope, and shock are less common.<sup>17-19</sup> Physical examination findings of tachycardia and hypotension may indicate hemodynamic compromise, and tachypnea and hypoxemia may indicate a significant degree of gas exchange perturbation. Other signs to seek are decreased lung breath sounds, a pleural friction rub, jugular venous distension, an accentuated pulmonic second heart sound, a parasternal lift, and leg swelling and tenderness suggestive of deep vein thrombosis (DVT). Nonetheless, the diagnosis of PE is often challenging, with less than 10% of patients evaluated for PE eventually being diagnosed with PE.<sup>13-16</sup>

Relevant history, physical examination, and PE pretest probability scores guide appropriate investigations for potential cardiopulmonary diagnoses (Figure 1). Clinical decision tools such as the Wells score, the Revised Geneva Score, and the Pulmonary Embolism Rule Out Criteria (PERC) are frequently used to synthesize the history and physical findings and inform a clinical pretest

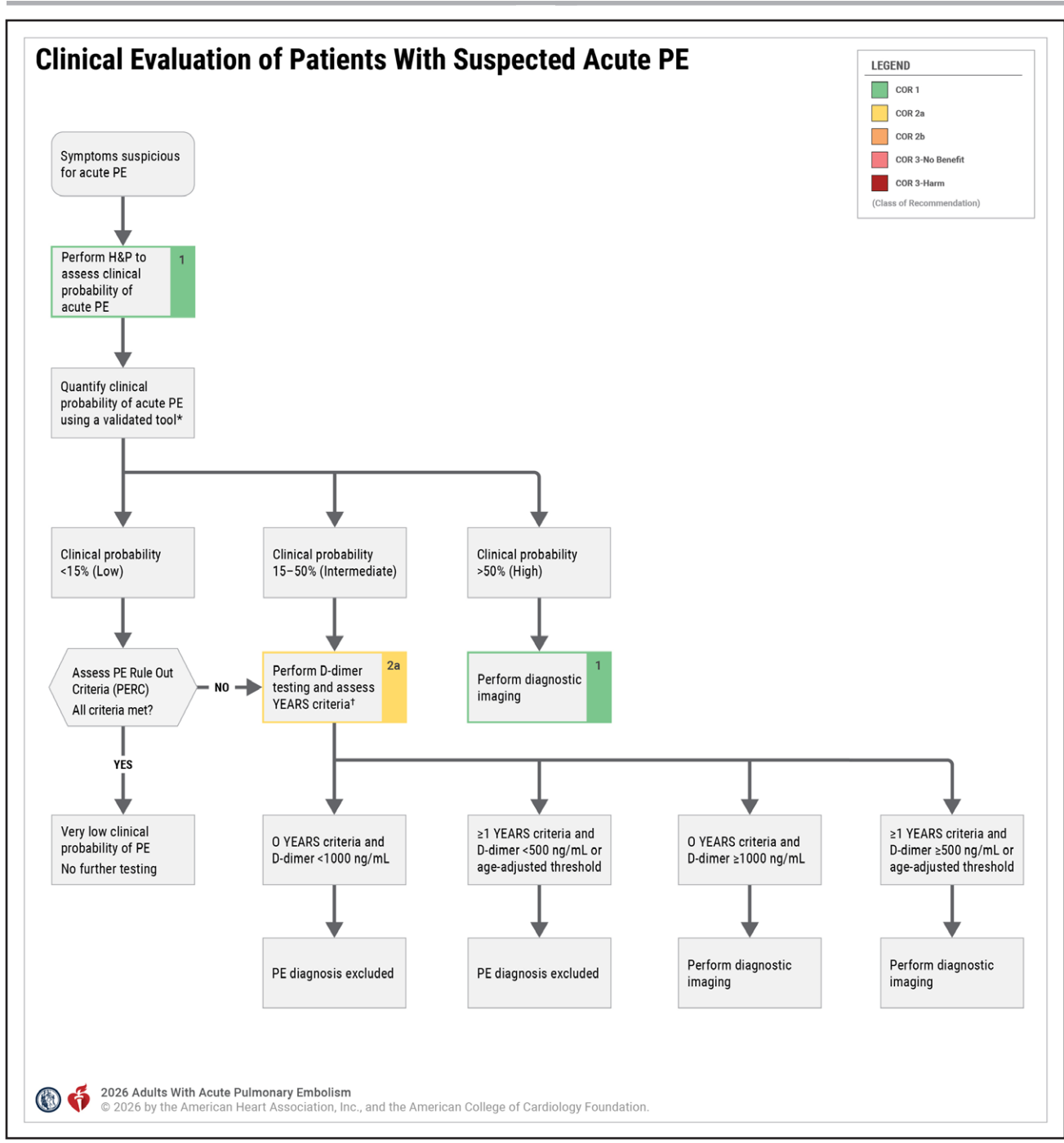
probability of PE (Table 3). Clinical decision tools that incorporate assessment of clinical suspicion of PE with laboratory testing are recommended to identify patients in whom diagnostic imaging is warranted from those in whom the diagnosis is unlikely and therefore imaging can be avoided.

D-dimer can aid in risk-stratifying patients with possible PE, balancing the potential harms of testing with the risk of a missed diagnosis.<sup>20,21</sup> The accepted safety threshold (ie, failure rate) for diagnostic tools in the evaluation of PE is 2%.<sup>20,21</sup> Acute PE is unlikely in patients who meet all 3 of the following criteria: 1) D-dimer levels that do not exceed the threshold of normal; 2) a low or intermediate clinical pretest probability (<50%) of PE; and 3) are not anticoagulated at baseline.<sup>2</sup> A D-dimer level that is below the threshold using either the age-adjusted D-dimer or the YEARS algorithm criteria can safely reduce the need for pulmonary imaging. It is possible that in high prevalence settings, use of these strategies might result in missed PEs.<sup>2,3</sup> Recent studies using D-dimer based approaches in pregnant patients with low and intermediate clinical probability of PE demonstrated both safety and reduced need for imaging (efficacy).<sup>10,22</sup> Importantly, most studies evaluating D-dimer-based diagnostic strategies excluded anticoagulated patients.



### Recommendation-Specific Supportive Text

1. During a targeted history and physical examination, assessment for PE risk factors should include recent surgery, hospitalization for medical therapy, immobility, pregnancy, estrogens, trauma, cancer, inflammatory disorders, and inherited and acquired thrombophilias, among others. Other risk factors, which may vary by sex, include atherosclerotic cardiovascular disease, pulmonary disease, cancer, chronic venous disease, prolonged immobility, and hormonal therapy.<sup>23</sup> These risk factors help to inform the pretest probability of acute PE. The indication for imaging for PE is influenced by the patient's clinical pretest probability. Randomized controlled studies and observational studies that use clinical assessment tools and laboratory testing (ie, D-dimer) as part of a diagnostic algorithm have demonstrated improved diagnostic performance of imaging and a reduction in unnecessary testing (Section 3.1.2, "Diagnostic Testing").<sup>1,2</sup>
2. Age-adjusted D-dimer strategies are safe in patients with low or intermediate clinical probability of PE, resulting in less than 2% missed VTE at 1 to 3 months. A prospective validation study of 3346 patients revealed a 3-month failure rate (missed VTE at 3 months) of 0.3% (95% CI, 0.1%-1.7%) for those >50 years of age who had a low or intermediate clinical probability of PE and a D-dimer value between the standard



**Figure 1. Clinical Evaluation of Patients With Suspected Acute PE.**

\*Indicates validated tools such as the Wells score, revised Geneva score, or clinical gestalt. †YEARS criteria include clinical signs of DVT, hemoptysis, or PE is the most likely diagnosis. Use of an age-adjusted D-dimer is an alternative to the use of the YEARS criteria. For pregnant patients, the pregnancy-adapted YEARS criteria should be used. DVT indicates deep vein thrombosis; and PE, pulmonary embolism.

(<500 µg/L) and age-adjusted (age×10 µg/L) thresholds.<sup>4,24</sup> A large individual-patient data meta-analysis confirmed these results.<sup>2</sup> Additionally, a multicenter cluster randomized trial found a low failure rate (<2% diagnosed with VTE by 3 months) in strategies using the age-adjusted D-dimer, even when combined with the YEARS algorithm, in patients with non-high

probability of PE (<50%).<sup>3</sup> Of note, these studies included D-dimer assays that report FEUs and excluded patients on therapeutic anticoagulation within the prior 24 hours.

3. The low specificity of the D-dimer, combined with decreasing computed tomography pulmonary angiography (CTPA) yield (proportion of CTPAs positive for PE), has generated a need for adjusted

**Table 3. Clinical Decision Rules**

Clinical Pretest Probability Score	Components	Points		Clinical Pretest Probability Grouping and Utilization
Wells Score for PE <sup>28</sup>	Clinical symptoms of DVT (leg swelling, pain with palpitation)	3		<b>Standard Wells Scoring:</b> Low: <2 Moderate: 2-6 High: >6  <b>Modified Wells Scoring:</b> PE likely: >4 PE unlikely: ≤4
	PE more likely than other diagnoses	3		
	Heart rate >100 bpm	1.5		
	Immobilization (≥3 days) or surgery in the previous 4 weeks	1.5		
	Previous DVT or PE	1.5		
	Hemoptysis	1		
	Cancer	1		
PE Rule Out Criteria <sup>21</sup>	Age <50 years			Assess if clinical pretest probability (gestalt) of PE is <15% (eg, Wells <2)  When all criteria are met, the likelihood of PE is low and no further testing is required.
	Heart rate <100 bpm			
	Oxyhemoglobin saturation ≥95%			
	No hemoptysis			
	No estrogen use			
	No prior DVT or PE			
	No unilateral leg swelling			
No surgery/trauma requiring hospitalization within the prior 4 weeks				
		Revised Geneva Score	Simplified Revised Geneva Score	
Revised Geneva Score <sup>29,30</sup>	Age >65	1	1	<b>Revised Geneva:</b> Low: 0-3 Intermediate: 4-10 High: ≥11  <b>Simplified Revised Geneva:</b> Low: 0-1 Intermediate: 2-4 High: 5-7 Unlikely: 0-2 Likely: 3-7
	Previous DVT or PE	3	1	
	Surgery under general anesthesia or fracture of the lower limbs within 1 months	2	1	
	Active cancers	2	1	
	Unilateral lower-limb pain	3	1	
	Hemoptysis	2	1	
	Heart rate 75-94 bpm	3	1	
	Heart rate ≥95 bpm	5	1	
Pain on lower limb deep vein palpation and unilateral edema	4	1		

DVT indicates deep vein thrombosis; and PE, pulmonary embolism. Adapted with permission from Klok et al.<sup>30</sup> Copyright 2008 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies. Additional material adapted with permission from Le Gal et al. and from *Annals of Internal Medicine*.<sup>29</sup> Copyright 2006 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

D-dimer thresholds in lower-risk patients. The derivation of the YEARS algorithm used a threshold of 500 µg/L in patients who had ≥1 of the following: clinical signs of DVT, hemoptysis, and/or PE as the most likely diagnosis. A D-dimer threshold of 1000 µg/L was used for patients with no YEARS criteria. The initial YEARS validation cohort demonstrated safety in patients across all probability levels.<sup>25</sup> A multicenter cluster randomized noninferiority trial in Europe compared the YEARS algorithm, incorporating age-adjusted D-dimer, with age-adjusted

D-dimer alone in patients with low and intermediate probability (<50%) of PE. This trial found the YEARS criteria plus age-adjusted D-dimer approach had low failure rates and improved efficiency compared with an age-adjusted approach alone.<sup>3</sup> Of note, the YEARS algorithm has only been studied in patients not on therapeutic anticoagulation.

- Historically, few studies have evaluated diagnostic strategies in pregnant patients with suspected PE. The use of CTPA among pregnant patients

undergoing evaluation for PE has increased over the past decade. Nonetheless, the detection rate is low, ranging from 0% to 10% in most studies, including a recent meta-analysis composed primarily of patients evaluated in the emergency department (ED) reporting that only 4.1% of CTPAs in pregnant patients were positive for PE.<sup>26,27</sup> Two prospective management studies investigated the use of a quantitative D-dimer in low-to-intermediate risk patients with the revised Geneva or YEARS algorithm and demonstrated low failure rates (ie, VTE within 3 months) of 0.0% (95% CI, 0.0%-1.0%) and 0.21% (95% CI, 0.04%-1.2%), respectively.<sup>10,22</sup> The YEARS algorithm, with a D-dimer threshold of 1000 µg/L in lower risk pregnant patients, resulted in the lowest volume of chest imaging. Furthermore, the pregnancy-adapted YEARS algorithm suggests that pregnant patients with lower extremity symptoms and a positive compression ultrasound study can be safely treated with anticoagulation therapy and do not necessarily require CTPA imaging.<sup>10</sup> Following this approach safely avoids 65% of CTPA tests for patients presenting in the first trimester of pregnancy.

**3.1.2. Diagnostic Testing**

Recommendations for Diagnostic Testing		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	A	1. In patients presenting with symptoms and signs suggestive of acute PE, imaging is recommended for those who are deemed high probability (>50% probability of PE) by a validated clinic risk prediction score or an elevated D-dimer level in order to confirm or exclude PE. <sup>1-7</sup>
1	A	2. In patients undergoing imaging evaluation for suspected PE, a positive CTPA or high probability ventilation/perfusion (V/Q) scan is sufficient to diagnose PE. <sup>1,2,4,8-11</sup>
1	B-R	3. In patients undergoing imaging evaluation, a CTPA is recommended in preference to a V/Q scan to confirm the diagnosis of acute PE. <sup>4,5,9,12</sup>
2a	B-NR	4. In pregnant patients presenting with symptoms, YEARS criteria suggestive of acute PE, and a normal chest x-ray, imaging evaluation with low-radiation dose CTPA is reasonable over low-dose perfusion scintigraphy. <sup>13,14</sup>
2a	B-R	5. In patients undergoing evaluation for PE, V/Q single-photon emission computed tomography (SPECT) is reasonable in preference to a planar V/Q scan as a diagnostic study. <sup>8,10</sup>
2a	B-R	6. In patients with suspected acute PE who cannot undergo a CTPA, it is reasonable to perform a V/Q scan in preference to contrast-enhanced magnetic resonance angiography (MRA) to improve the diagnostic yield. <sup>15-19</sup>
2b	B-NR	7. In patients with confirmed acute PE, obtaining lower extremity venous duplex ultrasound examination may be reasonable in patients with clinical findings suggestive of DVT or if the presence of DVT will change management or inform prognosis. <sup>5,20-26</sup>

Recommendations for Diagnostic Testing (Continued)		
COR	LOE	Recommendations
3: No Benefit	B-NR	8. In patients with suspected PE and a negative CTPA or normal V/Q SPECT, venous duplex ultrasonography is not useful for further PE diagnostic evaluation. <sup>4,5,8-10,27-29</sup>
3: No Benefit	B-NR	9. In patients with suspected acute PE, an echocardiogram is not recommended to confirm or refute the diagnosis of PE. <sup>30,31</sup>
3: No Benefit	B-R	10. In patients with suspected acute PE, computed tomographic venography of the inferior vena cava (IVC) and lower extremity veins is not recommended as a routine adjunct to CTPA to diagnose venous thrombosis. <sup>2,5,32</sup>
Reporting Findings on Diagnostic Imaging		
1	B-R	11. In patients presenting with an acute PE who undergo CTPA, reporting the numerical right ventricle (RV)/left ventricle (LV) ratio (measured by internal diameter assessed on axial or reformatted 4D-chamber view) is recommended over subjective quantification for risk stratification. <sup>33-37</sup>
1	B-NR	12. In patients with acute PE who undergo transthoracic echocardiography, RV dysfunction should be assessed and reported by the following parameters: RV/LV end-diastolic ratio; RV end-diastolic diameter; tricuspid annular plane systolic excursion (TAPSE); estimated right ventricular systolic pressure; RV free wall hypokinesis with sparing of the apex (McConnell's sign); tricuspid systolic velocity; paradoxical septal motion; and IVC respirophasic collapse to assist with risk stratification. <sup>31,38-44</sup>
2b	B-NR	13. In patients with acute PE, reporting of chronic features* on CTPA may be useful to identify patients at risk for chronic clinical sequelae of PE, including post-PE CTEPD. <sup>45-48</sup>

\*Examples include intravascular webs, pulmonary artery retraction or dilation, bronchial artery dilation, RV hypertrophy, and intraventricular septal flattening.

**Synopsis**

Imaging is essential to the diagnosis and management of patients with PE but must be placed within the context of the patient's clinical pretest probability for PE. The current standard imaging modality for diagnosis of acute PE is CTPA, given its wide accessibility, relative cost, contemporary (lower) radiation exposure, and excellent diagnostic performance. For patients in whom CTPA cannot be performed or is otherwise not optimal, a V/Q scan is appropriate as it has excellent diagnostic yield, especially when combined with SPECT. Echocardiography is an inadequate test for the diagnosis of PE but is important in the assessment of RV function for symptomatic patients with confirmed acute PE. Parameters of RV structure and function should be assessed and reported, including RV/LV end-diastolic ratio, RV end-diastolic diameter, TAPSE, estimated right ventricular systolic pressure, RV free wall hypokinesis with sparing of the apex (McConnell's sign), tricuspid systolic velocity, intracardiac thrombus paradoxical septal motion, and IVC respirophasic collapse. Evidence of RV dysfunction also should

be assessed and reported on CTPA, when acute PE is confirmed. Selective venous duplex ultrasonography of the legs may be useful in patients with clinical findings suggestive of DVT or in whom confirmation of DVT will influence management.

### Recommendation-Specific Supportive Text

1. The indication for imaging for PE is influenced by the patient's pretest probability. Randomized control studies and observational studies using clinical assessment tools and laboratory testing (ie, D-dimer) as part of a diagnostic algorithm have demonstrated that the diagnostic performance of imaging is improved, and unnecessary testing is reduced.<sup>1,2,4-6,9</sup>
2. In patients with a clinically probable PE, as assessed by available clinical tools and laboratory D-dimer testing, a positive CTPA is definitive for the diagnosis of PE as a stand-alone test.<sup>1,2,4,27</sup> A high probability V/Q scan also has excellent diagnostic accuracy for acute PE in this clinical setting. It is the imaging modality of choice in patients who cannot undergo CTPA (eg, patients with contraindication to CT).<sup>8-11</sup>
3. CTPA is the standard imaging modality for the diagnosis of PE, based on its wide availability and accessibility, reduced burden of overall cost compared with other testing, contemporary (lower) radiation exposure, and excellent diagnostic performance.<sup>2,4,5,9</sup> In older studies, CTPA was comparable to V/Q scanning (including with SPECT) when results were reported as "PE absent" or "PE present."<sup>2-5,10</sup> There is a lack of contemporary data comparing the performance of these technologies for the diagnosis of acute PE, although a comparison study is planned.<sup>12</sup> CTPA, however, is currently preferred over a V/Q scan to confirm the presence of acute PE because there is higher detection of peripheral (noncentral) PE on CTPA compared with V/Q scans.<sup>2,9</sup> Prospective studies demonstrate the excellent diagnostic performance of CTPA, which allows the provider to arrive at a management decision in most cases; the same is not true for V/Q scanning. Additionally, the RV can be assessed in the presence of confirmed PE, and alternative diagnoses may be identified with CTPA.<sup>12</sup>
4. Pregnancy is an acquired and independent risk factor for VTE, and PE accounts for up to 11% of pregnancy-related deaths in the United States.<sup>49</sup> Although CTPA is the standard for diagnosis in the general population, there is concern regarding radiation exposure to the pregnant patient and fetus. A recent prospective study, utilizing low-dose CTPA with a standardized protocol

and contemporary technology, found much lower rates of radiation absorbed in the breast tissue, uterus (fetal), and maternal effective dose than previously published.<sup>50</sup> The diagnostic accuracy of CTPA and lung scintigraphy during pregnancy was reported in a Cochrane analysis that included 11 studies using clinical follow-up for PE as a reference standard.<sup>13</sup> It found a high negative predictive value and high sensitivity for both CTPA and lung scintigraphy, including a combination of SPECT and planar V/Q as well as V/Q and perfusion-only scanning.<sup>13</sup> The median frequency of inconclusive results was similar between the 2 modalities, and the authors could not determine which test has the higher accuracy based on heterogeneity of the data and poor reference standards.<sup>13</sup> Retrospective data from an academic center with experience in low-dose perfusion scintigraphy-only lung scanning demonstrated 100% negative predictive value for the exclusion of PE in pregnant patients who had no abnormalities on chest x-ray.<sup>14</sup> In totality, both contemporary low-dose perfusion-only lung scanning and low-dose CTPA protocols appear effective and safe in experienced settings for the exclusion of PE in pregnant patients. Practically speaking, however, CTPA may be preferred for ease of use, accessibility, and opportunity for identifying alternative diagnoses and RV evaluation compared with perfusion-only scanning.

5. V/Q SPECT demonstrates greater reproducibility and specificity for the diagnosis of PE and has lower levels of radiation when compared with planar V/Q imaging.<sup>8,10</sup>
6. In some studies, MRA was inconclusive for the diagnosis of PE in 25% to 28% of patients.<sup>15,16</sup> Even when optimal imaging was obtained, the sensitivity was limited, especially for the diagnosis of segmental and subsegmental PE.<sup>15,16</sup> In other studies from experienced centers that used standardized protocols, including extended-contrast bolus duration to match acquisition length and a breath hold, the clinical performance of contrast-enhanced MRA was similar to CTPA for the diagnosis of acute PE and other clinically actionable diagnoses.<sup>17-19</sup> Yet, MRA is more expensive and less widely available than CTPA or V/Q SPECT and is typically not practical as a modality for PE diagnosis.<sup>17-19</sup> In most cases, however, V/Q SPECT is preferred for the diagnosis of PE in patients with a contraindication to CTPA (Recommendation #2).
7. In patients with confirmed acute PE, venous duplex ultrasonography identifies concomitant DVT in 44% to 71% of patients, depending on the

presence of DVT symptoms.<sup>22</sup> Routine evaluation for DVT in patients with suspected PE, however, does not improve diagnosis of PE and results in increased health care costs.<sup>25</sup> A randomized control trial in patients presenting with suspected PE that compared D-dimer, leg venous ultrasonography, and CTPA with a diagnostic strategy of D-dimer and CTPA alone demonstrated no difference in the rate of PE diagnosis and no difference in the rate of recurrent VTE at 3-month follow-up.<sup>5</sup> However, other studies of patients with confirmed symptomatic PE identified an increased risk for all-cause mortality and PE-related mortality in patients with concomitant DVT versus those without DVT.<sup>20-22,26</sup> Patients with symptomatic DVT were at especially high risk.<sup>22</sup> There are no data supporting or refuting the role of identifying DVT at the time of PE diagnosis as an adjunct to clinical risk prediction tools or other parameters of risk stratification, such as biomarkers or evidence of RV dysfunction. There are scenarios, however, in which identification of DVT may alter clinical management for the patient, including the presence of iliofemoral DVT for which catheter-based intervention of the DVT would be considered to reduce the risk of post-thrombotic syndrome or would influence a decision around the use of IVC filters if anticoagulation could not be administered. Furthermore, establishing a baseline imaging exam in order to avoid future concern for anticoagulation failure can be considered in select cases.<sup>23,24</sup>

8. Well-executed CTPA is excellent for the evaluation of PE affecting the main and lobar pulmonary arteries. Randomized clinical trials and meta-analyses have demonstrated an overall low rate of PE recurrence, out to 3 months of follow-up, when the CTPA is negative, regardless of the clinical pretest probability for PE.<sup>4,5,9,27</sup> Adjunctive testing with duplex venous ultrasonography when the CTPA is negative is not helpful to identify higher rates of PE.<sup>5</sup> V/Q SPECT also demonstrates high specificity and sensitivity for the detection of PE (Recommendation #5).<sup>8,10,29</sup>
9. In patients with suspected PE, echocardiography alone is not sufficient to confirm or rule out the diagnosis. Most patients with acute PE will not show evidence of RV dysfunction; furthermore, signs of RV dysfunction on echocardiography have low sensitivity for PE diagnosis.<sup>30,31</sup> The performance of echocardiography to detect PE improves in patients with hemodynamic compromise, but the overall specificity remains suboptimal (64%); therefore, the diagnosis of PE should be confirmed with a direct and dedicated PE imaging test.<sup>30</sup>

10. Computed tomographic venography (CTV) of the IVC and proximal lower extremity veins does not significantly improve the performance of CTPA alone for the diagnosis of PE.<sup>2</sup> In 1 study, CTPA-CTV identified DVT in 105 of 164 patients with PE.<sup>5</sup> The thrombi were detected in the IVC or pelvic veins alone in 3 patients (3%), thigh veins alone in 89 (85%), and both in 13 (12%).<sup>2</sup> Thus, the majority of DVT would have been identified by lower extremity venous ultrasonography.<sup>5</sup> Another prospective study of 235 patients presenting to the ED with clinical suspicion for PE were evaluated with CTPA, CTV, and duplex ultrasonography of the lower extremity veins. The combined modality of CTPA-CTV resulted in a 3.8% increase in VTE diagnosis (ie, PE not identified on CTPA but DVT present); however, 6 of 9 cases were false positives, and CTV missed 6 DVT cases that were identified with venous duplex ultrasonography. Compared with venous duplex ultrasonography, CTV had a high negative predictive value (93.2%) but lower positive predictive value (66.7%), indicating that venous duplex ultrasonography is preferred for the detection of DVT.<sup>32</sup> Additionally, CTV results in additional radiation exposure for the patient.
11. When CTPA is obtained for PE diagnosis, the parameters to assess RV strain should be reported and include the numerical RV/LV ratio (measured by internal diameter assessed on axial or reformatted 4D-chamber view) rather than subjective quantification.<sup>33-35,37</sup> The presence of RV dysfunction as assessed by CTPA is an independent predictor for in-hospital death, 30-day mortality, and clinical deterioration related to PE diagnosis.<sup>33-36</sup> Utilizing a cut-point of  $\geq 1.0$  for the RV/LV ratio by CTPA yields sensitivity of 85% (95% CI, 81%-89%) and specificity of 72% (95% CI, 67%-77%), compared with 92% (95% CI, 89%-95%) and 56% (95% CI, 46%-66%), respectively, with a cut-point of  $\geq 0.9$  for the RV/LV ratio.<sup>33</sup> The degree of RV enlargement relative to the LV may be even more predictive than a binary normal/abnormal assessment.
12. In patients who undergo transthoracic echocardiography as part of the evaluation of acute PE, parameters of RV dysfunction and strain should be reported as comprehensively as possible based on local expertise. These parameters include RV/LV end-diastolic ratio, RV end-diastolic diameter, TAPSE, estimated right ventricular systolic pressure, RV free wall hypokinesis with sparing of the apex (McConnell's sign), tricuspid systolic velocity, paradoxical septal motion, and IVC respirophasic collapse.<sup>31,38-44</sup> Physicians with specialized training

in echocardiography, including goal-directed echocardiography or formal transthoracic echocardiography, are able to detect parameters of RV dysfunction in the setting of acute PE with good performance.<sup>40–42</sup> The sensitivity and specificity of performance increases if >1 parameter of RV dysfunction is present (Table 4).<sup>31,41</sup>

13. The presence of chronic features of PE on CTPA that is performed for the diagnosis of acute PE may identify patients at risk for long-term sequelae of PE (eg, CTEPD, post-PE impairment).<sup>45–48</sup> CTPA has high sensitivity and specificity in the detection of CTEPD when the examination is evaluated by an expert radiologist.<sup>47</sup> Cohort studies found that CTEPD correlated strongly during follow-up with the presence of  $\geq 3$  of the following radiologic parameters on imaging: intravascular webs, pulmonary artery (PA) retraction or dilation, bronchial artery dilation, RV hypertrophy, or intraventricular septal flattening, and these features may help with early identification of at-risk patients.<sup>46,48</sup> Pulmonary venous flow reduction (PVFR) was investigated in 1 retrospective study evaluating preoperative patients for pulmonary endarterectomy for CTEPD.<sup>45</sup> PVFR was defined as the presence of a filling defect of at least 2 cm in a pulmonary vein draining into the left atrium and left atrium attenuation ( $>160$  Hounsfield units).<sup>45</sup> The study reported high reproducibility for the identification of PVFR in patients with CTEPD and higher sensitivity and specificity when compared with patients with acute PE.<sup>45</sup> PVFR is not a feature of pulmonary arterial hypertension.

**Table 4. Optimal Methods of RV Dysfunction Assessment on Echocardiogram<sup>44</sup>**

	Recommended Technique for Assessment	Definition of Parameter
RV dimension	1) End-diastole from a right ventricle-focused apical 4-chamber view 2) Apical 4-chamber view	1) EDD $>30$ mm <sup>31,37,42,51</sup> 2) RV basal EDD $>42$ mm <sup>44,51</sup>
RV/LV	End-diastolic ratio (apical or subcostal view)	RV/LV $>0.9$ <sup>37,42,51</sup>
TAPSE <sup>42</sup>	Measures the distance of systolic excursion of the RV annular segment in cm, on M-mode, along a longitudinal plane, from a standard apical 4-chamber view from end-diastole to end-systole	TAPSE $<1.6$ cm is abnormal <sup>42,44,51</sup>
Doppler evidence of pulmonary hypertension	Tissue Doppler imaging	Pulmonary acceleration time $<90$ ms, or the presence of an RV/atrial gradient $>30$ mm Hg <sup>31,51</sup>
Tricuspid systolic velocity	Apical or subcostal 4-chamber view	Tricuspid systolic velocity $>2.6$ m/sec <sup>31,51</sup>

EDD indicates end-diastolic diameter; LV, left ventricle; RV, right ventricle; and TAPSE, tricuspid annular plane systolic excursion.

### 3.2. PE Outcomes Risk Stratification

PE represents a wide spectrum of presentations, ranging from asymptomatic disease to cardiogenic shock and cardiac arrest. Accordingly, PE necessitates swift and precise risk assessment to determine prognosis, guide therapeutic decision-making, and improve patient outcomes. The classification of PE has continuously evolved in response to the recognition that outcomes vary widely, even within broad categories. In 2011, an AHA scientific statement recommended

**Table 5. Progression of Acute PE Risk Categorization Schemas**

Year	Organization	Risk Category	Clinical Criteria
2011	AHA Scientific Statement <sup>1</sup>	Low risk	Normotensive; no right ventricular dysfunction or myocardial necrosis (elevated troponin)
		Submassive	Systolic BP $\geq 90$ mm Hg and either right ventricular dysfunction or myocardial necrosis
		Massive	Systolic blood pressure $<90$ mm Hg for $>15$ minutes or requiring inotropic support
2019	ESC Acute Pulmonary Embolism Risk Scheme <sup>2</sup>	Low risk	Nonelevated risk score (eg, PESI class I-II or sPESI=0) Normal right ventricle on imaging
		Intermediate-low risk	Elevated risk score (eg, PESI class III-IV or sPESI $\geq 1$ ) None or 1 positive of either troponin or right ventricular dysfunction on imaging
		Intermediate-high risk	Elevated risk score (eg, PESI class III-IV or sPESI $\geq 1$ ) Both positive troponin and right ventricular dysfunction on imaging
		High risk	Hemodynamic instability
2026	AHA/ACC Acute PE Clinical Categories	A	Subclinical – incidental and asymptomatic PE
		B	Symptomatic PE with low clinical severity score (eg, PESI class I-II, sPESI=0, Hestia=0)
		C	Symptomatic PE with elevated clinical severity score (eg, PESI class III-V, sPESI $\geq 1$ , Hestia $\geq 1$ )
		D	Incipient cardiopulmonary failure (eg, normotensive shock)
		E	Cardiopulmonary failure

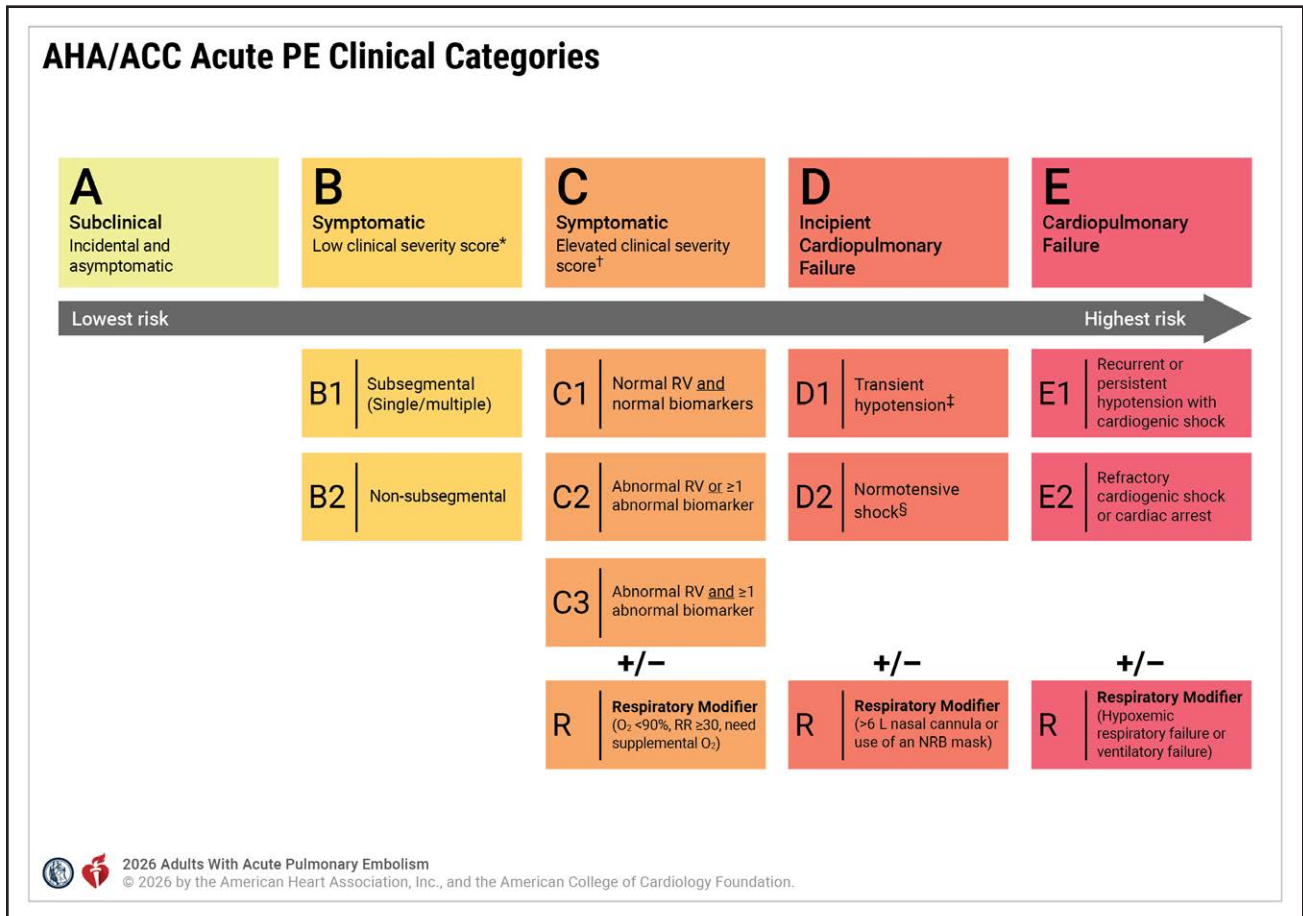
ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; PESI, Pulmonary Embolism Severity Index; and sPESI, simplified Pulmonary Embolism Severity Index.

3 categories: low risk, submassive, and massive PE.<sup>1</sup> Subsequently, in 2019, the European Society of Cardiology developed a risk stratification schema that included 4 categories: low risk, intermediate-low risk, intermediate-high risk, and high risk<sup>2</sup> (Table 5). The need to further clarify heterogeneity in outcomes within risk categories, recognize presentations dominated by respiratory rather than hemodynamic compromise, and identify patients with pre-cardiopulmonary failure states has emerged as a critical priority in evidence-based clinical practice. The AHA/ACC Acute PE Clinical Categories (Figure 2) are designed to describe the severity and prognosis of PE by integrating various clinical, laboratory, and imaging parameters. Category A-E and subcategory 1-3 designations are selected according to the most severe clinical, laboratory, and imaging indicators. Of note, patients may transition among such categories as they are reassessed over time. A respiratory modifier (R) can be added to a

subcategory or designated its own subcategory in patients with prominent respiratory abnormalities.

The least severe category, Category A, focuses on asymptomatic and incidentally diagnosed PE. Patients with Category A acute PE are typically identified on a CT performed for another indication and in the absence of clinical suspicion of PE. An example patient with Category A1 acute PE is an asymptomatic patient with lung cancer found to have left lower lobe subsegmental PE on a cancer staging chest CT scan.

Category B focuses on patients with symptomatic acute PE and low risk of adverse outcomes by validated severity indices (eg, PESI [Pulmonary Embolism Severity Index]  $\leq 85$ , simplified PESI [sPESI]  $< 1$ , Hestia  $< 1$ ) (Section 3.2.1, "Risk Assessment Using Clinical Risk Scores"). Category B1 includes patients with single or multiple subsegmental PEs, while Category B2 includes patients with segmental and more proximal PEs. The intent for distinguishing subsegmental PEs is to recognize that



**Figure 2. AHA/ACC Acute PE Clinical Categories.**

When patients meet the respiratory modifier status criteria, then add "R" to the category description (eg, C3R, D2R). \*Low Clinical Severity Score includes PESI  $\leq 85$  or sPESI = 0 or Bova  $\leq 4$ . †Elevated Clinical Severity Score includes PESI  $> 85$  or sPESI  $\geq 1$  or Bova  $> 4$ . ‡Systolic blood pressure  $< 90$  or decrease  $> 40$  mm Hg lasting  $< 15$  min or responding to IV fluids. §Any: Lactate  $> 2$  mmol/L, acute kidney injury, urine output  $< 0.5$  mL/kg/hr, mental status change, cardiac index  $< 2.2$  L/min/m<sup>2</sup>, mean arterial pressure  $< 60$  mm Hg, increased shock score/stage (SCAI stage, CPES score). ACC indicates American College of Cardiology; AHA, American Heart Association; CPES, Composite Pulmonary Embolism Shock; IV, intravenous; NC, nasal cannula; NRB, nonbreather; O<sub>2</sub>, oxygen; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RR, respiratory rate; RV, right ventricle; and sPESI, simplified PESI.

triage (ie, home versus hospital) and the decision to anticoagulate may differ based on the location of the acute PE and the concomitant presence of DVT. An example patient with Category B2 acute PE might present with pleuritic pain after hip replacement and a sPESI of 0 and be found to have a segmental right lower lobe PE without RV enlargement on CT.

Category C focuses on symptomatic disease with increased risk of adverse outcomes by validated severity index (eg, PESI >85, sPESI  $\geq$ 1, Hestia  $\geq$ 1). The subcategories allow for recognition of the absence or presence of cardiopulmonary dysfunction. Biomarkers include cardiac troponin I/T and brain-type natriuretic peptide (Section 3.2.3, “Cardiac Biomarkers”). Abnormal RV size or function is determined by echocardiogram or CT (Section 3.2.4, “RV Imaging for Risk Stratification”). The respiratory modifier, R, is applied when hypoxemia or tachypnea is present or there is a need for supplemental oxygen. An example patient with Category C1R acute PE would be a patient with breast cancer and sudden dyspnea, tachycardia, and hypoxemia with bilateral lobar PE but no RV enlargement or troponin elevation.

Category D focuses on pre-cardiopulmonary failure states, such as normotensive shock or approaching need for ventilatory support. The subcategories differentiate cardiovascular and pulmonary compromise (Section 3.2.2, “Hemodynamic Assessment”). Category D1 identifies patients with transient or recurrent hypotension (including relative hypotension compared with the patient’s baseline blood pressure) that is short-lived or responds to volume expansion and is not accompanied by any signs of reduced perfusion or end-organ dysfunction. Conversely, Category D2 requires a marker of decreased perfusion or end-organ dysfunction (eg, acute ischemic kidney injury, persistently elevated lactate) accompanied by transient hypotension. A trial of intravenous fluids is generally considered 500 to 1000 mL of intravenous normal saline. Increased shock scores include SCAI SHOCK stage B or C.<sup>3</sup> An example patient with a Category D2 acute PE is a patient who recently underwent spine surgery, develops sudden onset dyspnea, tachycardia, and hypoxemia, has normal systolic blood pressure, and is found to have acute PE in both right and left main pulmonary arteries along with increasing creatinine and low mean arterial pressure (MAP). The respiratory modifier, R, would be applied if the patient required either >6 L nasal cannula or use of a nonrebreather mask.

The most severe category, Category E, focuses on cardiopulmonary failure states. The subcategories differentiate patients with recurrent or persistent hypotension (hemodynamic collapse) with cardiogenic shock from patients with refractory cardiogenic shock or cardiac arrest. Category E1 is compatible with SCAI SHOCK stage C.<sup>3</sup> Category E2 is defined by refrac-

tory cardiogenic shock (SCAI D-E) or cardiac arrest without restoration of spontaneous circulation after 30 minutes of resuscitation. Respiratory failure in category E-R is defined by the need for noninvasive or invasive positive pressure ventilation. An example patient with Category E2R acute PE is a patient admitted with COVID-19 pneumonia on mechanical ventilation, diagnosed with saddle PE, severe RV hypokinesis on echocardiogram, and hypotension despite 3 vasopressors.

### 3.2.1. Risk Assessment Using Clinical Risk Scores

**Recommendations for Risk Assessment Using Clinical Risk Scores**  
Referenced studies that support recommendations are summarized in the Evidence Table.


COR	LOE	Recommendations
1	B-R	1. In patients diagnosed with acute PE in AHA/ACC PE Categories A and B, use of the Hestia, PESI, and/or sPESI risk scores is recommended to identify patients with a low risk for short-term adverse outcomes. <sup>1-4</sup>
2a	B-NR	2. In hemodynamically stable patients diagnosed with acute PE in AHA/ACC PE Categories C and D, using a validated PE-specific risk score is reasonable to identify patients with a higher risk for short-term adverse outcomes. <sup>5-8</sup>
2b	B-NR	3. In hemodynamically stable patients diagnosed with acute PE in AHA/ACC PE Categories C and D, the National Early Warning Score (NEWS) and its updated version, NEWS2, may be reasonable alternatives to a PE-specific risk score to identify patients with a higher risk for short-term adverse outcomes who may require monitoring for clinical deterioration. <sup>9-12</sup>

### Synopsis

Individual clinical factors have been linked to short-term outcomes after an acute PE has occurred, including fixed patient characteristics (such as age or prior medical conditions) and dynamic measurements that may change over time (such as vital signs or biomarkers). Many PE-specific risk scores have been developed to predict short-term outcomes after acute PE (Table 6).<sup>13</sup> PE-specific scores include the Bova score, the Hestia criteria (originally developed to identify patients suitable for outpatient treatment), the PESI, and the sPESI. Generic measures of risk that were not developed specifically for PE, such as the NEWS and NEWS2, have been evaluated in acute PE, but are less well-validated.<sup>11,12</sup>

Risk scores are most accurate in identifying patients with a low risk of short-term adverse outcomes. Hestia, PESI, and sPESI all have good predictive ability in identifying low-risk patients suitable for outpatient management.<sup>1-4</sup> It has been more challenging to identify which patients will do poorly. None of the currently available risk scores strongly predict clinical deterioration in patients with hemodynamically stable PE. One limitation is that

**Table 6. Acute PE Clinical Risk Prediction Scores Used in the Acute Care Setting**

Risk Score Name	Risk Score Components	Range of Risk Score	Risk Categories and Definitions
PESI	Age Male (10 pts) History of cancer (30 pts) History of heart failure (10 pts) Chronic lung disease, (10 pts) Heart rate $\geq$ 110 bpm (20 pts) Systolic blood pressure $<$ 100 mm Hg (30 pts) Respiratory rate $\geq$ 30 bpm (20 pts) Temperature $<$ 36°C (20 pts) Altered mental status (60 pts) Oxygen saturation $<$ 90% (20 pts) Calculate score by adding age (in years) and points by risk factor	Class I to V	Class I (lowest risk): $\leq$ 65 pts Class II: 66-85 pts Class III: 86-105 pts Class IV: 106-125 pts Class V: (highest risk) $\geq$ 126 pts
sPESI	Age $>$ 80 yrs History of cancer Chronic cardiopulmonary disease Systolic blood pressure $<$ 100 mm Hg Heart rate $\geq$ 110 bpm Arterial oxygen saturation $<$ 90% Calculate score by adding 1 pt for each of the risk factors	Low or High	0 points: Low risk of 30-day mortality $\geq$ 1 point: High risk of 30-day mortality
Bova Score	Systolic blood pressure 90-100 mm Hg (2 pts) Cardiac troponin elevation (2 pts) Right ventricular dysfunction (2 pts) Heart rate $\geq$ 110 bpm (1 pt) Calculate score by adding pts for each of the risk factors	0 to 7	Stage I (lowest risk): 0-2 pts Stage II: 3-4 pts Stage III (highest risk): $>$ 4 pts 
Hestia Criteria	Is the patient hemodynamically unstable? Is thrombolysis or embolectomy necessary? Does the patient have active bleeding or a high risk of bleeding? Does the patient require $>$ 24 hours of oxygen to maintain oxygen saturation $>$ 90%? Is pulmonary embolism diagnosed during anticoagulant treatment? Does the patient have severe pain requiring intravenous pain medication for $>$ 24 h? Are there medical or social reasons for hospitalization $>$ 24 hours (eg, infection, cancer, lack of support system)? Does the patient have a creatinine clearance of $<$ 30 mL/min? Does the patient have severe liver impairment? Is the patient pregnant? Does the patient have a documented history of heparin-induced thrombocytopenia?	Negative versus Positive	If answers to all criteria are "No," the Hestia rule is negative; consider outpatient management. If answer to $\geq$ 1 of the criterion is "Yes," the Hestia rule is positive; consider hospitalization.
CPES Score	Elevated cardiac troponin Elevated B-type natriuretic peptide Moderately or severely reduced RV function Central thrombus burden (saddle PE) Concomitant deep vein thrombosis Heart rate $\geq$ 100 bpm Calculate score by assigning 1 pt for each of the factors	0 to 6	0-5 pts: Lower risk for normotensive shock (cardiac index $\leq$ 2.2 L/min/m <sup>2</sup> ) 6 pts: Higher risk for normotensive shock
Shock Index	Heart rate divided by systolic blood pressure	Continuous	Lower scores associated with lower risk Lack of consensus on which cut-points to use for PE risk stratification
NEWS and NEWS2	Respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, level of consciousness, and need for supplemental oxygen Points are assigned based on individual measurements in each category	0 to 20	NEWS2 $\geq$ 9: High risk <sup>12,21</sup>

CPES indicates Composite Pulmonary Embolism Shock; NEWS, National Early Warning Score; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricle; and sPESI, simplified PESI.

risk schemes were developed using factors measured at the time of presentation or diagnosis. An intriguing avenue for investigation is the role of longitudinally measured dynamic variables in scores such as the NEWS2 to better distinguish patients who will clinically deteriorate.<sup>14</sup>

### Recommendation-Specific Supportive Text

1. The Hestia, PESI, and sPESI scores can all identify patients at low risk for short-term adverse outcomes, such as all-cause mortality, PE-related mortality, recurrent thromboembolism, and major bleeding<sup>1-4,15</sup> (Table 6). For example, the Hestia criteria were originally developed as a list of medical and social conditions that preclude outpatient treatment and have also shown good performance in identifying patients at low risk for adverse outcomes after PE.<sup>15</sup> To demonstrate safety and effectiveness, the multicenter, international HOME PE (Hospitalization or Out-treatment Management of Patients With Pulmonary Embolism) trial randomized patients to either sPESI-guided home treatment or Hestia-guided home treatment.<sup>2</sup> Clinicians could follow the risk score recommendations or overrule them; sPESI-guided management was overruled by clinicians more often than Hestia recommendations. Similar proportions of patients with PE were discharged home in the sPESI and Hestia arms, and there were no significant differences in adverse outcomes at 30 days.
2. The performance of PE-specific risk scores, including the Bova, Composite Pulmonary Embolism Shock, PESI, and sPESI scores, have been validated in hemodynamically stable patients with acute PE as approaches to identify patients at higher risk for adverse outcomes (eg, all-cause mortality, PE-related mortality, clinical decompensation).<sup>5-8,16-18</sup> Although scores generally show modest to good discriminatory ability in separating patients by their probability of developing adverse outcomes, none of the scores had consistently strong predictive ability in identifying which individual patients would have adverse outcomes. As a result, many patients with hemodynamically stable PE who are categorized as higher risk do not develop adverse outcomes. In the ideal situation, a clinical risk score should be able to identify patients who would benefit from different monitoring or management. As none of the PE-specific risk scores appear to have substantially superior performance, clinicians can choose to apply any of the validated PE-specific risk scores in hemodynamically stable PE to identify potentially higher risk individuals.
3. Generic measures of risk, such as the Shock Index, the NEWS, and its updated version, NEWS2, have also been compared with PE-specific risk scores in their ability to predict which hemodynamically stable patients will develop short-term adverse outcomes after PE, and

some studies have shown comparable performance to PE-specific scores.<sup>9-13,19,20</sup> An advantage of generic risk scores is that they are readily calculated based on commonly obtained clinical assessments, such as vital signs. As these assessments are dynamic, scores can change over time in individual patients with PE. Further investigation of which cut-points to use in PE and whether repeated and longitudinal measures of risk can better identify patients who are likely to develop impending adverse outcomes is needed.<sup>21</sup>

### 3.2.2. Hemodynamic Assessment

Recommendations for Hemodynamic Assessment		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	B-NR	1. In patients with acute PE in AHA/ACC PE Category D2, evaluating for the presence of normotensive shock* can be useful to identify patients at increased risk for clinical deterioration and in-hospital death. <sup>1</sup>
2a	B-NR	2. In patients with acute PE in AHA/ACC PE Category C3, a MAP <80 mm Hg may be useful to identify patients who may require escalation of therapy. <sup>2</sup>

\*Normotensive shock is defined as isolated hypoperfusion without hypotension identified with any of the following markers: serum lactate >2 mmol/L, urine output <720 mL in 24 hours, creatinine increase ≥0.3 mg/mL in 24 hours, cardiac index ≤2.2 L/min/m<sup>2</sup> from peripheral arterial and mixed venous oxygenation saturation values.



### Synopsis

Patients with acute PE in AHA/ACC PE Categories C1 through D represent a group of patients at risk for clinical decline. Several parameters may help to better refine these categories of patients and identify those at highest risk for adverse events or in-hospital mortality. In recent clinical trials, the first 24 to 72 hours appear to be a critical time during which hemodynamic collapse or changes in laboratory studies are most commonly observed.<sup>2-4</sup> Recent studies of patients with cardiogenic shock have defined a subset of patients with evidence of hypoperfusion and normotension as having “normotensive shock.”<sup>5,6</sup> In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, markers of end-organ malperfusion (elevated lactate, acute kidney injury or reduced urine output, and/or reduced cardiac index) were associated with higher in-hospital mortality than hypotension alone.<sup>7</sup> Other studies have shown that a MAP >80 mm Hg is associated with better outcomes and reduced in-hospital death for patients with acute PE.<sup>8,9</sup> Clinical scores are being developed and validated that incorporate clinical markers of cardiovascular compromise, RV dysfunction, and clot burden to identify normotensive patients with PE who are higher risk as well.<sup>1,10</sup> More granularity of the patient with PE may help to define the population that is at highest risk for clinical decline and therefore may have the best risk-benefit margin for advanced therapies.

## Recommendation-Specific Supportive Text

1. Normotensive shock has been defined in patients as the presence of isolated hypoperfusion without hypotension.<sup>5,6</sup> One study used data from the FLASH (FlowTrierer All-Comer Registry for Patient Safety and Hemodynamics) registry to investigate the prevalence of isolated hypoperfusion in patients with intermediate risk PE undergoing mechanical thrombectomy.<sup>1</sup> The rate of isolated hypoperfusion was 34%, and roughly one-third of patients who underwent thrombectomy had normalization of the cardiac index. This may help to refine risk stratification of patients with acute PE by identifying those at high risk for hemodynamic deterioration (ie, AHA/ACC PE Category D2).
2. Observational cohort data suggest that patients with acute PE and a MAP >80 mm Hg are at very low risk for in-hospital death or adverse outcomes. In 1 retrospective study of 122 patients with intermediate-high risk PE, those with a MAP of 80 to 90 mm Hg had few adverse events. The Italian Pulmonary Embolism Registry receiver operating characteristic analysis established 81.5 mm Hg (area under the curve, 0.77 ± 0.3) as the optimal cut-off value for MAP as a predictor of 48 h clinical deterioration.<sup>9</sup> Sensitivity was 77.5%, specificity was 95.0%, positive predictive value was 63.2%, and negative predictive value was 97.7%. Therefore, in patients with PE of AHA/ACC PE category C3 severity, a MAP >80 mm Hg may help to stratify patients at low risk for clinical decompensation.

In the PEITHO (Pulmonary Embolism Thrombolysis) trial, the mean time between randomization and the primary efficacy endpoint of hemodynamic collapse or escalation of care to lysis occurred at 1.5 to 1.79 days ± 1.5 days.<sup>2</sup> This trial included patients with evidence of RV dysfunction by echocardiography or CT, as well as a positive troponin, which correlates with patients with AHA/ACC PE category C3 severity (Section 3.2.1, “Risk Assessment Using Clinical Risk Scores”). Therefore, close monitoring of patients in this category within the first 24 to 72 hours for worsening clinical status can be useful to identify those who may require escalation of therapy.

### 3.2.3. Biomarkers for Risk Stratification

Recommendations for Risk Stratification of PE Using Biomarkers Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	B-NR	1. In patients with acute PE and an elevated clinical severity score without features of hypotension or shock (ie, AHA/ACC PE Category C), measurement of at least 1 cardiac biomarker (ie, troponin, brain natriuretic peptide [BNP]) is recommended to assist with risk stratification for short-term complications and/or mortality. <sup>1-11</sup>

Recommendations for Risk Stratification of PE Using Biomarkers (Continued)		
COR	LOE	Recommendations
1	B-NR	2. In patients with acute PE (ie, AHA/ACC PE Categories C to E) who are undergoing evaluation at an acute care facility, measurement of lactate (either venous or arterial) is recommended to assist with risk stratification for short-term complications and/or mortality. <sup>12-18</sup>

## Synopsis

Cardiac biomarkers are important tools to assist in risk stratification of PE. Cardiac biomarkers (troponin and BNP) have been incorporated into clinical risk tools and can be used to identify patients at risk of short-term complications and mortality. Lactate is an additional marker of risk, particularly among normotensive patients hospitalized with acute symptomatic PE in whom it may indicate subclinical end-organ hypoperfusion. An elevated lactate level correlates with early complications and mortality and provides incremental data in addition to cardiac biomarkers alone. Lactate levels have also been used to assist in determining whether advanced therapies should be selected. Lactate (arterial or venous) should be measured whenever cardiac biomarkers are being assessed for risk stratification, and the threshold for determining an elevated level should be based on the local assay utilized.

## Recommendation-Specific Supportive Text

1. One meta-analysis of 46 studies published from 2000 through 2018 evaluated the prognostic value of troponin levels on mortality in patients with PE.<sup>2</sup> Among 10842 patients with PE, the effect of elevated troponin on all-cause mortality had a pooled odds ratio (OR) of 4.33. When stratified by different troponin assays, each assay had an associated risk with all-cause mortality, with an overall OR of 4.80 for 90-day mortality.

Another meta-analysis that included 12 studies published through 2008 evaluated the prognostic value of BNP level on mortality in patients with acute PE. Among 868 patients with PE included in this meta-analysis, an elevated BNP level was associated with a 6.57-odds of short-term all-cause mortality and a 7.47-odds of serious adverse events.<sup>11</sup> Different biomarker thresholds may also be useful for identifying patients at low versus higher risk of serious adverse events.<sup>19</sup>

2. A meta-analysis of 6 studies published through 2021 evaluated the prognostic value of serum lactate (arterial or venous) on mortality in patients with acute PE.<sup>14</sup> Among 1706 patients with PE included in this meta-analysis, elevated lactate levels were associated with a 5.13-odds of all-cause mortality among unselected PE patients and a 4.54-odds of all-cause mortality among normotensive patients with acute PE.

There was also a 9.05-odds higher risk of PE-related mortality with elevated lactate compared with normal levels.<sup>14</sup>

### 3.2.4. Right Ventricular Imaging for Risk Stratification

Recommendations for Right Ventricular Imaging for Risk Stratification Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	A	1. In patients with acute PE and an elevated clinical severity score but without evidence of shock (ie, AHA/ACC PE Categories C-D), RV imaging is recommended for short-term risk stratification. <sup>1-4</sup>
2a	B-NR	2. In patients with acute PE and an elevated clinical severity score but without evidence of persistent hypotension or shock (ie, AHA/ACC PE Categories C-D), use of echocardiography over CT is preferred for short-term risk stratification. <sup>1,5-8</sup>

### Synopsis

RV imaging with echocardiography or chest CT can identify patients with PE and increased risk of adverse clinical outcomes and is recommended for risk stratification of patients with acute symptomatic PE and an elevated clinical severity score who do not have severe cardiopulmonary compromise or cardiopulmonary failure (AHA/ACC PE Categories C-D).

### Recommendation-Specific Supportive Text

1. In the largest randomized controlled trial (RCT) of thrombolysis for acute PE to date, RV imaging with echocardiography or CT was utilized to identify 1006 patients at increased risk of adverse clinical outcomes.<sup>1</sup> In an analysis of a prospective registry, triage of patients with PE and low-risk for adverse events by sPESI score, RV assessment that included echocardiography, CT, and cardiac biomarkers demonstrated superior prognostic performance for prediction of 5-day clinical deterioration.<sup>2</sup> A subsequent systematic review and meta-analysis of 22 studies, encompassing 3295 patients with PE and low risk of adverse outcomes by PESI, sPESI, or Hestia criteria, echocardiographic or CT-determined RV dysfunction identified a cohort with increased odds of all-cause mortality (OR, 4.19 [95% CI, 1.39-12.58]).<sup>3</sup> An individual patient data meta-analysis of 5010 patients with acute PE at low risk for adverse outcomes demonstrated that RV dysfunction detected by echocardiogram, CT, or BNP/NT-proBNP was associated with increased odds of short-term death (OR, 4.81 [95% CI, 1.98-11.68]), 3-month mortality (OR, 4.03 [95% CI, 2.01-8.08]), and PE-related death (OR, 22.9 [95% CI, 2.89-181]).<sup>4</sup>
2. In the large, multicenter RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry, 15 375 patients with acute PE underwent echocardiographic

assessment early in their clinical course.<sup>9</sup> RV hypokinesis was associated with a 4-fold increased odds of PE-related mortality (OR, 3.11 [95% CI, 1.85-5.21]). In a subsequent systematic review and meta-analysis of 55 studies encompassing 17 090 patients with acute PE, RV dysfunction on echocardiography correlated with an increased odds of all-cause mortality (OR, 2.0 [95% CI, 1.66-2.40]) and PE-related mortality (OR, 4.01 [95% CI, 2.79-5.78]).<sup>10</sup> Among patients with PE determined to have intermediate risk of adverse outcomes, RV dysfunction on echocardiography differentiated patients with increased odds of PE-related mortality (OR, 6.16 [95% CI, 1.33-28.4]). When compared with echocardiographic measurement of RV dysfunction, septal deviation on CT scans had a sensitivity of 0.31 (95% CI, 0.25-0.38) and a specificity of 0.98 (95% CI, 0.90-1.00), while increased RV/LV ratio on CT scans had a sensitivity of 0.83 (95% CI, 0.78-0.87) and a specificity of 0.75 (95% CI, 0.66-0.82).<sup>11</sup> In a prospective study of critically ill patients with suspected PE, point-of-care ultrasound demonstrated acceptable accuracy for identification of RV dysfunction.<sup>8</sup> Based on such data, point-of-care ultrasound may be used as an alternative to formal transthoracic echocardiography if the latter is unavailable.

### 3.2.5. Quantification of Thrombus Burden for Short-Term Risk Stratification

Recommendation for Quantification of Thrombus Burden for Short-Term Risk Stratification Referenced studies that support the recommendation are summarized in the Evidence Table.		
COR	LOE	Recommendation
3: No Benefit	B-NR	1. In patients with acute PE in AHA/ACC PE Categories A-C, quantification of angiographic thrombus burden for short-term risk stratification is not recommended. <sup>1-4</sup>

### Synopsis

Although chest CT allows for quantification of thromboembolic volume and the severity of pulmonary angiographic obstruction, current data support neither the integration of measures of thrombus burden (such as modified Miller score or refined modified Miller score) into short-term risk stratification of patients with PE nor the ability to determine whether reperfusion therapy is indicated. However, anatomic characterization of thrombus burden can be helpful in assessing the feasibility, safety, and efficacy of various advanced therapies in those patients selected for advanced therapy.

### Recommendation-Specific Supportive Text

1. A meta-analysis of 19 studies reporting on the prognostic value of CT-assessed embolic burden observed no direct correlation between a high obstruction index and prognosis but, instead, demonstrated an

increased all-cause mortality with a lower obstruction index (OR, 2.24 [95% CI, 1.29-3.89]).<sup>1</sup> A subsequent prospective observational cohort study of 271 patients with PE also showed no association between thrombus burden and adverse clinical events after excluding patients with a shock index >1 (OR, 2.56 [95% CI, 0.62-10.64]).<sup>2</sup> A retrospective observational cohort study of 1743 patients with CT-confirmed PE found no association between proximal thrombus burden and all-cause 30-day mortality.<sup>3</sup> Although not widely available currently, techniques for quantifying loss of small pulmonary vessel vascular volume may offer better prediction of short- and long-term mortality in PE.<sup>4</sup> The role of assessment of angiographic thrombus burden in higher-risk patients with PE (AHA/ACC PE Categories D-E) is uncertain and warrants investigation.

## 4. ACUTE MANAGEMENT

Anticoagulation therapy is the foundation of acute PE management. Use of DOACs and LMWH allow for rapid and predictable anticoagulation therapy in most patients with acute PE. Further management strategies are dictated by individual risk factors for adverse events. These include the measurement of biomarkers, RV size and function on imaging, and hemodynamics (Sections 3.2.2, “Hemodynamic Assessment,” 3.2.3, “Biomarkers for Risk Stratification,” and 3.2.4, “Right Ventricular Imaging for Risk Stratification”). Informed by these risk factors, decisions can be made about the utility of advanced interventions, including catheter-directed thrombolysis (CDL), mechanical thrombectomy, surgical embolectomy, and extracorporeal membrane oxygenation (ECMO). Use of a PERT to facilitate decision-making around acute interventions is recommended (Figure 3).

### 4.1. Hospitalization Admission Decision Considerations

#### 4.1.1. Suitability for Outpatient Management of PE

Recommendations for Suitability for Outpatient Management of PE		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	B-R	1. In patients diagnosed with acute PE in a clinic or an ED, it is reasonable to use a decision tool* to identify suitability for outpatient treatment. <sup>1</sup>
2a	B-R	2. In select patients diagnosed with acute PE in AHA ACC PE Categories A and B in a clinic or ED, outpatient treatment† is a reasonable option compared with hospitalization, when the rate of 90-day adverse outcomes is low and it aligns with patient goals. <sup>2</sup>

\*Decision tool options include the Hestia rule, the PESI, and the sPESI.

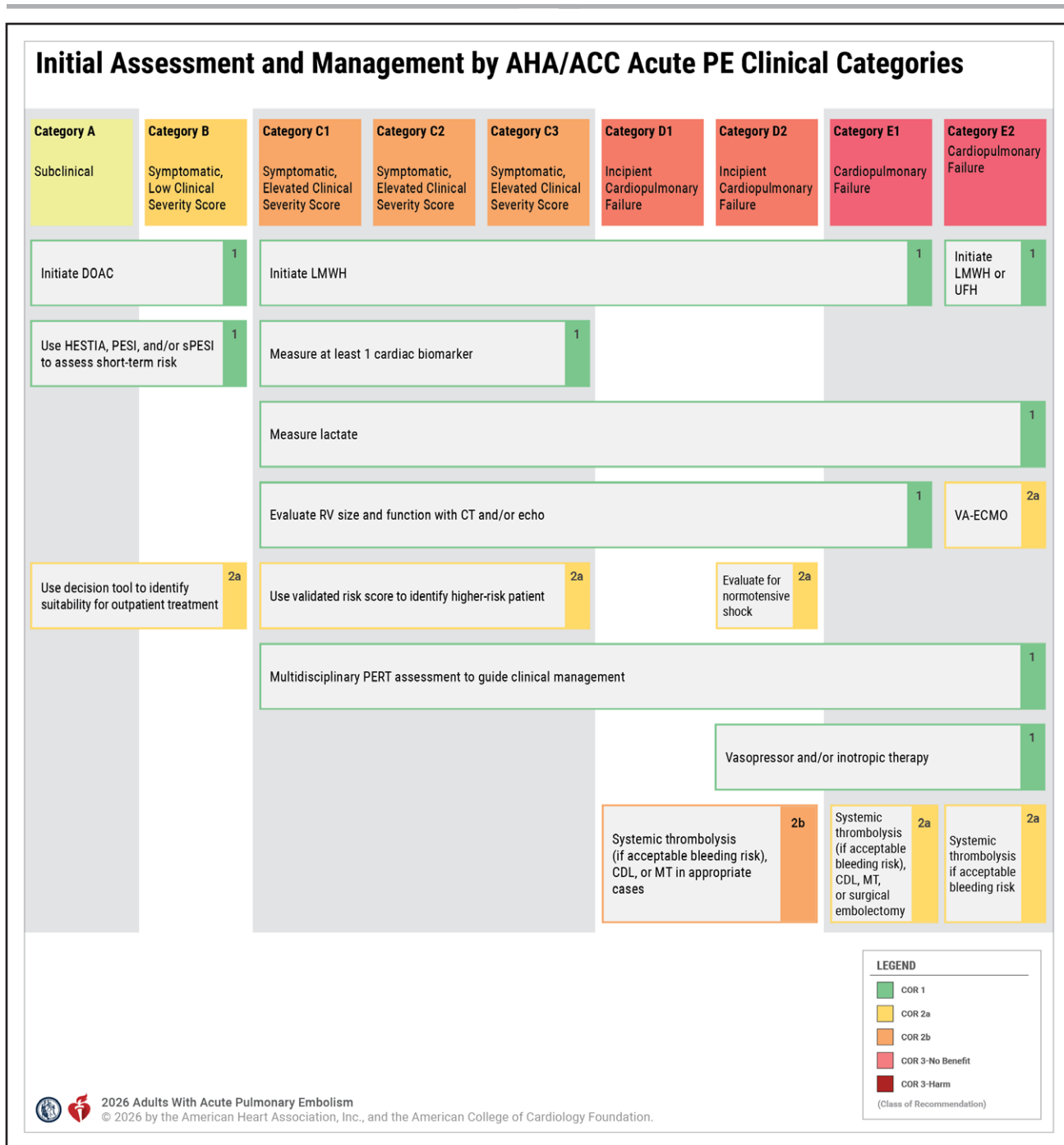
†Patients suitable for discharge from the outpatient or emergency setting must have immediate access to anticoagulant medication and rapid, reliable, expert follow-up in place.

## Synopsis

Outpatient treatment of patients with acute PE varies across regions and countries.<sup>3,4</sup> A Cochrane review<sup>2</sup> compared outpatient treatment with inpatient treatment for patients with low-risk acute PE and demonstrated no difference in adverse clinical outcomes. There have been many management studies assessing a single decision tool to determine outpatient management of PE.<sup>5-12</sup> Decision tools that have been studied include the Hestia rule, the PESI, and the sPESI (See Table 6). All prospective studies evaluating the PESI incorporated multiple items found in the Hestia rule as exclusion criteria, making it challenging to attribute safety findings to the PESI alone. The only RCT comparing different decision tools to determine outpatient treatment of PE showed that physician determination and shared decision-making with patients frequently overrides the decision tool results.<sup>1</sup>

### Recommendation-Specific Supportive Text

- Five studies, comprising a total of 1504 patients, used the absence of Hestia criteria (or a very close variant of this rule) to determine which patients with acute PE could be treated as outpatients.<sup>5,6,8,9,13</sup> Three studies, including a total of 592 patients, used a PESI category of I or II to determine home treatment of PE patients.<sup>11,12,14</sup> These studies prospectively followed participants for 90 days. The 90-day mortality, bleeding, and recurrent VTE rates were low (each outcome occurring in <1.5% of the study population).<sup>15</sup> One study prospectively compared decision rules for outpatient treatment. The HOME-PE trial randomized patients with acute PE to assessment with the Hestia rule or the sPESI to guide treatment as outpatients or hospitalization.<sup>1</sup> There was no significant difference in the composite rate of recurrent VTE, major bleeding, or all-cause death between the groups within 30 days of randomization. In the Hestia arm, 38.4% (378/984) were treated as an outpatient versus 36.6% (361/986) in the sPESI arm. The Hestia rule was negative in 39.4% (388/984) of patients, and the sPESI was 0 points in 48.4% (477/986) of patients. Among those who were treated as outpatients, the composite rates were low in both the Hestia arm (1.3% [5/375]) and the sPESI arm (1.1% [4/359]). Although significantly more patients qualified for outpatient treatment in the sPESI arm compared with the Hestia arm, similar proportions were treated at home in both arms, suggesting shared decision-making and physician judgment were overriding factors. An individual-patient meta-analysis reported the 30-day mortality for outpatient management of PE as 0.30% (95% CI, 0.09-0.51), recurrent VTE as 0.57% (95% CI, 0.28-0.86), and major bleeding as 0.45% (95% CI, 0.19-1.71).<sup>16</sup>
- There are 2 RCTs comparing outpatient treatment with inpatient treatment for select patients with acute PE.



**Figure 3. Initial Assessment and Management by AHA/ACC Acute PE Clinical Categories.** Initial assessment and management of acute PE by category with associated COR 1 and 2a recommendations along with select COR 2b recommendations. Additional COR 2b recommendations that are not included in this figure may be appropriate in select clinical cases. ACC indicates American College of Cardiology; AHA, American Heart Association; CDL, catheter-directed thrombolysis; COR, class of recommendation; CT, computed tomography; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular-weight heparin; MT, mechanical thrombectomy; PE, pulmonary embolism; PERT, PE response team; PESI, Pulmonary Embolism Severity Index; RV, right ventricle; sPESI, simplified PESI; UFH, unfractionated heparin; and VA, venoarterial.

One trial, conducted in Switzerland, France, Belgium, and the United States (across 19 centers) recruited 344 patients with a PESI category of I or II, (with additional exclusion criteria applied).<sup>14</sup> Patients were treated with LMWH plus warfarin and were followed for 90 days. This trial found no significant difference

in clinical outcomes between outpatient and inpatient treatment groups. A second trial conducted in 35 US hospitals recruited 114 patients who had a negative Hestia rule assessment, a normal serum troponin, no contraindications to anticoagulation, and no barriers to treatment or follow-up.<sup>6</sup> Patients randomized to

outpatient treatment were prescribed rivaroxaban and were followed for 90 days. This trial found no significant difference in clinical outcomes between groups. A Cochrane review meta-analysis of these 2 trials concluded there was no significant difference in the relative risk of all-cause mortality (at 30 or 90 days), major bleeding, minor bleeding, or recurrent VTE at 90 days (all outcomes had low-certainty evidence). There was no difference in patient satisfaction (moderate-certainty evidence).<sup>2</sup>

#### 4.1.2. Placement in the Hospital

Recommendations for Triage and Placement in the Hospital Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	C-EO	1. In patients with acute PE who are receiving thrombolytic therapy (systemic or CDL), placement in a unit that can provide close monitoring, such as an intensive care unit (ICU) or intermediate level of care unit, is recommended to monitor for adverse events.
2a	B-R	2. In patients admitted to the hospital with acute PE who undergo mechanical thrombectomy (MT) and are hemodynamically stable, admission to a level of care that can provide continuous telemetry and nursing care familiar with the postprocedural complications of the device used is reasonable. <sup>1</sup>

### Synopsis

The triage of patients with acute PE can be very challenging given their vast array of clinical presentations. Once diagnosed, all patients with acute PE should be triaged based on clinical outcomes risk stratification (Section 3.2). Employment of this strategy facilitates triage to the appropriate level of care. Level of care decisions should be made based on the clinical status of the patient (hemodynamics and respiratory status), potential need for advanced therapies (eg, catheter-based interventions, inotropic drugs, ECMO), and the expertise and availability of the facility. All triage decisions must consider the complete clinical context, ideally performed within a PERT model (Section 4.1.4, "Pulmonary Embolism Response Team").

### Recommendation-Specific Supportive Text

1. For patients with acute PE who are treated with catheter-based interventions, the appropriate level of post-procedure care must consider end-procedural hemodynamics, risks for bleeding, and periprocedural complications. To date, there are no studies specifically evaluating the triage of patients after catheter-based interventions for PE. However, in patients receiving CDL, a level of care in which the patient can be closely monitored is recommended given the presence of indwelling catheters and the ongoing administration of thrombolytic agents.<sup>2</sup>
2. In patients treated with nonlytic-based therapies (eg, MT), admission to a level of care that can provide

continuous telemetry and nursing care familiar with the postprocedural complications of the device used is reasonable. The PEERLESS (Large-Bore Mechanical Thrombectomy vs. Catheter-Directed Thrombolysis for Treatment of Intermediate-Risk Pulmonary Embolism) trial randomized 550 patients to CDL or MT. More than 60% of patients treated with MT received post-procedural care in non-ICU settings with very low adverse event rates.<sup>1</sup> Consideration of the level of care in which the patient can be monitored for access site complications, given the size of the sheath used and/or other bleeding complications associated with ongoing anticoagulation is recommended when deciding on placement in the hospital. Importantly, all postprocedural triage decisions must consider the complete clinical context of the patient, the procedural outcome, the potential for postprocedural complications associated with the device utilized, and the resources available at the individual hospital providing care to the patient with acute PE.

#### 4.1.3. Interhospital Transfers

Recommendations for Interhospital Transfers Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2b	C-LD	1. For patients with acute PE who exhibit high-risk features* but are hemodynamically stable (AHA/ACC PE Categories C3-D), transferring to a center that can provide advanced therapies† may be considered to ensure access to appropriate interventions. <sup>1</sup>
3: Harm	C-EO	2. Unstable patients with acute PE (AHA/ACC PE Category E) should not be transferred to another medical center before stabilizing their condition.

\*High-risk features include RV dysfunction and elevated cardiac biomarkers.  
†Advanced therapy examples: surgical embolectomy, CDL, MT, ECMO, and placement of an IVC filter.

### Synopsis

Patients with acute PE may benefit from transferring to a tertiary care center when requiring advanced interventions or specialized care unavailable at their initial hospital. These centers provide advanced imaging, specialized testing, and multidisciplinary teams encompassing specialists in emergency medicine, pulmonary medicine, vascular medicine, general cardiology, hematology, interventional cardiology, interventional radiology, critical care, cardiothoracic surgery, vascular surgery, pharmacy, and others. Patients presenting with hemodynamic instability—manifesting as hypotension or shock—mandate immediate advanced measures, potentially including thrombolytic therapy, catheter-directed interventions, or mechanical circulatory support where such therapies are available.<sup>2</sup> However, there are limited data to help triage which patients will benefit from transfer. In a single-center, retrospective study of 532 patients, a higher Bova score required more advanced measures in the

receiving hospital.<sup>3</sup> Importantly, patients deemed unsuitable for transfer must be treated according to the best local expertise.

**Recommendation-Specific Supportive Text**

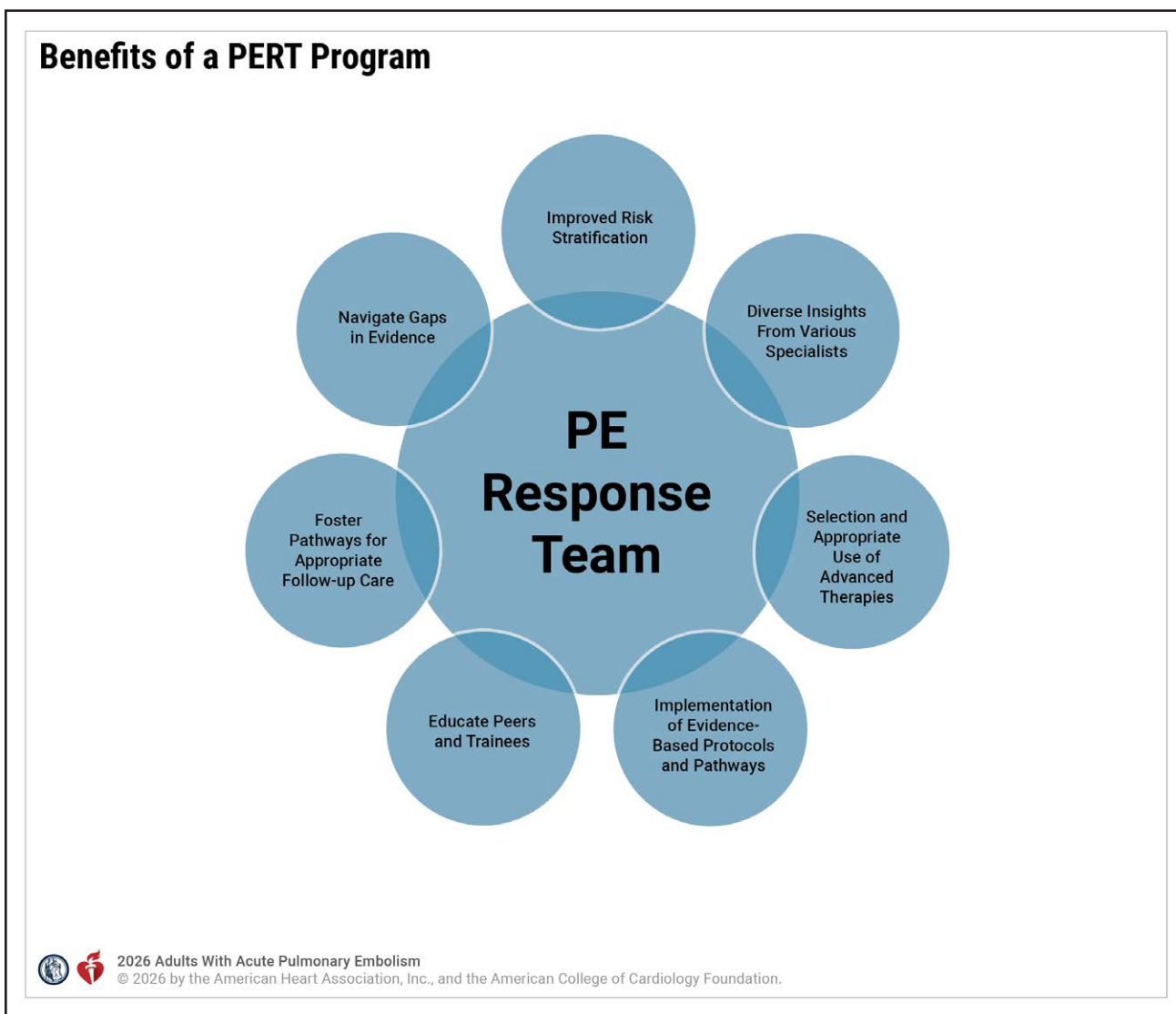
1. High-risk features (eg, RV dysfunction, elevated cardiac biomarkers) may warrant transfer for intensive monitoring and specialized treatments. Patients with comorbidities like preexisting pulmonary hypertension (PH) or cancer may also benefit from tertiary center expertise. Decisions regarding transfer must be tailored to each patient's needs, ensuring timely access to appropriate care for optimal outcomes.<sup>1</sup>
2. Hemodynamically unstable patients with PE risk cardiovascular collapse. Thus, immediate stabilization

prior to transfer is crucial, and potentially lifesaving interventions that are widely available, such as intravenous thrombolytic therapy, should not be delayed.

**4.1.4. Pulmonary Embolism Response Team**

Recommendation for PERT		
Referenced studies that support the recommendation are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	B-NR	1. In patients with acute PE who are at increased risk of adverse outcomes (ie, AHA/ACC PE Categories C-E)*, a multidisciplinary PERT assessment is recommended to improve in-hospital clinical care delivery. <sup>1-18</sup>

\*AHA/ACC PE Categories A or B with multiple comorbidities may also benefit from a PERT (eg, Category B with intracranial hemorrhage).



**Figure 4. Benefits of a PERT Program.**

PERT teams can make a significant impact on the clinical care delivery model by improving risk stratification, expediting initiation of treatments, such as anticoagulation therapy, and aiding the clinician in selecting the most appropriate advanced interventions when deemed appropriate. PERT indicates pulmonary embolism response team. Modified with permission from Bejjani et al.<sup>3</sup> Copyright 2022 MDPI.

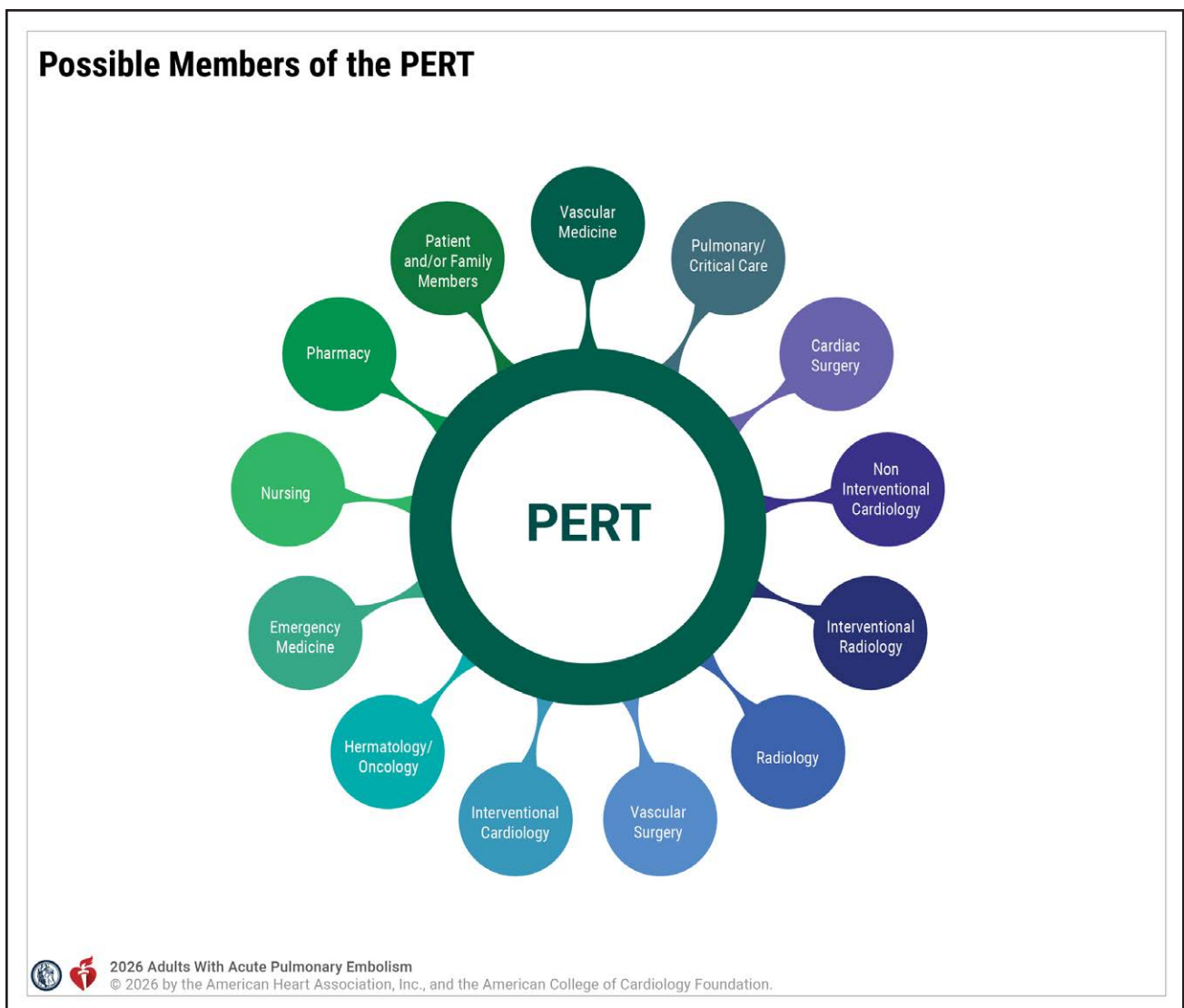
## Synopsis

The implementation of a high-functioning PERT can make a significant impact on the clinical care delivery model by expediting initiation of treatments, such as anticoagulation therapy, and aiding the clinician in selecting the most appropriate advanced interventions when deemed appropriate, while decreasing hospital length of stay (Figure 4). PERTs function similarly to code stroke or ST-elevation myocardial infarction teams. When activated, PERTs play a significant role in improving the overall outcomes of patients through early management of the symptoms and signs of acute PE. The members of a multidisciplinary PERT may vary among facilities, depending on the resources available. Figure 5 illustrates the various disciplines that may be employed to make up an ideal and effective PERT. The organization and activation of each PERT will depend on the needs and

resources of each institution. Figure 6 demonstrates an example of how a PERT activation might flow.

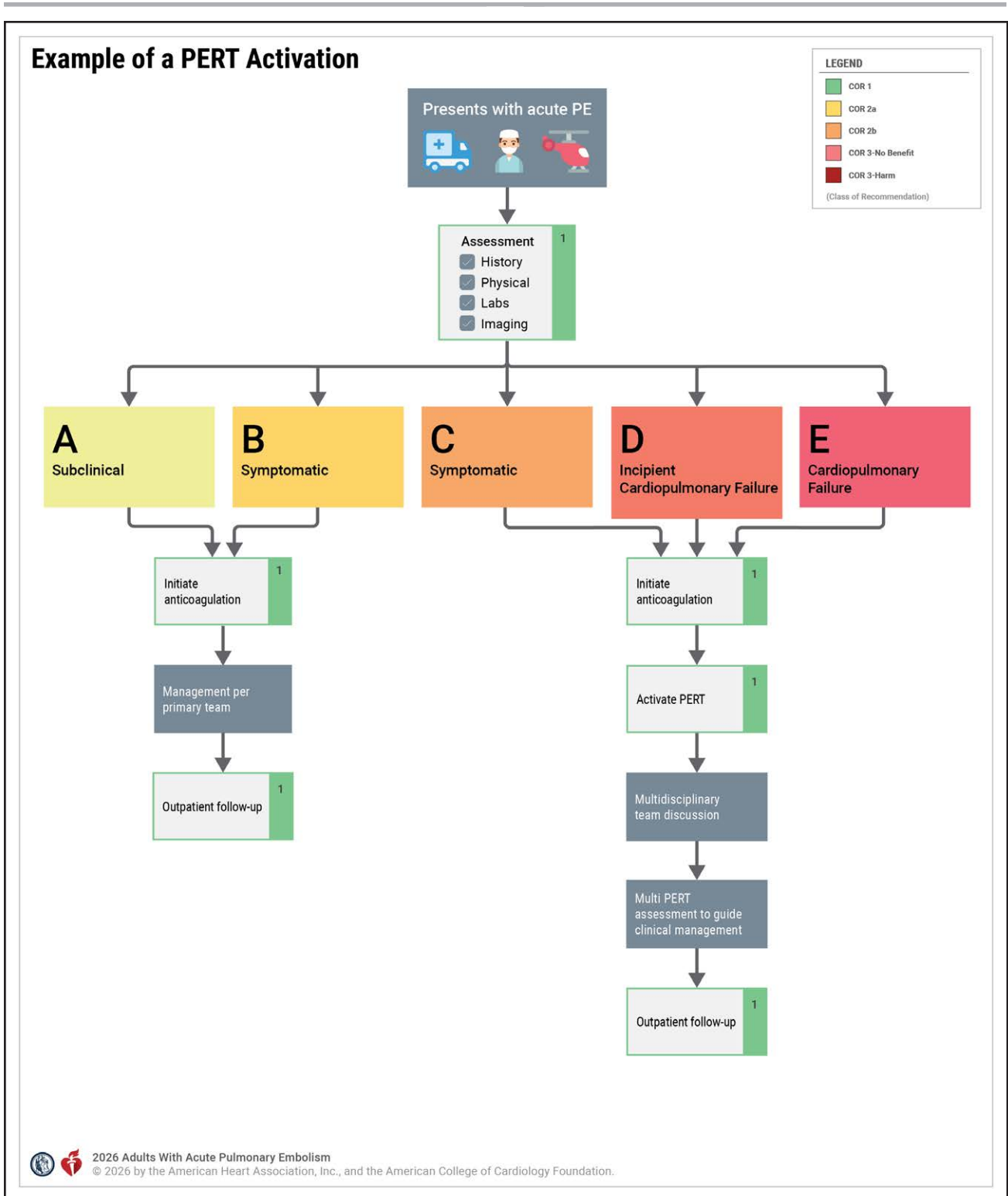
## Recommendation-Specific Supportive Text

1. There are many benefits to implementing a PERT program for the acute care setting to expedite patient care and improve outcomes. For example, anticoagulation is crucial for treating PE and should be initiated promptly (Section 4.2.1, "Anticoagulation Therapy"). Studies show that PERTs reduce the time to therapeutic anticoagulation, with significant reductions observed in multiple patient cohorts.<sup>5,7,8,13</sup> PERTs also decrease the use of IVC filters, as evidenced by several retrospective analyses and a meta-analysis.<sup>2,4-6</sup> Additionally, PERT implementation is associated with reduced hospital and ICU length of stay in most studies, although some found no difference.<sup>1,7,9</sup> The impact



**Figure 5. Possible Members of the PERT.**

Not all PERT programs will include all of these specialties. PE indicates pulmonary embolism; and PERT, pulmonary embolism response team. Modified from Rosovsky et al.<sup>18</sup> Copyright 2018, with permission from Elsevier.



**Figure 6. Example of a PERT Activation.**

The model and process of PERT activation. When a PE is diagnosed, the designated in-house PERT physician is paged, pertinent clinical information is gathered, and the severity of the case is assessed. If necessary, members of a multidisciplinary team discuss the case via phone, virtual meeting, or in person. Diagnostic and treatment options are discussed, recommendations are generated, and appropriate resources are mobilized. Upon discharge, patients follow up in a multidisciplinary clinic. COR indicates class of recommendation; PE, pulmonary embolism; PERT, pulmonary embolism response team. Modified from Rosovsky.<sup>18</sup> Copyright 2018, with permission from Elsevier.

of PERTs on mortality is mixed, with some studies showing decreased mortality rates while others found no change.<sup>1,4,5,7,14</sup> Overall, PERTs improve clinical outcomes in several areas, but their effect on mortality is not yet conclusively established.

## 4.2. Medical Management

### 4.2.1. Anticoagulation Therapy

**Recommendations for Anticoagulation Therapy**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	General Recommendations
1	B-R	1. In patients with acute PE who do not have an absolute contraindication to anticoagulation therapy, anticoagulation therapy should be initiated to reduce the risk of recurrent VTE and death. <sup>1</sup>
1	B-R	2. In patients with acute PE in AHA/ACC Categories C1-E1 who require parenteral anticoagulant therapy initially, LMWH is recommended over UFH to reduce recurrent VTE and major bleeding. <sup>2</sup>
1	B-R	3. In patients with acute PE who are eligible for oral anticoagulation, DOACs are recommended over vitamin K antagonists (VKAs), unless contraindicated, to prevent recurrent VTE and reduce major bleeding. <sup>3,4</sup>
2a	C-EO	4. In patients with suspected acute PE in AHA/ACC PE Category C2 or higher and in whom the bleeding risk is low, it may be beneficial to administer therapeutic anticoagulation when imaging is delayed or not immediately accessible.
<b>Anticoagulation Therapy and Special Considerations</b>		
<b>Obesity</b>		
2a	B-NR	5. In patients with obesity (body mass index [BMI] >30 kg/m <sup>2</sup> ) and acute PE who are receiving oral anticoagulant therapy, treatment with a DOAC (unless contraindicated) over a VKA is reasonable to prevent recurrent PE and reduce major bleeding. <sup>5-10</sup>
2b	B-NR	6. In patients with class III obesity (BMI >40 kg/m <sup>2</sup> ) and acute PE who are receiving LMWH therapy, reducing the dose of LMWH may be reasonable to reduce the risk of bleeding. <sup>11,12</sup>
<b>Thrombotic Antiphospholipid Antibody Syndrome</b>		
1	A	7. In patients with acute PE and established thrombotic antiphospholipid antibody syndrome, a VKA is recommended in preference to a DOAC for the prevention of venous and arterial thrombosis. <sup>13-16</sup>
2b	B-R	8. In patients with acute PE determined to have only a single anticardiolipin antibody or a β <sub>2</sub> -glycoprotein antibody, a DOAC might be a reasonable alternative to a VKA to prevent recurrent PE. <sup>13-15</sup>
<b>Primary or Metastatic Brain Tumor</b>		
2b	C-LD	9. In patients with primary or metastatic brain tumors and acute PE who are otherwise eligible for oral anticoagulation, a DOAC may be considered over LMWH to reduce the risk of ICH. <sup>17-19</sup>
<b>Chronic Kidney Disease</b>		
1	A	10. In patients with mild-to-moderate (stage 2-3) chronic kidney disease (CKD) and acute PE who require oral anticoagulant therapy, a DOAC is recommended over a VKA to reduce major bleeding. <sup>20-22</sup>

<b>Recommendations for Anticoagulation Therapy (Continued)</b>		
COR	LOE	Recommendations
2b	B-NR	11. In patients with severe kidney disease (stage 4-5) or endstage kidney disease on hemodialysis and confirmed PE who require oral anticoagulant therapy, it is uncertain whether apixaban is better than VKA to reduce major bleeding. <sup>23,24</sup>
<b>Pregnancy</b>		
1	C-LD	12. In patients who are pregnant, have acute PE, and can receive anticoagulation, either LMWH or UFH are recommended to prevent recurrent VTE. <sup>25</sup>
3: Harm	C-LD	13. In patients who are pregnant and have acute PE, DOACs and warfarin are potentially harmful and may result in miscarriages or fetal anomalies. <sup>26</sup>
<b>Breastfeeding</b>		
1	C-LD	14. In patients with acute PE who are breastfeeding and require anticoagulation, LMWH, UFH, or warfarin are recommended over a DOAC, to prevent potential bleeding in the infant. <sup>26,27</sup>
<b>Chronic Liver Disease</b>		
2a	C-LD	15. In patients with Child-Pugh class A chronic liver disease and acute PE, treatment with a DOAC instead of a VKA is reasonable to reduce bleeding. <sup>28</sup>
2b	C-LD	16. In patients with Child-Pugh class B chronic liver disease and acute PE, treatment with a DOAC instead of a VKA may be reasonable to reduce bleeding risk. <sup>28</sup>
3: Harm	C-LD	17. In patients with Child-Pugh class C chronic liver disease and acute PE, treatment with a DOAC instead of a VKA is not recommended due to potential for increased bleeding. <sup>28</sup>
<b>Anticoagulation Therapy and Endovascular Procedures</b>		
1	C-LD	18. In patients with acute PE undergoing CDL, concurrent therapeutic anticoagulation (LMWH or UFH) or subtherapeutic anticoagulation (UFH) is recommended over no anticoagulation to prevent recurrent PE. <sup>3,29</sup>
1	B-NR	19. In patients with acute PE who have undergone an endovascular procedure or received thrombolytic therapy, initial parenteral anticoagulation with LMWH is preferred over UFH to provide reliable therapeutic anticoagulation and reduce the risk of recurrent VTE. <sup>30-32</sup>
2a	C-LD	20. In patients with acute PE likely to undergo endovascular procedures for PE management, LMWH is reasonable over UFH to provide more effective anticoagulation. <sup>29</sup>
<b>Anticoagulation Monitoring and Special Considerations</b>		
1	C-LD	21. In patients with acute PE in whom LMWH is monitored, measuring a peak anti-Xa level 3 to 5 hours after an LMWH dose once a steady state is reached (≥3 doses) is recommended in preference to checking trough or random levels in order to most accurately identify if the patient is within the expected therapeutic range. <sup>33</sup>
2a	C-LD	22. In patients with acute PE who have severe CKD (CrCl of <30 mL/min) and are being treated with LMWH, it is reasonable to monitor anti-Xa levels to guide dose adjustment in order to reduce bleeding risk. <sup>34,35</sup>
2b	C-LD	23. In pregnant patients treated with LMWH for acute PE, the usefulness of monitoring the peak anti-Xa level at least once per trimester is not well established to guide dose adjustment and reduce bleeding and/or thromboembolic risk. <sup>36,37</sup>

Recommendations for Anticoagulation Therapy (Continued)		
COR	LOE	Recommendations
2b	C-LD	24. In patients who weigh >150 kg or have a BMI of >40 kg/m <sup>2</sup> and are receiving LMWH for treatment of acute PE, the benefit of monitoring anti-Xa levels is not established to avoid supratherapeutic levels of LMWH after initial therapy. <sup>34,38</sup>
2b	C-LD	25. In patients with acute PE treated with LMWH in the ICU, the benefit of monitoring anti-Xa levels is not established to avoid supratherapeutic and/or subtherapeutic levels. <sup>39</sup>
3: No Benefit	A	26. In most patients with acute PE treated with weight-based LMWH, laboratory monitoring of anti-Xa level and dose adjustment is not indicated to reduce recurrent VTE or bleeding. <sup>40-45</sup>

## Synopsis

Anticoagulation is the mainstay of therapy in patients with confirmed acute PE. DOACs are preferred for long-term management due to their efficacy in preventing recurrent thrombosis, ease of use, and lower risk of major bleeding compared with VKAs. For patients requiring initial parenteral therapy, LMWH is recommended over UFH due to its reduced risk of recurrent VTE and lower incidence of complications like heparin-induced thrombocytopenia. Patients with specific comorbidities, including obesity, CKD, and liver disease, require tailored dosing strategies. For instance, dose reductions for LMWH may be reasonable in severely obese patients to mitigate bleeding risks. In pregnant patients, DOACs and VKAs are contraindicated due to fetal and neonatal risks. In breastfeeding patients, DOACs are contraindicated as they might cross into breastmilk and deliver an anticoagulant effect on the nursing baby. VKAs are preferred for patients with thrombotic antiphospholipid antibody syndrome to reduce the risk of recurrent thrombotic events, particularly arterial. Finally, specific populations (eg, severe renal or liver impairment) require cautious use of anticoagulation for whom shared decision-making is paramount.

## Recommendation-Specific Supportive Text

1. The role of anticoagulation in acute PE has been established since 1960, when 35 patients were randomized to anticoagulation or no anticoagulation.<sup>1</sup> In this small, randomized trial, there were 5 deaths in the no anticoagulation group and no deaths in the anticoagulation group. This has been further supported by observational studies showing higher rates of death when acute PE is not treated with anticoagulation therapy.<sup>46</sup>
2. A meta-analysis shows that the use of LMWH reduces recurrent VTE risk more effectively than UFH without increasing major bleeding risk in patients with acute PE.<sup>2</sup> LMWHs have predictable pharmacokinetics, do not require routine monitoring, and are associated with a lower incidence of heparin-induced thrombocytopenia.<sup>2,30,47</sup> LMWH

offers the convenience of once or twice daily dosing and comes in prefilled syringes that facilitate outpatient treatment when indicated.

3. DOACs, including oral factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) and oral direct thrombin inhibitors (dabigatran), are preferred for long-term management of acute PE due to their efficacy, safety, and ease of use compared with traditional oral VKA therapies.<sup>48,49</sup> Meta-analyses and systematic reviews encompassing thousands of patients in RCTs showed that DOACs generally provide comparable efficacy in preventing recurrent PE and DVT compared with LMWH bridging to VKAs.<sup>50</sup> Additionally, DOACs are associated with a lower risk of major bleeding events (especially intracranial hemorrhage [ICH]) compared with VKA therapy, enhancing their safety profile.<sup>49</sup> DOACs, compared with warfarin, are associated with a lower rate of fatal bleeding, case-fatality rate of major bleeding, cardiovascular mortality, and all-cause mortality.<sup>51,52</sup> The convenience of fixed dosing and fewer drug and dietary interactions make DOACs a preferred choice over VKAs, improving patient adherence and quality of life.<sup>53</sup>
4. It is reasonable to anticoagulate patients without elevated bleeding risk and high pretest probability for PE while awaiting imaging to make a definitive diagnosis.<sup>54,55</sup> The benefit of this strategy is greatest for patients with acute PE who are at higher risk of adverse outcomes and should be considered in patients with a suspected AHA/ACC PE Category C2 acute PE or higher.
5. Due to increased protein binding and volume of distribution in patients with obesity, the plasma concentration of DOACs may be diluted. This has led to concern over the effectiveness of these agents compared with VKAs for the treatment of established VTE in obese patients. Although there are no RCTs in this population, meta-analyses (mostly consisting of post-hoc analysis of obese patient subpopulations from phase III trials) have shown that apixaban and rivaroxaban may be superior in efficacy and safety when compared with VKAs.<sup>59</sup> Data from claims databases and retrospective cohort studies show similar findings.<sup>56</sup> A multicenter retrospective cohort study in patients with severe obesity (BMI ≥50 kg/m<sup>2</sup> or body weight ≥150 kg) also found that apixaban and rivaroxaban are equally safe and effective compared with VKAs.<sup>57</sup> In patients who have undergone bariatric surgery, however, DOACs should be avoided for at least 4 weeks after their procedure due to concerns about decreased absorption.<sup>54,55</sup>
6. Obese patients have a lower proportion of lean body mass as a percentage of total body weight. As a result, LMWH dosing based on total body weight could cause supratherapeutic anticoagulation and

consequent bleeding. Reducing the dose in these patients, however, could result in a higher risk of recurrent thrombosis. There is 1 small RCT evaluating a lower versus a standard dose of enoxaparin (0.8 mg/kg versus 1.0 mg/kg actual body weight twice daily) in patients with severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>). The study found that a higher percentage of patients in the reduced dose group met initial therapeutic levels, and patients in the standard group were more likely to reach supratherapeutic levels.<sup>12</sup> There were no clinical events reported. A meta-analysis of mostly retrospective studies showed a reduced rate of major bleeding in patients receiving a reduced dose of enoxaparin.<sup>11</sup> Systematic reviews have also confirmed lower rates of supratherapeutic levels and no clear evidence of increased thrombotic events in obese patients receiving a reduced dose of enoxaparin.<sup>11,58,59</sup> Definitions of obesity varied in the studies, with a BMI ranging from  $\geq 30$  to  $\geq 40$  kg/m<sup>2</sup>.

7. Thrombotic antiphospholipid syndrome (APS) requires long-term anticoagulation due to the high risk of recurrent thrombosis among untreated patients. Randomized trials and meta-analyses of these trials have revealed mixed results regarding the rates of recurrent thrombotic events with DOACs versus VKAs in patients with thrombotic APS. However, the studies have consistently shown an increase in the risk of subsequent arterial thrombotic events among patients with thrombotic APS who are treated with DOACs versus VKAs. Most studies found no difference in the rate of subsequent venous thrombotic events or major bleeding between DOAC and VKA treatment.<sup>13-16,60</sup> Subgroup analyses have shown an increased risk of stroke in patients receiving DOACs and recurrent events in those with triple-positive antibodies (positive for lupus anticoagulant, anticardiolipin antibodies, and anti- $\beta$ -2-glycoprotein-I antibodies) and a history of arterial thromboses.<sup>13,15</sup> Furthermore, the risk of future thromboembolic event in patients with thrombotic APS is usually venous thrombosis (84%) compared with arterial thrombosis. In patients with arterial thrombosis associated with APS, the recurrence is less predictable, with a mix of arterial, venous, and a combination of arterial and venous.<sup>60</sup> Thus, these data argue against the use of DOACs in the majority of patients with thrombotic APS, especially those with a history of arterial thrombosis.
8. Subgroup analyses of randomized trials have shown noninferiority of DOACs to VKA in patients with thrombotic APS and a single low titer anticardiolipin antibody or beta-2-glycoprotein-I antibody (designated as low risk for APS) as long as they have not had a history of arterial thrombosis.<sup>14</sup> In a meta-analysis of 4 randomized trials including patients

with APS, the rates of arterial thromboembolism, VTE, and bleeding were not statistically elevated with either VKA or DOAC in patients with single- or double-positive antibodies.<sup>16</sup> Thus, in patients with established single-antibody APS, it is reasonable to consider a DOAC in patients who would prefer to avoid the monitoring associated with a VKA.

9. Patients with acute PE and primary or metastatic malignant brain tumors are at increased risk of recurrent VTE. Use of anticoagulation is of concern due to the risk of ICH. Although intracranial cancer is not an absolute contraindication to anticoagulation, the risk of intracranial bleeding increases with the use of anticoagulants.<sup>17</sup> Meta-analyses of retrospective case series have consistently shown that the baseline risk (ie, off anticoagulation) of ICH is higher in patients with metastatic brain cancer compared with those with primary brain cancer; that anticoagulant therapy is associated with an increase in ICH and major ICH in patients with primary brain cancer but not in those with metastatic brain cancer; and the risk of ICH is lower in patients with either primary or metastatic brain cancer treated with DOACs compared with those treated with LMWH.<sup>17-19</sup> These series consisted of a mix of patients with newly diagnosed venous thrombosis requiring anticoagulation in the setting of a central nervous system cancer as well as those already on anticoagulation for a pre-existing VTE or stroke prevention in atrial fibrillation, in the setting of a newly diagnosed brain tumor.
10. Patients with CKD are at an increased risk of both VTE and bleeding. Each of the DOACs rely on renal excretion (dabigatran 80%, edoxaban 50%, rivaroxaban 33%, and apixaban 27%).<sup>61</sup> Meta-analyses of patients with CKD in the phase 3 trials assessing the efficacy and safety of the DOACs in patients with VTE found that DOACs are noninferior to VKAs in recurrent VTE prevention and are associated with lower rates of major bleeding in patients with moderate (stage 2-3; estimated glomerular filtration rate [eGFR] 30-89 mL/min/1.73 m<sup>2</sup>) kidney dysfunction.<sup>20-22,61</sup>
11. Patients with stage 4 (eGFR between 15-29 mL/min/1.73 m<sup>2</sup>) CKD, stage 5 (eGFR <15 mL/min/1.73 m<sup>2</sup>) CKD, and patients receiving renal replacement therapy were excluded from phase 3 randomized clinical trials that assessed the efficacy and safety of the DOACs in patients with acute PE. However, data derived from the US Renal Data System registry of patients with stage 4 and higher CKD, including patients receiving renal replacement therapy, suggest that apixaban is as safe and efficacious as a VKA.<sup>23,24</sup> It should be noted that although the registry data included only patients with VTE, most of the trials in the meta-analysis

- included patients receiving DOACs for stroke prevention in atrial fibrillation. It is also unclear whether patients in the registry received loading doses of apixaban. Robust data are lacking regarding rivaroxaban, edoxaban, or dabigatran in this population.
12. Pregnant patients with acute PE should receive anticoagulation to prevent recurrence, which may threaten the life of the mother and/or the fetus. LMWH and UFH do not cross the placenta and, therefore, are safe for the fetus.<sup>62–65</sup> Currently, LMWH is used more commonly than UFH in pregnant patients with acute PE given predictable dose-response, longer plasma half-life, and lower risk of osteoporosis and heparin-induced thrombocytopenia.<sup>66–68</sup>
  13. A systematic review of studies of women exposed to DOACs during pregnancy revealed a higher-than-expected rate of fetal anomalies.<sup>26</sup> VKAs cross the placenta and have a dose-dependent relationship with adverse fetal outcomes.<sup>69</sup>
  14. There are limited experience and safety data available for DOACs during pregnancy and breastfeeding. A recent systematic review emphasizes that while DOACs offer practical advantages, their safety profile is not well-established, making LMWH, UFH, and warfarin the preferred options for anticoagulation in breastfeeding patients.<sup>26</sup> It is not well established whether DOACs or their metabolites are excreted in human breastmilk.<sup>70</sup> Animal studies have demonstrated excretion with all 4 DOAC agents in breastmilk.<sup>27</sup>
  15. All DOACs have a degree of hepatic clearance (75% for apixaban, 65% for rivaroxaban, 50% for edoxaban, and 20% for dabigatran), raising the concern for elevated plasma levels of a DOAC and subsequently increased bleeding in patients with liver disease.<sup>28</sup> Data derived from a large claims database and other retrospective cohort studies suggest that DOACs, apixaban and rivaroxaban in particular, are noninferior in efficacy to VKA and are safe alternatives due to their lower incidence of major bleeding in patients with acute PE and mild hepatic impairment (eg, Childs-Pugh A).<sup>28,56,71</sup>
  16. Data from a claims database and other retrospective cohort studies indicate that DOACs, such as apixaban and rivaroxaban, may be safe with lower rates of major bleeding in patients with acute PE and moderate hepatic impairment (eg, Childs-Pugh B).<sup>28,56,71</sup>
  17. Because patients with elevated liver enzymes and severe hepatic dysfunction were excluded from major VTE trials, the safety of DOACs in these populations remains unknown. In cases where severe hepatic impairment is present (Child-Pugh C), there is potential for increased risk of major bleeding due to diminished liver function. Therefore, the use of DOACs for patients with acute PE and severe hepatic impairment may result in harm and should be avoided.<sup>28,56,71</sup>
  18. Thrombolytic agents primarily break down fibrin, thereby reducing or eliminating existing clots. In contrast, anticoagulant medications inhibit the clotting cascade and prevent new clots from forming. This is especially important for patients receiving CDL, given that lower doses of thrombolytic agents are used compared with systemic thrombolysis, and there is increased endothelial damage from the catheter insertion and manipulation. As such, there is reason to believe that concurrent use of both agents may be beneficial in patients with acute PE who require rapid removal of existing thrombus. However, both classes of medications are associated with bleeding risk, and their combination may increase that risk to unacceptable levels. A meta-analysis demonstrated no difference in bleeding between therapeutic and subtherapeutic anticoagulant dosing outside the setting of thrombolysis.<sup>29</sup> A randomized trial of pharmacomechanical CDL in patients with acute proximal DVT allowed for a broad range of anticoagulation strategies and did not report that concurrent use of an anticoagulant increased bleeding risk over that associated with CDL.<sup>3</sup> LMWH is more likely than UFH to reach therapeutic levels quickly and remain in the therapeutic range. Still, there is insufficient evidence to recommend LMWH over UFH during thrombolytic drug infusion.
  19. One small single-center RCT compared the safety of UFH with LMWH after systemic thrombolysis with alteplase.<sup>31</sup> There were no significant differences in the primary outcome of major hemorrhage or the secondary outcomes of any hemorrhage, death, or a composite outcome of all of these. A multicenter observational study of 249 patients demonstrated similar rates of major hemorrhage with LMWH compared with UFH, but the LMWH group had a large survival advantage. However, these results are subject to selection bias and require validation in a prospective trial.<sup>32</sup> A meta-analysis of multiple RCTs found that UFH bridging to warfarin compared with LMWH bridging to warfarin was associated with a higher risk of recurrent (hazard ratio, 1.42 [95% CI, 1.15–1.79]).<sup>30</sup> These results can be extrapolated to patients receiving thrombolytic therapy.
  20. There is little evidence supporting the choice of anticoagulant prior to procedures. A retrospective observational study of patients undergoing CDL included 45 patients treated with LMWH and 111 with UFH.<sup>29</sup> The UFH group was more ill, with more patients classified with massive PE, and more of them received preprocedural systemic thrombolysis. There was no difference in major bleeding between the groups (0% with LMWH and 2.7% with UFH,  $P=0.6$ ). There was no adjustment

- for differences in illness severity between groups; therefore, the findings are at risk for selection bias.
21. When monitoring for LMWH is indicated, it should be done after the drug has achieved a steady state (3-5 half-lives) and at the peak level. Most LMWHs peak at 3 to 5 hours from administration. The test of choice is the anti-Xa level, ideally calibrated with a specific LMWH to improve consistency. Expected on-therapy levels will differ among different LMWHs and frequency of administration (daily versus twice-daily dosing).<sup>33</sup>
  22. Given that LMWH is primarily excreted through the kidneys, its half-life is extended in patients with impaired renal function. To mitigate the risk of drug accumulation, dose adjustments and once-daily administration are advised for individuals with decreased creatinine clearance, as opposed to twice-daily and fixed dosing. Owing to the impact of various factors on drug levels, monitoring is recommended upon reaching a steady state. In such patients, the prolonged half-life of LMWH with CKD suggests that waiting for a greater number of doses than for patients without CKD may more accurately represent the steady state.<sup>34,35</sup>
  23. The physiologic changes of pregnancy significantly impact the pharmacokinetics of LMWH, rendering weight-based dosing unreliable. During the second trimester, increased plasma volume and glomerular filtration can result in lower serum drug concentration, while drug clearance decreases during the third trimester.<sup>36,37</sup> Furthermore, the half-life of LMWH may be shortened, leading to reduced trough levels. However, no clinical trials define target peak or trough levels. As such, there is insufficient evidence to recommend that clinicians routinely monitor peak anti-Xa levels at least once per trimester and adjust LMWH doses.
  24. Weight-based dosing of LMWH may result in supratherapeutic anticoagulation in obese patients, as the volume of distribution is estimated to be equivalent to a patient's plasma volume without accounting for adipose tissue. One study found no difference in anti-Xa peak levels or the percentage of supratherapeutic anti-Xa levels in patients with BMI >30 kg/m<sup>2</sup> and up to 150 kg of body weight, compared with patients with a normal BMI.<sup>34</sup> Another study compared patients with weight >140 kg who received enoxaparin 1 mg/kg twice daily versus lower doses.<sup>38</sup> Patients receiving 1 mg/kg twice daily were more frequently supratherapeutic (70% versus 30%) compared with those who received lower doses. However, patients on lower doses were subtherapeutic 16% of the time versus 6% for the higher doses, which was not significantly different. There were no differences in recurrent thrombosis or bleeding regardless of

the initial dose. There are no large RCTs that have compared standard weight-based dosing with a lower starting dose or a capped dose of LMWH in patients with obesity and acute PE. Therefore, for patients weighing >150 kg, it is prudent to make an individualized decision regarding dosing. This decision should carefully consider clinical severity and the patient's risk of bleeding. Monitoring and adjusting the dose of LMWH based on anti-Xa levels can potentially reduce the risk of exposure to supratherapeutic levels of the medication. Although direct correlation between anti-Xa levels and the risk of bleeding is not established, some studies have indicated an association between the two.<sup>25,31,32</sup>

25. The absorption and distribution of subcutaneous LMWH can be significantly altered in critical illness. One study indicated that medical patients in the ICU were less likely to achieve target anti-Xa levels compared with medical patients not in the ICU.<sup>39</sup> A subgroup analysis showed that patients with sepsis had lower anti-Xa peak levels than those without sepsis.<sup>39</sup> Critical illness-related factors contributing to these differences may include reduced antithrombin level, compromised perfusion from sepsis or the use of vasopressors, advanced age, and lower hemoglobin levels.<sup>3,39</sup> However, no prospective studies have compared weight-based dosing to anti-Xa laboratory monitoring and dose adjustment of LMWH therapy in critically ill patients. Furthermore, clinical outcomes from retrospective studies comparing different LMWH dosing strategies in critically ill patients are lacking.<sup>72,73</sup> Given these complexities, in patients with acute PE treated with LMWH in the ICU, the benefit of monitoring anti-Xa levels is not established to avoid supratherapeutic and/or subtherapeutic levels.
26. A recent systematic review and meta-analysis of 48 randomized and nonrandomized trials reported that measuring anti-Xa levels for patients receiving LMWH therapy was associated with more frequent dose adjustment but had no clinically significant correlation with bleeding or thromboembolic risk as compared with not measuring anti-Xa levels.<sup>74</sup>

#### 4.2.2. Hemodynamic Pharmacotherapy

**Recommendations for Hemodynamic Pharmacotherapy**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	C-LD	1. For patients with cardiogenic shock due to acute PE (AHA/ACC PE Categories D2-E2), the use of vasopressors and/or inotropes is recommended to improve cardiac output and systemic perfusion. <sup>1-4</sup>
2b	C-LD	2. In patients with acute PE in AHA/ACC PE Categories D1-2 in whom there are concerns for reduced preload based on clinical assessment, the use of volume management with normal saline or other volume expanders may be considered to improve cardiac output and blood pressure. <sup>5</sup>

Recommendations for Hemodynamic Pharmacotherapy (Continued)		
COR	LOE	Recommendations
2b	B-R	3. For patients with acute PE in AHA/ACC PE Categories C2-E, the use of inhaled pulmonary vasodilators may be considered to reduce RV afterload. <sup>6-8</sup>

## Synopsis

Pharmacological hemodynamic support is a critical component of comprehensive management of acute PE, particularly for patients with hemodynamic instability, RV dysfunction, and for those awaiting advanced therapies. However, randomized trials directly comparing pharmacological strategies for hemodynamic support in this population are lacking. Published evidence suggests that several approaches may be reasonable, including cautious fluid expansion to optimize preload, vasopressors to maintain systemic perfusion, diuresis to reduce RV wall stress in cases of volume overload, and inhaled pulmonary vasodilators to lower pulmonary vascular resistance (PVR) and enhance RV function. Although available data suggest that judicious use of these therapies is generally safe and may offer clinical benefit, additional high-quality studies are needed to better define their role.<sup>9</sup>

## Recommendation-Specific Supportive Text

1. Patients with profound hypotension due to acute PE may require vasopressor therapy, and selection of the most appropriate agent depends on the intended effects on the heart and vasculature.<sup>10</sup> Based on indirect evidence in animal models and humans with cardiogenic shock, norepinephrine (NE) is generally considered the vasopressor of choice.<sup>2,3</sup> NE increases systemic vascular resistance (SVR) and has modest inotropic effects. At doses  $\leq 15$   $\mu\text{g}/\text{min}$ , NE has little to no effect on PVR. Therefore, it has a favorable net increase in the SVR/PVR ratio.<sup>11</sup> However, at doses exceeding 15  $\mu\text{g}/\text{min}$ , NE may increase PVR. Therefore, instead of further increasing the dose of NE, a second vasopressor agent (eg, vasopressin, phenylephrine) should be added.<sup>11</sup> In patients with acute PE who have persistently low cardiac output despite the use of vasopressors, the addition of an inotropic agent may be indicated. A hemodynamic study of 10 patients with acute PE with circulatory failure requiring admission to the ICU suggests that a continuous infusion of dobutamine (up to 10  $\mu\text{g}/\text{kg}/\text{min}$ ) may increase cardiac index at the expense of decreased SVR.<sup>1</sup> Thus, dobutamine may be considered as an adjunct to NE in patients with acute PE with low cardiac output and hypotension (AHA/ACC PE Category E1-2) and may be considered as the initial agent of choice in patients with normotensive cardiogenic shock (AHA/ACC PE Category D2).<sup>12</sup>
2. Patients with acute PE and RV failure are often preload-dependent.<sup>13</sup> However, data exploring the

hemodynamic impact of RV preload optimization in this population remain limited. In 1 study of 13 patients with acute PE and circulatory compromise (cardiac index  $< 2.5$  L/min/m<sup>2</sup>) but preserved systemic blood pressure (characteristics of AHA/ACC PE Category D1-2), cautious fluid administration ( $\leq 500$  mL) was associated with improved cardiac output.<sup>5</sup> Conversely, animal studies suggest that excessive volume expansion may worsen RV function.<sup>14</sup> Thus, in clinical practice, volume administration should be approached cautiously; small boluses ( $\leq 500$  mL) may be considered in selected normotensive patients with signs of low cardiac output, while larger volumes or indiscriminate fluid loading should be avoided due to the risk of RV overload.

3. Although vasodilators are commonly used to treat pulmonary arterial hypertension, their lack of pulmonary selectivity and risk of systemic hypotension have limited their use in acute PE. In contrast, selective pulmonary vasodilation, such as with inhaled agents, may reduce PVR and RV afterload without compromising systemic blood pressure.<sup>11</sup> A recent multicenter RCT evaluated inhaled nitric oxide in normotensive patients with acute PE and RV dysfunction. Although inhaled nitric oxide did not improve the primary composite outcome (normalization of troponin and echocardiographic findings at 24 hours), a post-hoc analysis showed a significant improvement in RV size and function at 24 hours.<sup>7</sup> Thus, the use of inhaled pulmonary vasodilators may be considered to reduce RV afterload in patients with acute PE who meet ACC/AHA Categories C2-E criteria. In contrast, small, randomized trials of nonselective vasodilators such as oral sildenafil and intravenous epoprostenol have shown minimal or no benefit on primary clinical outcomes (eg, RV end-diastolic diameter, cardiac index) in patients with acute PE.<sup>6,8</sup>

### 4.2.3. Sedation and Ventilatory Strategies

Recommendations for Sedation and Ventilatory Strategies		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	C-LD	1. In patients with acute PE in AHA/ACC PE Categories C-E who require sedation for intubation, hemodynamic supportive therapies (vasopressors, inotropes, and/or venoarterial [VA]-ECMO) should be available to support the patient in the event the patient becomes unstable. <sup>1-3</sup>
2a	C-LD	2. For patients with acute PE and moderate-severe hypoxia, use of heated high-flow nasal cannula (HFNC) oxygenation rather than standard nasal cannula oxygenation can be beneficial to improve oxygenation. <sup>4,5</sup>
3: Harm	C-LD	3. In patients with acute PE in AHA/ACC PE Categories C-E, deep sedation and mechanical ventilation should not be performed, unless clinically indicated, in order to avoid hemodynamic collapse. <sup>1-3</sup>

## Synopsis

Anxiolytic and/or analgesic drugs, especially sedation for intubation, can result in catastrophic hemodynamic collapse in patients with compensated or decompensated RV dysfunction secondary to acute PE. RV pressure-volume overload associated with acute PE may cause RV dilation and decreased RV function, resulting in decreased LV filling and cardiac output. Compensatory increases in heart rate and SVR maintain systemic and myocardial perfusion. Anything that reduces or eliminates these compensatory mechanisms, including most anxiolytic medications and/or analgesic medications, can cause or exacerbate hemodynamic decompensation. Studies of specific sedation strategies in patients with acute PE are sparse. A few single-center case series report a disproportionately high incidence of sedation-associated cardiac arrest among patients with hemodynamically stable or unstable PE.<sup>1,2</sup> Thus, any amount of sedation should be administered with caution when there is evidence or concern for RV dysfunction.<sup>1-3</sup> In addition, deeper sedation and intubation should be avoided unless there is a strong clinical indication, such as profound hypoxia refractory to noninvasive oxygenation strategies, or for airway protection, and the treatment team is readily prepared to support the patient with vasopressors, inotropes, or VA-ECMO in the event of hemodynamic collapse.

Also, acute hypoxemic respiratory failure is common in patients with acute PE. Modalities for support of oxygenation and ventilation include conventional nasal cannula, HFNC, noninvasive mechanical ventilation (NIV), and invasive mechanical ventilation, each with unique effects on both gas exchange and hemodynamics. Available evidence from RCTs and systematic reviews performed in patients with various causes of acute hypoxemic respiratory failure demonstrate that, compared with conventional nasal cannula, the use of either HFNC or NIV is well tolerated, improves oxygenation and work of breathing, and may reduce the rate of intubation and mortality.<sup>6-10</sup> No published studies have examined outcomes in patients with acute PE treated with either NIV or invasive mechanical ventilation. One small single-center RCT demonstrated that, compared with nasal cannula, HFNC improved oxygenation in patients with acute PE, and this is further supported by small uncontrolled studies.<sup>4,5,11-13</sup>

## Recommendation-Specific Supportive Text

1. Among patients with acute PE and RV dysfunction, there is a causal relationship of sedation with hemodynamic decompensation due to blunting of the compensatory sympathetic response. Thus, in situations in which anxiolytic and/or analgesic medications are needed, and especially when deep sedation is required for intubation, the care team should be prepared to manage hemodynamic decompensation with vasopressors, inotropes, and/or VA-ECMO when available. The importance of

readily available rescue therapy was demonstrated in 2 studies in which rapid employment of emergency cardiopulmonary bypass in patients who experienced cardiac arrest after anesthesia induction resulted in hospital mortality rates that were similar to patients with acute PE who did not require cardiopulmonary resuscitation (CPR) after anesthesia induction.<sup>2,3</sup>

2. Compensatory increase in sympathetic activity is essential to maintain systemic perfusion in patients with acute PE and RV dysfunction. PE-associated RV dysfunction results in decreased LV filling and cardiac output. Sedation strategies that decrease endogenous sympathetic response mitigate the sympathetic response and may cause hemodynamic decompensation and cardiac arrest, even in patients who are hemodynamically stable.<sup>1-3</sup> This has been demonstrated in 2 case series of patients undergoing general anesthesia for surgical embolectomy. In 1 series, CPR was required in 19% of patients after anesthesia induction, even though all were hemodynamically stable at the time of induction.<sup>2</sup> Another case series of patients with acute PE treated with surgical embolectomy reported the need for CPR related to anesthesia induction in 28% (9/32) of patients.<sup>3</sup> A single-center analysis of sedation strategies utilized in catheter-directed therapies of patients with acute PE and characteristics of AHA/ACC PE Category C2-3 reported a strong association of sedation strategy with the need for CPR and in-hospital mortality.<sup>1</sup>
3. Both induction for intubation and mechanical ventilation blunt adrenergic tone, decrease RV preload, and increase RV afterload. All of these factors serve to increase the risk of cardiac arrest due to decompensated acute RV failure.<sup>1,2</sup> Thus, anesthesia induction and mechanical ventilation should be avoided whenever possible. When needed based on clinical circumstances, treating clinicians should prepare for potential hemodynamic decompensation.

## 4.2.4. Mechanical Circulatory Support

**Recommendations for Mechanical Circulatory Support**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In patients with known or suspected acute PE on VA-ECMO, continuation of parenteral systemic anticoagulation is recommended in the absence of bleeding to prevent further thrombotic or embolic complications. <sup>1,2</sup>
2a	B-NR	2. In patients with acute, refractory cardiogenic shock as a result of known or suspected acute PE (AHA/ACC PE Category E2), it is reasonable to institute VA-ECMO, provided appropriate resources are available, to stabilize hemodynamics and improve oxygenation. <sup>3-6</sup>
2b	C-LD	3. In patients with acute PE in AHA/ACC PE Category E2 who are placed on VA-ECMO support, the usefulness of additional advanced therapies is not well established. <sup>7-9</sup>

### Synopsis

Mechanical circulatory support may be of benefit for patients in cardiogenic shock as a consequence of known or suspected PE with evidence of RV dysfunction. Use of these supportive measures will depend on local resources and expertise but most commonly include VA-ECMO. VA-ECMO serves to rapidly decrease RV preload while delivering oxygenated blood to peripheral tissues and end organs, thus halting the deleterious effects of hypoxia and cardiogenic shock. Risks and benefits of continued anticoagulation while on mechanical circulatory support should be constantly re-evaluated. Data are limited on the benefit of advanced therapies (eg, MT, CDL) for patients with acute PE who are being supported with VA-ECMO.

### Recommendation-Specific Supportive Text

1. For patients on VA-ECMO, systemic anticoagulation is recommended to prevent possible thrombotic complications despite the lack of high-quality evidence. Bleeding complications are more frequent than thrombotic complications for patients on VA-ECMO, and limited reports of the use of VA-ECMO without concomitant anticoagulation have not found any increase in thrombotic complications. This caveat is especially important for patients with PE, given the increased percentage of patients who undergo either systemic anticoagulation or thrombolysis prior to the initiation of VA-ECMO.<sup>1,2</sup>
2. VA-ECMO improves oxygen delivery for patients in cardiogenic shock. In patients with acute PE and cardiogenic shock (AHA/ACC PE Category E2) as a result of fulminant RV dysfunction, VA-ECMO is a useful mechanism to provide end-organ perfusion while allowing for RV recovery or subsequent PE intervention. Studies, including an observational international registry and single-center case series, support the use of VA-ECMO in patients with refractory shock due to acute PE.<sup>3-6</sup>
3. The role of advanced intervention (eg, MT, CDL) for patients on VA-ECMO for acute PE is not known. Multiple series have reported resolution of thromboembolism in selected patients with acute PE and characteristics of AHA/ACC PE Category E2 who were managed on VA-ECMO. The need for adjunctive intervention should be based on individual assessment of a patient's clinical status.<sup>7-9</sup>

### 4.3. Role of the Inferior Vena Cava Filter

Recommendations for Inferior Vena Cava Filters		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	B-R	1. In patients with acute PE who cannot tolerate anticoagulation but in whom an IVC filter is deemed necessary, retrievable IVC filters are recommended over permanent filters to reduce the short-term incidence of recurrent PE while minimizing long-term adverse outcomes. <sup>1,2</sup>

Recommendations for Inferior Vena Cava Filters (Continued)		
COR	LOE	Recommendations
1	C-LD	2. In patients with retrievable IVC filters, retrieval should be attempted as soon as the risk of PE has sufficiently decreased and anticoagulation tolerated in order to minimize the risk of long-term filter-related complications. <sup>3</sup>
2a	B-R	3. In patients with acute PE who cannot tolerate anticoagulation, IVC filters can be useful to reduce the short-term incidence of recurrent PE. <sup>1,2,4-7</sup>
2a	C-LD	4. In patients with indwelling IVC filters, the use of a structured follow-up program is reasonable to increase retrieval rates and detect complications. <sup>5-8</sup>
2b	C-LD	5. In patients with acute PE in AHA/ACC PE Categories D-E, and who are undergoing advanced interventions such as systemic thrombolysis, CDL, MT, or surgical embolectomy, the benefit of IVC filter placement is uncertain to reduce the short-term incidence of recurrent PE and mortality. <sup>9-11</sup>
2b	C-LD	6. In patients with recurrent PE despite optimal therapeutic anticoagulation who are in AHA/ACC PE Categories B-E, IVC filter placement may be considered to reduce the short-term incidence of additional recurrent PE. <sup>1,2,4,12</sup>
3: Harm	A	7. In patients with acute PE who are therapeutically anticoagulated, routine IVC filter placement should not be performed. <sup>5-8</sup>

### Synopsis

IVC filters mechanically intercept venous thrombi from migration to the pulmonary circulation. Employing percutaneous insertion techniques, these filters offer versatility in their application, existing in both permanent and retrievable forms. Indications for IVC filter placement include scenarios where anticoagulant therapy is absolutely contraindicated and when there are instances of recurrent PE despite optimal anticoagulation. Although certain potential indications, such as addressing free-floating thrombi in patients without contraindications to anticoagulation, remain under scrutiny, the utility and scope of IVC filters continue to evolve in clinical practice.

### Recommendation-Specific Supportive Text

1. In patients with acute PE who cannot receive anticoagulation, retrievable IVC filters are preferred over permanent filters due to their ability to offer short-term protection against recurrent PE while avoiding the long-term complications associated with permanent filter placement. The PREPIC trial demonstrated that IVC filters led to significantly higher rates of DVT and IVC thrombosis over time without improving long-term survival, supporting the concern that permanent filters increase the risk of chronic thrombotic complications.<sup>1</sup> The PREPIC2 trial, which studied retrievable IVC filters in patients receiving anticoagulation, found no added benefit in preventing recurrent PE.<sup>13</sup> Further support comes from a meta-analysis that confirmed that



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although IVC filters are associated with a reduction in PE recurrence (~50%), they also significantly increase the risk of DVT (~70%), with no mortality benefit.<sup>4</sup> These findings reinforce the importance of minimizing filter dwell time and avoiding permanent filters when retrievable options are available. Permanent filters should be reserved for rare cases in which retrievable IVC filters are not feasible (eg, mega cava [IVC >30 mm]).<sup>14</sup>

2. Timely retrieval of retrievable IVC filters is essential to minimize long-term risks associated with prolonged indwelling time. Data from the PREPIC trial showed that patients who received IVC filters in addition to anticoagulation experienced higher rates of DVT and IVC thrombosis compared with those treated with anticoagulation alone, indicating an increased long-term thrombotic risk with IVC filter use even after anticoagulation is initiated.<sup>1</sup> The US Food and Drug Administration (FDA) issued a safety communication recommending IVC filter retrieval within 29 and 54 days after placement, once the risk of PE has subsided, based on evidence of complications such as device migration, filter fracture, IVC perforation, and embolization when filters are left in place too long.<sup>15</sup> Filter retrieval also becomes progressively more difficult with time. One study found challenging retrievals were more common after 50 days, and failed retrievals were more frequent after 90 days of dwell time.<sup>16</sup> Additional registry data demonstrated that successful retrievals had a mean dwell time of 85 days, while unsuccessful retrievals averaged 145 days.<sup>17</sup> Moreover, delayed retrieval often requires advanced techniques—such as large-bore sheaths, longer procedural times, or general anesthesia—raising procedural complexity and patient risk.<sup>18,19</sup> Longer dwell times are also associated with filter embedment and IVC perforation, as shown in multiple studies.<sup>20,21</sup> Given these risks, IVC filters should be retrieved as soon as it is safe to do so to prevent complications and improve patient outcomes.
3. The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) trial demonstrated that IVC filter placement significantly reduced the incidence of PE recurrence but was counterbalanced by an increased risk of DVT and no survival benefit over long-term follow-up.<sup>4</sup> All patients in PREPIC were anticoagulated, limiting direct applicability to those who cannot receive anticoagulation. The PREPIC2 trial found no additional benefit to filter placement in anticoagulated patients, reinforcing that filters should be reserved for those in whom anticoagulation is truly contraindicated.<sup>2</sup> A meta-analysis found that IVC filters reduce the risk of subsequent PE by approximately 50%, despite increasing DVT risk, with no significant effect on all-cause mortality.<sup>3</sup> Another study,

focusing on patients with acute VTE and significant bleeding risk where anticoagulation was limited, found that IVC filters were associated with improved short-term survival.<sup>5</sup> The PRESERVE (Predicting the Safety and Effectiveness of Inferior Vena Cava Filters) study, a large prospective multicenter trial evaluating real-world IVC filter use, showed high procedural success and a 96.4% rate of freedom from symptomatic PE at 12 months, supporting both safety and effectiveness when filters are appropriately used.<sup>7</sup> One multicenter study on trauma patients showed that retrievable filters were often placed due to anticoagulation contraindications and were associated with low short-term PE rates.<sup>6</sup> These findings align with observational evidence suggesting acute-phase mortality reduction in select high-risk groups.<sup>10</sup>

4. The use of structured follow-up programs is an evidence-based strategy to significantly increase IVC filter retrieval rates and reduce long-term complications. Despite national efforts, retrieval rates for retrievable filters remain suboptimal.<sup>15</sup> However, findings from the PRESERVE study and multiple institutional reports demonstrate that implementing a retrieval plan at the time of filter placement—paired with ongoing patient reassessment—leads to higher retrieval success.<sup>7</sup> Studies consistently show that multidisciplinary approaches involving standardized protocols, provider education, and dedicated filter clinics improve filter management. For example, protocols that include referral to specialty clinics, scheduled follow-up appointments, and structured decision-making criteria for filter removal have all been associated with improved outcomes.<sup>22–24</sup> Similarly, automated reminder systems for patients and providers have been shown to improve the timeliness of retrieval and reduce the rate of filter-related complications.<sup>25</sup> Additional interventions—such as enhanced patient instructions at discharge, proactive provider communication, and institutional quality improvement programs—have all demonstrated measurable improvements in retrieval rates and filter safety.<sup>26–28</sup> Collectively, these findings strongly support the implementation of a structured, protocol-driven follow-up system for all patients with indwelling IVC filters, especially those placed under temporary indications.
5. In patients with acute PE in AHA/ACC PE Categories D-E who are undergoing advanced interventions such as systemic thrombolysis, CDL, MT, or surgical embolectomy, the benefit of IVC filter placement remains uncertain in reducing the short-term recurrence of PE and overall mortality. Although IVC filters may prevent embolization, evidence suggests that this does not translate into improved clinical outcomes, particularly when

patients are able to receive or resume anticoagulation. The management of patients with acute PE and cardiopulmonary compromise is complex and rapidly evolving. The routine use of IVC filters alongside advanced reperfusion strategies has not been definitively shown to improve survival or reduce recurrent embolic events.<sup>29</sup> IVC filter placement should be highly selective, tailored to patients with persistent contraindications to anticoagulation or those at extreme risk for recurrence.<sup>29</sup> Given the risks of IVC filter-related complications, including DVT, filter migration, and caval thrombosis, retrievable filters should be removed as soon as the risk of PE has decreased or anticoagulation becomes feasible.<sup>15</sup>

6. A retrospective cohort study evaluating all-cause mortality according to the use of IVC filters in patients with recurrent PE within 3 months of an index event showed mortality was lower in those who received an IVC filter compared with those who did not.<sup>12</sup> The major limitation of the study was the assumption that the majority of the patients with PE were also treated with anticoagulation.
7. In patients with acute PE who are effectively anticoagulated, routine placement of an IVC filter offers no clinical benefit and exposes patients to unnecessary risks. The PREPIC and PREPIC2 trials demonstrated that adding an IVC filter to anticoagulation did not reduce the incidence of recurrent PE but was associated with a higher risk of DVT.<sup>12</sup> Additionally, the long-term follow-up of the PREPIC study suggested a possible link between IVC filters placement and risk of developing postthrombotic syndrome. Similarly, a systematic review and meta-analysis found no mortality benefit from IVC filter use in anticoagulated patients and confirmed the association with increased thrombotic complications.<sup>4</sup> Even in carefully selected high-risk patients, filter use is not without consequences. In the PRESERVE study, postfilter VTE events occurred in 93 patients (6.5%), including DVT in 74 patients (5.2%), PE in 23 patients (1.6%), and IVC thrombotic occlusions in 15 patients (1.1%).<sup>7</sup> The other observed complications of long-term indwelling filters include migration, fracture, perforation of the IVC wall, adjacent organ involvement, and thrombosis.<sup>6,8,15,16,20,21,30</sup>

#### 4.4. Advanced Management

Recommendations for Interventional Advanced Management		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	C-LD	1. In patients with acute PE in AHA/ACC PE Categories C3-E2 who have evidence of free-floating right atrial and/or RV clot-in-transit, the utilization of advanced therapies over anticoagulation alone is reasonable to reduce the risk of clinical deterioration. <sup>1</sup>

Recommendations for Interventional Advanced Management (Continued)		
COR	LOE	Recommendations
2b	B-R	2. In patients with acute PE in AHA/ACC PE Categories C2-D2 and without contraindications to thrombolysis, and in whom advanced therapy is being considered, the usefulness of either CDL or MT over the other is uncertain for reduction in mortality or major bleeding. <sup>2</sup>

#### Synopsis

Free-floating intracardiac clot-in-transit is discovered with echocardiographic or CT imaging in 2% to 4% of patients diagnosed with acute PE.<sup>1</sup> Historically, variable strategies have been considered for management, including anticoagulation alone, surgical embolectomy, systemic thrombolysis, CDL, and MT (Table 7). High-quality comparative data addressing this clinical situation are not currently available and are unlikely to emerge in the near future.

Patients with characteristics of AHA/ACC PE Categories C2-D2 acute PE are being actively enrolled in several large cardiovascular outcome trials examining either CDL or MT against anticoagulation alone. In patients deemed appropriate for a catheter-directed therapy, many factors influence the choice between CDL and MT, including operator experience, anatomic clot location, the perceived urgency of the clinical syndrome, and patient comorbidities.

#### Recommendation-Specific Supportive Text

1. A retrospective analysis of the PERT Consortium Registry revealed an independent association between clot-in-transit and mortality among 1442 patients with presentations consistent with AHA/ACC PE Category E (OR, 2.26 [95% CI, 1.13-4.52]; *P*=0.02).<sup>1</sup> A prior analysis of the International Cooperative Pulmonary Embolism Registry showed a similar magnitude of risk associated with clot-in-transit among a broader range of patients with acute PE consistent with AHA/ACC PE Categories C-E.<sup>3</sup> A pooled analysis of 316 patients with right heart thrombi reported improved survival among those treated with systemic thrombolysis compared with those treated only with anticoagulation.<sup>4</sup> Although no studies are available that have evaluated the efficacy of catheter-based or surgical therapies in patients with clot-in-transit, the mechanisms of action inherent to these approaches have led to increasing interest in their use in these patients.
2. The PEERLESS trial randomized 550 patients with acute PE clinical characteristics consistent with AHA/ACC PE Categories C2-D2 to treatment with either MT or CDL. There were no significant differences seen in the rates of 30-day mortality or major bleeding between the groups in this study. A combined

**Table 7. Summary of Advanced Therapy Recommendations (COR LOE\*)**

AHA/ACC PE Risk Outcomes Category	Systemic Lysis	CDL	MT	Surgery
A-C1	3-Harm A	3-NB C-EO	3-NB C-EO	3-NB C-EO
C2	3-Harm B-R	2b C-LD (unclear)	2b C-LD (unclear)	3-NB C-EO
C3	2b C-LD (unclear)	2b C-LD (unclear)	2b C-LD (unclear)	3-NB C-EO
D1-2	2b C-LD (may be considered)	2b B-NR (may be considered)	2b B-NR (may be considered)	2b C-LD (unclear)
E1	2a C-LD	2a C-LD	2a B-NR	2a B-NR
E2	2a C-LD	N/A	N/A	3-NB B-NR

ACC indicates American College of Cardiology; AHA, American Heart Association; CDL, catheter-directed thrombolysis; COR, Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; MT, mechanical thrombectomy; NB, no benefit; NR, nonrandomized; R, randomized.

\*See Table 2, "Applying the ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care."

endpoint of clinical deterioration and physician-driven bailout to an additional advanced therapy was more frequent in the group receiving CDL. However, rates of protocol-defined clinical deterioration alone were not significantly different between the groups.<sup>2</sup>

**4.4.1. Systemic Thrombolysis**

Recommendations for Systemic Thrombolysis Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	C-LD	1. In patients with acute PE in AHA/ACC PE Categories E1-2 and acceptable bleeding risk, in whom advanced therapy is being considered, systemic thrombolysis and anticoagulation is reasonable over anticoagulation alone to reduce mortality and recurrent PE. <sup>1-3</sup>
2b	C-LD	2. In patients with acute PE in AHA/ACC PE Categories D1-2 and an acceptable bleeding risk, in whom advanced therapy is being considered, systemic thrombolysis and anticoagulation may be considered over anticoagulation alone to prevent further clinical deterioration. <sup>1,4</sup>
2b	C-LD	3. In patients with acute PE in AHA/ACC PE Category C3 and acceptable bleeding risk, in whom advanced therapy is being considered, the use of systemic thrombolysis and anticoagulation over anticoagulation alone to prevent further clinical deterioration is uncertain. <sup>1,4,5</sup>
2b	C-LD	4. In patients with acute PE being treated with systemic thrombolysis, lower dose systemic thrombolytics may be considered to reduce the risk of bleeding. <sup>6-10</sup>
3: Harm	B-R	5. In patients with acute PE in AHA/ACC PE Categories A1-C2, systemic thrombolysis should not be used over anticoagulation alone due to increased risk of major bleeding and ICH. <sup>5,11,12</sup>

**Synopsis**

Four small RCTs with a total of 224 patients with high-risk PE reported that systemic thrombolysis therapy compared with anticoagulation with heparin alone leads to improvement in pulmonary obstruction accompanied by a reduction in RV dilatation on echocardiography.<sup>2,3,13,14</sup> The FDA has approved 3 agents for use in PE thrombolysis,

including streptokinase, urokinase, and rt-PA (alteplase). Tenecteplase, although not FDA approved for PE, has also been tested in several clinical studies.<sup>1,15-17</sup> The first-generation agents (streptokinase and urokinase) are not used in contemporary practice because they require longer infusion times and are not readily available. Standard dose rt-PA (100 mg in 2 hours) is the most commonly used thrombolytic agent in patients with PE, although there are no head-to-head trials of the agents to suggest superiority of a specific thrombolysis agent.<sup>18</sup>

**Recommendation-Specific Supportive Text**

1. Meta-analyses of systemic thrombolysis trials that included, but were not limited to, patients with hemodynamically significant PE, defined primarily as the presence of cardiogenic shock or systolic blood pressure <90 mm Hg, found that systemic thrombolysis was associated with a significant reduction in the combined endpoint of all-cause death or clinical deterioration requiring rescue treatment.<sup>1,4</sup> However, only 1 of the trials exclusively focused on patients with acute PE that would fit within AHA/ACC PE Categories E1-2, and this study enrolled only 8 patients prior to being stopped.<sup>13</sup> Available evidence limited to 4 small RCTs with a total of 224 patients for patients with high-risk PE (AHA/ACC PE Categories E1-2) suggests that systemic thrombolysis compared with anticoagulation alone leads to rapid improvement in pulmonary obstruction in patients with PE, accompanied by a reduction in RV dilation on echocardiography.<sup>2,3,13,14</sup> Of note, the definition and inclusion criteria for acute PE were different among the studies. Indeed, a systematic review and meta-analysis of 15 randomized trials reported that systemic thrombolysis was associated with a trend toward reduction of early mortality among the modest percentage of patients with PE that would fit within AHA/ACC PE Categories E1-2.<sup>1</sup> Moreover, there was a 9.9% rate of severe bleeding and a 1.7% rate of ICH with thrombolysis.
2. The vast majority of patients who present with PE do not have hypotension at presentation.<sup>5</sup> The largest randomized trial of normotensive patients



with acute PE and elements of increased risk for adverse events (consistent with AHA/ACC PE Categories C3-D2) randomized 1006 patients with PE and RV dysfunction to tenecteplase and heparin versus heparin therapy alone.<sup>1</sup> Thrombolysis prevented cardiovascular collapse but increased major (including intracranial) bleeding, with closely balanced benefits and harms. An important finding was that rescue thrombolysis was beneficial in patients who developed cardiovascular collapse after initially being treated with anticoagulant therapy alone.<sup>2</sup> The principal component of the benefit of immediate thrombolysis was a reduction in the rate of cardiovascular collapse needing rescue thrombolytic therapy. It is possible that a similar benefit could occur when providing rescue thrombolysis only to those who decompensate, rather than subjecting a larger number of patients to the risk of immediate thrombolysis.<sup>19</sup>

3. One meta-analysis of 16 trials of 2115 patients with acute PE, of which 8 trials (n=1755) enrolled patients with acute PE consistent with AHA/ACC PE Categories C3-D2, reported that systemic thrombolysis reduced all-cause mortality (OR, 0.53 [95% CI, 0.32-0.88]; number needed to treat = 59) at the expense of excess ICH (OR, 4.6 [95% CI, 1.8-12.0]; number needed to harm = 78).<sup>5</sup> Another meta-analysis that included 21 trials with a total of 2401 participants with characteristics of AHA/ACC PE Categories C3-D2 showed that, compared with heparin alone, thrombolytics plus heparin probably reduced both the odds of death (OR, 0.58 [95% CI, 0.38-0.88]) and recurrence of PE (OR, 0.54 [95% CI, 0.32-0.9]). Effects on mortality weakened, however, in the analysis of participants with submassive PE (OR, 0.61 [95% CI, 0.37-1.02]).<sup>4</sup> Major hemorrhagic events were more common in the thrombolysis group than in the heparin alone group (OR, 2.84 [95% CI, 1.92-4.20]). Taken together, the role of systemic thrombolysis is less certain among patients with acute PE in AHA/ACC PE Category C3.
4. There is a lack of high-quality evidence regarding dosing of thrombolytic agents to treat acute PE. Evidence is emerging that lower-dose thrombolysis (25-50 mg rt-PA), compared with standard dose (100 mg rt-PA), may be as efficacious and associated with a reduced risk for major bleeding.<sup>10,18,20</sup> A prospective cohort trial of 37 consecutive patients with massive PE reported that an extended infusion of low-dose 25 mg rt-PA was safe and effective therapy.<sup>20</sup> A retrospective evaluation of 83 patients with acute PE and vital sign abnormalities, treated with 25 mg rt-PA over 6 hours reported a lower risk of hemodynamic decompensation and PH compared with anticoagulation alone.<sup>21</sup> A prospective, randomized, multicenter trial of 118 patients with

acute PE and either hemodynamic instability or massive PA obstruction reported that 50 mg rt-PA compared with 100 mg rt-PA had similar efficacy and better safety.<sup>22</sup> Another randomized study evaluated 50 mg rt-PA plus anticoagulation compared with anticoagulation alone in patients with moderate PE, defined as CTPA involvement of >70% involvement of thrombus in  $\geq 2$  lobar or left or right main PAs or by a high probability V/Q scan showing V/Q mismatch in  $\geq 2$  lobes.<sup>23</sup> The study found that this dose of thrombolysis was safe and effective, resulting in a significant reduction in the PA pressure that was maintained at 28 months.<sup>23</sup> Of note, this study was unblinded and performed at a single center with a small sample, limiting its power and external validity. Furthermore, the definition of moderate PEs did not include those patients with RV strain or elevated troponin levels. Based on the available data to date, low-dose rt-PA regimens appear to be associated with similar efficacy and a lower bleeding risk compared with standard dose thrombolytic treatment; however, more robust high-quality evidence is needed.<sup>6-8</sup> The ongoing PEITHO-3 trial assessing the efficacy and safety of a reduced-dose alteplase regimen with standard heparin anticoagulation will provide additional insight.<sup>24</sup>

5. Systemic thrombolysis is associated with an incremental increase in major bleeding risk, in particular a greater risk of ICH. Overall, data suggest that patients with the highest risk of mortality from PE and the lowest risk of bleeding would obtain the greatest net benefit from thrombolysis, whereas those with the lowest risk of mortality from PE and the highest risk of bleeding would obtain the least benefit and are likely to be harmed.<sup>5,17,19,25</sup> In the PEITHO trial, which enrolled patients with acute PE fitting AHA/ACC PE Categories C3-D2, extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group ( $P < 0.001$ ). Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 patients; 1 patient (0.2%) in the placebo group had a stroke that was hemorrhagic ( $P = 0.003$ ).<sup>11</sup>

#### 4.4.2. Catheter-Directed Thrombolysis

**Recommendations for Catheter-Directed Thrombolysis**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
2a	C-LD	1. In patients with acute PE in AHA/ACC PE Category E1, CDL plus anticoagulation is reasonable to prevent further clinical deterioration and early mortality. <sup>1,8</sup>
2b	B-NR	2. In patients with acute PE in AHA/ACC PE Categories D1-2 in whom advanced therapy is being considered, CDL plus anticoagulation may be considered to prevent further clinical deterioration. <sup>2</sup>

Recommendations for Catheter-Directed Thrombolysis (Continued)		
COR	LOE	Recommendations
2b	C-LD	3. In patients with acute PE in AHA/ACC PE Categories C2-3, the benefit of CDL plus anticoagulation compared with anticoagulation alone to prevent short-term fatal/nonfatal clinical deterioration, and improve long-term mortality, functional capacity, and quality of life is unclear. <sup>3</sup>
2b	C-LD	4. In patients with acute PE in AHA/ACC PE Categories D1-E1 in whom thrombolysis is being considered, the efficacy of CDL over systemic thrombolysis to reduce short-term fatal/nonfatal clinical deterioration, and improve long-term survival, functional capacity, and quality of life is unclear, but CDL may be considered over systemic thrombolysis to reduce major bleeding risks. <sup>4</sup>
3: No Benefit	B-NR	5. In patients with acute PE who are undergoing CDL, a reduced thrombolytic dose of <5 mg of alteplase per PA is not recommended over a standard dose of 5 to 10 mg of alteplase per PA to reduce the risk of bleeding and/or reduce the rate of fatal or nonfatal clinical deterioration. <sup>3,5</sup>
3: No Benefit	C-EO	6. In patients with acute PE in AHA/ACC PE Categories A-C1, CDL is not recommended over anticoagulation alone for improving clinical outcomes or symptoms.

## Synopsis

CDL is the administration of a thrombolytic drug (most commonly rt-PA) via a multi-side-hole transcatheter pulmonary catheter to dissolve a PE. The catheter used for CDL may be standard or specialized (ultrasound-assisted or featuring an expandable infusion basket). Although >1000 patients treated with CDL have been prospectively studied, <200 have been randomized against anticoagulants alone.<sup>1</sup>

## Recommendation-Specific Supportive Text

1. Patients in AHA/ACC PE Category E1 are generally deemed to require advanced therapies beyond anticoagulation, one of which can be CDL. A systematic review and meta-analysis of 594 patients, most of whom were retrospectively studied, suggested that catheter-based techniques (67% of these patients received CDL) were associated with improved survival to discharge.<sup>6</sup>
2. Small RCTs have demonstrated that CDL relieves RV dysfunction faster than anticoagulants alone, as measured by the RV/LV ratio.<sup>7,8</sup> Major bleeding risk in these studies with CDL was low. Patients with acute PE and evidence of RV dysfunction showing signs of impending deterioration (AHA/ACC PE Categories D1-2) may benefit from reperfusion, and CDL may be an appropriate option.<sup>7,8</sup>
3. Patients with acute PE in AHA/ACC PE Categories C2-3 who are stable with anticoagulation alone have a low risk of clinical deterioration. Therefore, preventing deterioration with a reperfusion strategy

that carries risks is not indicated.<sup>9</sup> CDL trials have neither been designed nor adequately powered to identify a reduction in clinical deterioration by CDL compared with anticoagulants alone in this population.<sup>7,8</sup> Moreover, CDL plus anticoagulation likely has a higher risk of major bleeding than anticoagulation alone. A systematic review and meta-analysis suggested that patients who undergo CDL have a lower likelihood of death. However, this conclusion was limited by the quality of the studies, as 13 out of 15 included studies were observational.<sup>1</sup> A separate concern is that residual thrombus and RV dysfunction persist after acute PE and potentially cause reduced functional capacity, exercise intolerance, and reduced quality of life. It is unknown whether removing acute PE with CDL affects these long-term outcomes in patients with acute PE in AHA/ACC PE Categories C2-3.

4. The PEITHO trial demonstrated that systemic thrombolysis plus anticoagulation for patients who would fit into AHA/ACC PE Categories C3-D2 was efficacious in reducing the composite endpoint of death and clinical deterioration but caused more major and intracranial bleeding compared with placebo plus anticoagulation.<sup>8</sup> It is unknown whether CDL has a similar effect on fatal and nonfatal clinical deterioration for patients with acute PE in AHA/ACC PE Categories C3-D2, although as noted previously, CDL may improve RV dysfunction faster than anticoagulation alone. Although CDL and systemic thrombolysis have not been compared directly to one another, CDL may have a lower risk of major and intracranial bleeding than systemic thrombolysis based on prospective single arm studies.<sup>3-7,10</sup> CDL plus anticoagulation likely has a higher risk of major bleeding than anticoagulation alone. There have been no studies dedicated to evaluating the safety and efficacy of CDL in patients with acute PE fitting AHA/ACC PE Category E1. The previously noted systematic review and meta-analysis, which largely included patients fitting AHA/ACC PE Categories C2-D2, suggested that patients who undergo CDL have a lower likelihood of death than patients treated with anticoagulation alone.<sup>1</sup>
5. The range of doses of rt-PA in CDL studies has been 4 mg to 24 mg total over 2 to 24 hours, with reduced dose defined as <5 mg per PA and standard dose as 5 to 10 mg per PA.<sup>2,5,7,8,10,11</sup> Although a total dose of 24 mg has been associated with a high rate of major bleeding,<sup>2</sup> total doses up to 20 mg have not demonstrated a higher bleeding rate than lower dose regimens. One randomized trial suggested that lower dose regimens conferred a similar benefit to higher regimens as assessed by the postprocedure RV/LV ratio.<sup>3</sup> However, this trial did not include a control group, so the confounding

effect of anticoagulation on these regimens is unknown. Standard dose regimens have been associated with more thrombus removal than reduced dose regimens.<sup>3,5</sup>

6. CDL has not been studied in patients who would fit into AHA/ACC PE Categories A-C1. Advanced therapies beyond anticoagulation, including CDL, are generally unwarranted for these patients.

#### 4.4.3. Mechanical Thrombectomy

Recommendations for Mechanical Thrombectomy Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	B-NR	1. In patients with acute PE in AHA/ACC PE Category E1, it is reasonable to choose MT plus anticoagulation over anticoagulation alone to prevent further clinical decompensation and acute mortality. <sup>1-3</sup>
2b	B-NR	2. In patients with acute PE in AHA/ACC PE Categories D1-2 in whom advanced therapy is being considered, MT plus anticoagulation may be considered over anticoagulation alone to prevent further clinical deterioration. <sup>4-6</sup>
2b	C-LD	3. In patients with acute PE in AHA/ACC PE Categories C2-3, the benefit of MT plus anticoagulation compared with anticoagulation alone is unclear in preventing short-term fatal/nonfatal clinical deterioration and improving long-term survival and functional capacity. <sup>7</sup>
2b	B-NR	4. In patients with acute PE in AHA/ACC PE Categories D1-E1 in whom advanced therapy is being considered, the efficacy of MT to reduce short-term fatal/nonfatal clinical deterioration and improve long-term survival, functional capacity, and quality of life over systemic thrombolysis is unclear, but MT may be considered over systemic thrombolysis to reduce major bleeding risks. <sup>3,6</sup>
3: No Benefit	C-EO	5. In patients with acute PE in AHA/ACC PE Categories A-C1, MT is not recommended over anticoagulation alone for improving clinical outcomes or symptoms.

#### Synopsis

MT is a form of percutaneous therapy for acute PE in which a catheter is directed to the location of an indwelling thrombus in the pulmonary arterial system. This is commonly performed through the femoral vein, and the objective is to extract thrombus directly from the pulmonary circulation and externalize it from the body. There are several devices that have been designed and studied for this indication, encompassing a variety of techniques for treatment of PE, including large-, moderate-, and small-bore suction thrombectomy, clot fragmentation, rheolysis, maceration, extirpation, or a combined pharmacomechanical approach. MT permits immediate removal of thrombus, which may expedite symptom relief and hemodynamic improvement in select patients. Compared with other advanced therapies, the advantages to percutaneous MT devices include (1) they do not require concomitant administration of a lytic medication, (2) they

do not require an indwelling catheter and post-procedure ICU stay, and (3) in some cases older thrombus can be removed. Furthermore, MT has been used as an adjunctive form of treatment in patients with high-risk acute PE on mechanical circulatory support, such as ECMO.

#### Recommendation-Specific Supportive Text

1. The largest interventional trial in high-risk PE is the FLAME (FlowTrieve® for Acute Massive Pulmonary Embolism) study, a prospective, multicenter, parallel-group design of 115 high-risk patients with PE exhibiting characteristics of AHA/ACC PE category E1 who either underwent MT or other contemporary therapies. In patients selected for MT, the primary composite endpoint (all-cause mortality, bailout to alternate therapy, clinical deterioration, major bleeding) compared favorably to a prespecified performance goal (32.0%,  $P < 0.01$ ), with MT patients having a 17% (95% CI, 8.1-9.8%) incidence of the primary endpoint and 1.9% (95% CI, 0.0-10.1) in-hospital mortality. In patients selected for treatment with other therapies, the primary endpoint occurred in 63.9% (95% CI, 50.6-75.8%) of patients, and in-hospital mortality was 29.5% (95% CI, 18.5-42.6).<sup>3</sup>
2. In the FLARE (FlowTrieve® Pulmonary Embolectomy Clinical Study) trial, patients with characteristics fitting AHA/ACC PE Categories C3-D2 acute PE, large-bore percutaneous MT led to a reduced RV/LV ratio at 48 hours postprocedure.<sup>4</sup> Average postprocedure mean PA pressure decreased significantly compared with preprocedure, although this finding was limited to patients with PH on presentation.<sup>4</sup> In the similarly sized and designed EXTRACT-PE (Extraction of Acute Clot in Right Heart and Pulmonary Arteries) trial, moderate-bore embolectomy resulted in significant reductions in mean RV/LV ratio from baseline to 48 hours postprocedure.<sup>5</sup> The rate of major bleeding in both of these trials were comparably low at 1% and 1.7%, respectively. In the large US and European FLASH (FlowTrieve® for Acute Hemodynamic Improvement in Pulmonary Embolism) registry of 1000 patients treated with MT, mean PA pressures and cardiac indices were found to be significantly improved postprocedure.<sup>6</sup> For patients with preexisting PH, there was significant on-table reduction in mean PA pressure after percutaneous therapy. Notable improvements were also observed at follow-up with respect to RV/LV ratio, RV size, and systolic function.<sup>6</sup>
3. In the EXTRACT-PE (Extraction of Acute Clot in Right Heart and Pulmonary Arteries) trial of 119 patients treated with moderate-bore MT, the rate of clinical deterioration was low at 1.7%. Only 2 patients in this study received intraprocedural thrombolysis. All-cause mortality at 30 days was 2.5%, and symptomatic PE recurrence at 30 days

was 0.0%. However, data from this trial are limited in terms of longer-term survival and quality of life.<sup>5</sup> Among 800 patients in the full US cohort of the FLASH (FlowTrieve® All-Comer Registry for Patient Safety and Hemodynamics) registry, 76.7% had intermediate-high risk PE and were treated with MT. Major adverse events occurred in 1.8% of patients with all-cause mortality of 0.8% at 30-day follow-up. At 48 hours, there were significant improvements in RV/LV ratio and patients with severe dyspnea (66.5% to 15.6%,  $P < 0.0001$ ).<sup>7</sup> Although this study confirmed a favorable safety profile for large-bore MT and improvements in both hemodynamic and functional endpoints, these data also are limited to shorter term follow-up.

4. There are no randomized clinical trials designed to compare the effectiveness of MT with systemic thrombolysis for high-risk PE patients. Of the 61 patients within the context arm of the FLAME study, 68.9% were primarily treated with systemic thrombolysis. In the context arm, all-cause mortality was 29.5% (95% CI, 18.5-42.6), and clinical deterioration after primary treatment initiation was 21.3% (95% CI, 11.9-33.7). Bailout to alternate thrombus removal strategy occurred in 16 patients (26.2%), of which 13 patients received MT.<sup>3</sup> In the MT arm of this study, major bleeding occurred in 6 patients (11.3%) compared with the 15 patients (24.6%) within the context arm. This trial does not report on long-term survival or quality of life outcomes beyond 45 days.
5. MT has not been studied in comparison to heparin-based anticoagulation for patients with acute PE in AHA/ACC PE Categories A-C1. Therefore, catheter-directed MT is not warranted for these patient populations beyond systemic anticoagulation alone.

#### 4.4.4. Surgical Embolectomy

Recommendations for Surgical Embolectomy		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	B-NR	1. In patients with acute PE in AHA/ACC PE Category E1, surgical embolectomy compared with anticoagulation alone is reasonable to prevent further clinical decompensation and acute mortality. <sup>1-5</sup>
2b	C-LD	2. In patients with acute PE in AHA/ACC PE Categories D1-2 in whom advanced treatment is being considered, surgical embolectomy plus anticoagulation may be considered over anticoagulation alone to prevent further clinical deterioration. <sup>1-5</sup>
2b	B-NR	3. In patients with acute PE in AHA/ACC PE Categories D1-E1 who are surgical candidates and in whom advanced therapy is being considered, the benefits of surgical embolectomy to reduce short-term fatal/nonfatal clinical deterioration and improve long-term survival, functional capacity, and quality of life over systemic thrombolysis is unclear, but surgical embolectomy may be considered over systemic thrombolysis to reduce the risk of ICH. <sup>4,8,12</sup>

Recommendations for Surgical Embolectomy (Continued)		
COR	LOE	Recommendations
3: No Benefit	C-EO	4. In patients with acute PE in AHA/ACC PE Categories A-C3, surgical embolectomy is not recommended over anticoagulation alone for improving clinical outcomes or symptoms.
3: No Benefit	B-NR	5. In patients with acute PE in AHA/ACC PE Category E2 not on mechanical circulatory support, surgical embolectomy is not recommended over other advanced therapies for preventing short-term mortality. <sup>9</sup>

### Synopsis

Modern surgical pulmonary embolectomy is performed on cardiopulmonary bypass, typically through a sternotomy, with infrequent need for aortic cross-clamping. Cardiopulmonary bypass supports the systemic circulation and decompresses the failing RV to mitigate the high mortality associated with pulmonary embolectomy. Cardiopulmonary bypass functions by diverting venous return to the heart to a reservoir, pump, and oxygenator, upon which it is returned to the arterial system. Physiologically, drainage of most of the venous return results in immediate reversal of the pressure volume overload that causes RV failure associated with acute PE, thereby allowing the RV to recover by permitting it to contract in an unloaded state. Oxygenated arterial inflow supports and restores systemic perfusion. VA-ECMO functions in a comparable manner and with a similar physiological effect on the RV.

There are no prospective randomized trials comparing surgical embolectomy with other treatment modalities for acute PE. Most data are derived from retrospective cohort studies. These surgical series consist primarily of patients with acute PE who have characteristics of AHA/ACC PE Categories D2-E2 (30%-100%), including those who had CPR (10%-40%), as well as salvage cases after failed systemic thrombolytic therapy (10%-30%).<sup>2-8</sup> Survival in the context of the high acuity and clinical severity of these patients is quite favorable, with mortality rates ranging from 1% to 15%, depending on a variety of preoperative confounders.<sup>3</sup> Survival of >97% has been reported among those patients who did not require CPR. Morbidity is also low in the absence of preoperative CPR.<sup>2,3</sup> Generally, there is excellent RV recovery with normalization of filling pressures and echocardiographic function at early and midterm follow-up.<sup>2,3</sup> The need for durable postoperative mechanical circulatory support is not reported in modern surgical series.<sup>1-3</sup>

### Recommendation-Specific Supportive Text

1. In cohort studies of patients with acute PE undergoing surgical embolectomy, the vast majority were traditionally classified high-risk or massive PE patients and herein classified as AHA/ACC PE Categories D1-E2 (30%-100%).<sup>1-9</sup> However, there has been no direct comparison of the efficacy of anticoagulation-only

treatment and surgical embolectomy in this population. Studies of surgical pulmonary embolectomy consistently report high in-hospital survival among patients undergoing surgical pulmonary embolectomy who present with features of AHA/ACC PE Category E1, with survival rates >97% in many series and with minimal morbidity.<sup>3,5,7,8</sup>

2. Outcomes reported in a series of patients with acute PE with characteristics of AHA/ACC PE Categories D1-2 who are selected for surgical embolectomy are good, with low morbidity and in-hospital mortality (survival >97%).<sup>3,5,7,8</sup> Importantly, the efficacy of surgical embolectomy versus anticoagulation alone has not been studied in randomized trials.
3. There are several nonrandomized studies comparing systemic thrombolytic therapy and surgical embolectomy in patients with acute PE.<sup>4-8</sup> Compared with patients undergoing thrombolysis, many patients described in the surgical series were more critically ill and often were considered salvage cases after failed systemic thrombolysis. Although most of these studies were relatively small (n=45-136), there were several common features.<sup>1,10-12</sup> All-cause mortality was numerically, but not significantly, higher in the cohorts receiving systemic thrombolytic than surgical embolectomy, but this may be attributed to sample size limitations.<sup>1,10-12</sup> Systemic thrombolysis was a univariate and multivariate predictor of cardiac mortality in 1 study.<sup>10</sup> Mortality among patients who required surgical embolectomy after failed systemic thrombolytic treatment was numerically higher among systemic thrombolytic recipients in some series (27% versus 3.6%; *P*=0.1).<sup>1,12</sup> Fatal and nonfatal bleeding complications were higher with systemic thrombolysis than surgical embolectomy.<sup>12</sup> There were no reports of ICH after surgical embolectomy but a notable risk with systemic thrombolysis.<sup>1-9</sup> Although equivalent long-term survival has been reported, there is evidence that surgical embolectomy is associated with improved RV and pulmonary function as demonstrated by greater improvement on RV size, lower systolic PA pressure, and improved perfusion.<sup>1,11</sup>
4. There is no physiologic or clinical indication, nor any studies, for surgical embolectomy in patients with acute PE in AHA/ACC PE Categories A-C. Although patients with acute PE in AHA/ACC PE Categories C2-3 exhibit some signs of RV involvement, they are hemodynamically stable and do not have signs of end-organ hypoperfusion due to RV dysfunction.
5. The profound hemodynamic instability of patients with acute PE AHA/ACC PE Category E2 portends poor survival, regardless of treatment. Among surgical series, these patients account for the majority of postoperative deaths, largely from anoxic brain injury

as a consequence of preoperative cardiac arrest.<sup>1-9</sup> Thus, there is not sufficient evidence to recommend surgical embolectomy over other treatment modalities, such as VA-ECMO, in these patients.

## 5. MONITORING AND FOLLOW-UP

### 5.1. Post-Acute PE Management

#### 5.1.1. Follow-Up Care for Acute PE

Recommendations for Follow-Up Care for Acute PE		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	C-LD	1. In patients with acute PE, it is beneficial to have clinical follow-up within the first week of discharge to provide patient education, address barriers to anticoagulation therapy, ensure adherence to prescribed medications, and detect bleeding complications. <sup>1-3</sup>
1	C-EO	2. Patients with acute PE should have a clinical visit at or before 3 months after diagnosis to discuss duration of anticoagulation, review the need for further testing, and assess for persistent PE-related symptoms.
1	C-LD	3. Patients who have had acute PE should be asked about PE-related symptoms and functional limitations at every visit for at least 1 year to screen for CTEPD or other causes of dyspnea and functional limitation. <sup>4,5-8</sup>
1	B-NR	4. In patients with a history of acute PE who remain on anticoagulation into the extended phase (beyond 3-6 months from diagnosis), periodic reassessment of the risk and benefits of continued anticoagulation is recommended to ensure the safety and efficacy of continuing anticoagulation. <sup>9,10</sup>
2a	B-NR	5. In patients with acute PE, the use of general or disease-specific questionnaires is reasonable to screen for anxiety and depression at follow-up visits. <sup>11-14</sup>
2a	B-NR	6. In select complex patients* with acute PE, it is reasonable to have follow-up care occur in a specialized PE clinic <sup>†</sup> , if available, to optimize care. <sup>15</sup>
2b	B-NR	7. In patients who remain symptomatic 3 to 6 months after acute PE, it may be reasonable to obtain a performance test (six-minute walk test, incremental shuttle walk test, endurance shuttle walk test) to quantify physical limitations and identify which patients require more extensive evaluation. <sup>5,16</sup>
Cancer Screening and Thrombophilia Testing in the Absence of PE Risk Factors		
1	A	8. In patients with acute PE without associated identifiable risk factors, a thorough history, physical examination, and age-appropriate cancer screening should be obtained to diagnose undetected cancer. <sup>17-20</sup>
2b	C-LD	9. In patients without a major reversible risk factor <sup>21</sup> for acute PE who have a family history of thrombosis or are <55 years of age, it might be reasonable to perform testing for genetic and acquired thrombophilia if the thrombophilia tests results are anticipated to change management or better inform family risk discussions. <sup>22</sup>

Recommendations for Follow-Up Care for Acute PE (Continued)		
COR	LOE	Recommendations
<b>3: No Benefit</b>	<b>A</b>	10. In patients with acute PE, routine imaging with CT or positron emission tomography-CT is not recommended to diagnose undetected cancer. <sup>17,18</sup>
<b>Contraception, Pregnancy, and Hormonal Therapy</b>		
<b>1</b>	<b>C-EO</b>	11. Patients of childbearing potential with acute PE should be counseled about contraception and anticoagulation options in the event that they become pregnant.
<b>2a</b>	<b>C-EO</b>	12. In patients who have experienced a PE and become pregnant, management by a team specializing in thrombotic complications can be useful to minimize pregnancy-related complications.
<b>2a</b>	<b>C-LD</b>	13. For patients using anticoagulant therapy for the treatment or prevention of PE who have experienced or are at risk of abnormal uterine bleeding, it is reasonable to discuss medical management (eg, hormonal therapies), alternate anticoagulant strategies, and gynecologic interventional strategies to mitigate abnormal uterine bleeding risk rather than considering anticoagulation cessation. <sup>23-27</sup>
<b>2b</b>	<b>C-LD</b>	14. In patients with acute PE who require or are being considered for estrogen-containing hormone therapy, continuation or initiation of hormonal therapy might be considered if there is a favorable risk-benefit ratio and the patient remains on anticoagulation. <sup>26</sup>

\*Complex patients likely to benefit from specialized care are referenced in Table 8.

†Specialty clinics are defined as those with expertise in PE management, such as pulmonology/critical care, hematology, cardiology, vascular medicine or, if available, a multidisciplinary PERT clinic.

## Synopsis

A key component of PE management is appropriate follow-up in the outpatient setting. The primary objectives of outpatient follow-up are to assess symptom improvement, ensure anticoagulation appropriateness and compliance, evaluate individual risks of recurrent VTE and bleeding, investigate underlying thrombophilia when appropriate, and identify long-term sequelae of PE (eg, CTEPD). For patients with an uncomplicated course, follow-up with a primary care physician is often sufficient. In contrast, those with complex courses often require advanced care that can be provided in a specialty clinic or in a multidisciplinary manner (Table 8).

Initially, patient education and medication adherence are emphasized, especially for outpatient-managed PE. This interaction can occur in person or virtually, facilitated by nurses, advanced practice providers, pharmacists, or physicians. At approximately 3 months after acute PE, a dedicated visit with a physician or advanced practice provider should occur to discuss the duration of anticoagulation, evaluate for ongoing symptoms, and assess the need for further testing. The clinical evaluation, patient's family history, and circumstances of the acute PE will guide the need to explore potential underlying causes (eg, thrombophilia, cancer, or concurrent diseases).

**Table 8. Indications for Referral to a Specialized Clinic for Management**

Indication	Description
Complex anticoagulation management	Patients requiring frequent adjustments or monitoring of anticoagulation therapy, including labile INRs, or fluctuating renal function, anticoagulation failure, allergies, high-risk/active bleeding
VTE history or recurrent PE	Patients with a history of recurrent VTE or those with an elevated risk of recurrence
Unresolved symptoms	Patients with ongoing symptoms such as dyspnea or exercise intolerance, potentially indicating CTEPD, may require specialty care
Pregnancy-related PE	Pregnant or postpartum patients with PE may require specialized management due to the associated complexities of anticoagulation during pregnancy and the postpartum period
Complicated clinical presentation	Patients with a PE in the setting of complex medical conditions (cancer, severe chronic illnesses), which may complicate standard treatment
Expert second opinion	Patients or referring physicians seeking a second opinion on management of complex patient care

CTEPD indicates chronic thromboembolic pulmonary disease; INR, international normalized ratio; PE, pulmonary embolism; and VTE, venous thromboembolism.

Assessment of functional limitations and determining the need for additional imaging are crucial for detecting CTEPD and evaluating for other diagnoses that may contribute to functional limitation. Beyond physical symptoms, evaluating quality of life, depression, and anxiety is important for patients who have experienced PE. Additionally, females of reproductive age should receive counseling regarding contraception, pregnancy planning, and menstrual bleeding.

## Recommendation-Specific Supportive Text

1. Although there are no clinical studies that have randomized patients to different intervals of follow-up, most programs caring for patients with acute PE in the outpatient setting include communication with the patient shortly after discharge from the hospital. These programs have demonstrated low rates of adverse events or repeat hospitalization when there is an outpatient management strategy in carefully selected patients.<sup>3</sup> Initial follow-up encounters can be facilitated by nurses, advanced practice providers, pharmacists, or physicians and performed in person or by telehealth. These early postdiagnosis visits should focus on patient education and address initial barriers to care and anticoagulation therapy, as well as questions from the patients or their families. The interval of this initial follow-up encounter for most programs is between 48 hours and 7 days.<sup>1,2,14</sup>
2. The initial treatment phase for patients with an acute PE lasts for 3 to 6 months (Section 5.2.1,

- “Recurrent Pulmonary Embolism”). Therefore, a visit within this period provides an excellent opportunity to discuss several important aspects with the patient. These include duration of anticoagulation, the risk of VTE recurrence, strategies to detect risk factors that may influence the duration of anticoagulation (such as cancer or thrombophilia), and periprocedural management of anticoagulation. Additionally, it is essential to address contraception and hormonal risks associated with VTE recurrence for females of reproductive age.
- Between one-third and one-half of the patients who have had a symptomatic PE will report dyspnea or limitations to physical activity on follow-up for months to years after a PE.<sup>4–6</sup> The prevalence of shortness of breath is higher after an acute PE associated with RV dysfunction and can be a presenting symptom of CTEPD.<sup>28</sup> CTEPD with PH complicates 2.3% to 4% of acute PEs. However, the diagnosis of CTEPD is often delayed given overlaps with other conditions (eg, deconditioning, anemia, heart failure, obstructive sleep apnea, ventilatory problems), all of which should be promptly identified and addressed to improve patient outcomes and quality of life.<sup>4,5,7,28</sup> A study of protocols with follow-up at 2 to 4 months after the diagnosis of an acute PE with RV dysfunction revealed limited activity due to fatigue or shortness of breath in half of the patients.<sup>28</sup> In those patients, 77% had an abnormal perfusion scan or echocardiogram. In the remaining 23%, other etiologies of fatigue and shortness of breath were identified. This emphasizes the importance of follow-up to evaluate symptomatic patients. The International Consortium for Health Outcomes Measurement consensus recommendation on PE suggests evaluating the patients at 3 months, 6 months, 1 year, and annually as long as the patient is under care.<sup>9</sup>
  - As clinical circumstances are not static, periodic reevaluation of bleeding risk and thrombosis recurrence risk in patients requiring extended phase anticoagulation (beyond the initial 3–6 months after diagnosis) is recommended. During these evaluations, it is essential to review the need for continued anticoagulation and consider the choice of anticoagulant based on individual factors, such as interactions with concurrent medications, kidney function, and liver function. In a population system monitoring anticoagulation with DOACs, approximately 13% of patients experienced critical alerts.<sup>9</sup> These alerts were related to inadequate dosing of the anticoagulant or drug-drug interactions. Fortunately, most electronic medical records systems offer real-time alert systems for prescriptions with potential interactions. However, it is equally important to establish effective workflows to address the alerts or clinical changes promptly.<sup>10,29,30</sup>
  - Depression, anxiety, and post-traumatic stress disorder are common in patients who have experienced PE and may persist over time.<sup>14,31–33</sup> Many patients report a lack of support and information during follow-up care, leading to delays in addressing these issues. It is crucial for health care professionals to recognize not only the physical, but also the psychological, aspects of VTE management in order to improve patient outcomes.<sup>12</sup> Screening for depression, anxiety, and post-traumatic stress disorder, and an evaluation of quality of life with general or disease-specific questionnaires, are suggested for appropriate management and referral of these patients.<sup>11,13,32</sup>
  - In areas where such care is available, it is reasonable that PE follow-up occurs in a specialty clinic. This is of particular importance in patients whose initial PE presentation was complicated by hemodynamic instability, recurrent or unprovoked thrombosis, or prolonged hospitalization (Table 8). A multidisciplinary clinic can be staffed by specialists in pulmonary/critical care, hematology, cardiology, vascular medicine, and/or pharmacy. This model of care is supported by retrospective studies and expert consensus recommendations.<sup>15,34,35</sup> In such a clinic, patients should be assessed for appropriate anticoagulation dosage and duration, undergo thrombophilia testing (when appropriate), aid with IVC filter retrieval (if necessary), and be assessed for the sequelae of PE (eg, CTEPD).<sup>36</sup> The timing of follow-up in a specialty clinic should be based on the level of acuity and complexity of the patient’s initial presentation but should occur within 1 to 3 months.
  - Even though the cardiopulmonary exercise test is considered the gold standard for diagnosing CTEPD, there are limitations related to availability and cost. Alternative performance tests that require minimal equipment or that can be conducted in office settings offer valuable insights. These tests help quantify exercise capacity, identify patients at risk of exercise limitation, and track longitudinal changes in exercise capacity.<sup>16</sup> Among these tests, the six-minute walk test stands out as a simple yet effective tool.<sup>37</sup> Being one of the most used tests to address cardiopulmonary function, it can be performed in almost any setting. It requires a 30-meter walking path, where patients walk at a comfortable pace for 6 minutes. The distance walked in a six-minute walk test at 1 month after an acute PE is predictive of exercise limitation at 1 year.<sup>5</sup> Other tests include the incremental shuttle walk test and the endurance shuttle walk test, which measure walking distance in a 10-meter shuttle course at incremental and constant speed, respectively. The

incremental shuttle walk test is associated with activity levels in patients after acute PE.<sup>16,38</sup>

8. In patients with acute PE, cancer is diagnosed in 4% to 10% during the first year when no major reversible risk factors for PE are identified (eg, surgery).<sup>20,39</sup> The incidence of cancer increases with age.<sup>20</sup> Almost half of cancers are diagnosed through a thorough medical history and physical examination. Therefore, performing a comprehensive medical history, physical examination, and age-appropriate cancer screening in accordance with national guidelines remains an appropriate strategy to identify undetected cancers.<sup>17,19,20</sup>

9. Thrombophilia testing is not recommended in patients who had a PE associated with major reversible risk factors, such as surgery, major trauma, or immobilization.<sup>21</sup> The risk of recurrence in these patients is low, and the duration of anticoagulation therapy will be limited regardless of the presence or absence of a thrombophilia.<sup>40</sup> In cases where no clearly provoking factor for PE can be identified, testing for hereditary thrombophilia does not significantly alter the duration of the patient's anticoagulant treatment. Furthermore, it is important to recognize that thrombophilia testing can have unintended consequences, including the potential for discrimination and psychological well-being.<sup>41-43</sup>

Isolated heterozygosity for common genetic mutations (eg, factor V Leiden, prothrombin gene mutation) are not consistently associated with an increased risk of recurrence. Consequently, these mutations usually do not influence the duration of anticoagulation therapy. Deficiencies in natural anticoagulants (antithrombin, protein C, protein S), however, are linked to a higher risk of recurrence and may necessitate extended anticoagulation.<sup>44</sup> These thrombophilias are infrequent but tend to manifest at an earlier age and often coincide with a family history of thrombosis.<sup>22</sup>

Before proceeding with thrombophilia testing, the potential risks and benefits should be thoroughly discussed, as well as how the test results will impact the patient's management. Genetic counseling is advisable before undergoing genetic testing. Shared decision-making with the patient should include a discussion of the potential implications of testing on their overall care. If it is decided to proceed with thrombophilia testing, genetic and immunologic testing can be performed at any time. However, coagulation-based tests are often affected by consumption of factors during the acute phase of a PE and by administration of anticoagulant medications. Therefore, coagulation-based tests should not be performed during the acute phase of a PE, and potential interference with anticoagulants should be considered to ensure reliable results.<sup>45</sup>

10. Extended screening strategies (including fludeoxyglucose-positron emission tomography or CT) slightly increase the number of diagnosed cancers early in the follow-up, but differences are lost at 1 year. More importantly, they do not demonstrate a benefit in mortality in patients with an acute PE or detect cancers at an earlier (and potentially curable) stage.<sup>17-20</sup> Extended cancer screening results in additional downstream procedures and economic costs.<sup>17-20</sup>
11. All available oral anticoagulants have the potential for adverse events, including teratogenicity during pregnancy.<sup>46,47</sup> Patients should be counseled on effective contraception if pregnancy is not desired. Additionally, patients should be advised to notify their medical team promptly if they become pregnant while on an oral anticoagulant in order to transition to an agent that is considered safe during pregnancy. Patients who wish to pursue pregnancy should discuss their plans with their medical team to arrange for appropriate timing, follow-up, and a safe anticoagulation strategy.
12. Patients with PE who become pregnant or have a desire to become pregnant should be managed and counseled by a team with experience in complex and high-risk pregnancies. Ideally, an interdisciplinary team should include physicians with expertise in thrombosis, maternal-fetal medicine, and cardiopulmonary medicine, depending on the clinical situation and functional status of the patient. Patients on oral anticoagulation may need to transition to an alternative agent (eg, LMWH). Patients with a prior PE who are not currently using anticoagulation may require thromboprophylaxis during pregnancy and the postpartum period.<sup>48</sup> There should be advanced planning for the delivery in order to minimize the risk of bleeding in the patient and fetus.
13. Abnormal uterine bleeding (AUB), including menorrhagia, intermenstrual or postmenopausal bleeding, is common in women on anticoagulants.<sup>25</sup> Although major bleeding and clinically relevant nonmajor bleeding events are uncommon (0%-2%) in patients with AUB associated with anticoagulant use, bleeding frequently impacts their quality of life and often leads to discontinuation of anticoagulant therapy. The risk of AUB varies among different anticoagulant agents. Compared with warfarin, rivaroxaban and edoxaban have a higher risk of bleeding, whereas dabigatran is associated with a lower risk of bleeding, and apixaban shows no significant difference in bleeding risk.<sup>23-26,49,50</sup> It is important to note that there are no randomized trials of direct comparisons among all the available oral anticoagulants in this circumstance. Individual patient factors and preferences should guide the choice of anticoagulants, considering both efficacy and bleeding risk.

Managing AUB in women on anticoagulants requires a careful and individualized approach. The PALM–COEIN acronym (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified) can guide the diagnosis of the underlying cause. Medical management is often the first line of treatment, with options such as high-dose progestin-only therapy, combined hormonal contraceptives (if the patient is on anticoagulation), and the levonorgestrel intrauterine system. In cases where medical management is insufficient, surgical interventions like endometrial ablation may be considered.<sup>26,51</sup> Interdisciplinary collaboration with gynecology is of paramount importance to provide an individualized plan for diagnosis and management. Despite the risk associated with oral estrogen-progestin combination contraceptives and other estrogen-containing hormonal replacement therapy, these medications may be indicated for contraception, management of uterine bleeding, dysmenorrhea, hyperandrogenic symptoms, menopausal vasomotor symptoms, and others.<sup>52</sup>

14. A post hoc analysis of the EINSTEIN (Efficacy and Safety of Rivaroxaban for the Treatment of Symptomatic Deep-Vein Thrombosis) study cohorts and the MEGA (Multiple Environmental and Genetic Assessment) study showed no increase in VTE recurrence in premenopausal or postmenopausal women receiving estrogen-containing hormonal therapies while on therapeutic anticoagulation.<sup>26,53</sup> Continuation of hormonal therapy can be considered when clinically important, as long as the patient is on therapeutic anticoagulation. There is no information, however, regarding the safety of hormonal therapy while taking lower doses of anticoagulants for extended secondary prophylaxis.

**5.1.2. Patient Activity and Travel**

Recommendations for Patient Activity and Travel		
Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
2a	A	1. In patients recovering from acute PE, it is reasonable to encourage early ambulation rather than bed rest in order to reduce the risk of complications. <sup>1</sup>
2a	B-R	2. In patients with a history of acute PE, use of compression stockings during long-haul (≥5 h) travel can be useful to lower the risk of DVT. <sup>2,3</sup>
2b	C-EO	3. In patients with a history of acute PE related to travel or immobility who are not currently receiving anticoagulation therapy, it may be reasonable to use a one-time prophylactic dose of an oral anticoagulant or a parenteral LMWH on the day of long-haul travel to reduce the risk of recurrent VTE.
2b	C-LD	4. For patients recovering from acute PE in AHA/ACC PE Categories C2-E, it may be reasonable to restrict long-haul travel for 4 weeks after initiation of treatment or when symptoms have resolved to reduce risk of adverse events. <sup>1</sup>

**Synopsis**

Many patients with acute PE and their clinicians wonder about safe methods of mobilization and transportation. Once anticoagulation has been initiated, early ambulation can reduce venous stasis and help to prevent further deconditioning, if safe from an overarching medical standpoint. Another area of particular concern is subsequent travel and associated interventions to reduce the risk of PE-related risks and recurrence. Travel, whether by car, train, or airplane, often involves limited mobility, which can increase VTE risk through venous stasis. The period shortly after diagnosis of an acute PE is when the RV and lung parenchyma are often healing from the acute PE insult and VTE recurrence risk is highest. Therefore, it may be prudent for patients to take precautionary measures during this time. This can include frequent ambulation, limiting long-distance travel, and the use of compression stockings to reduce venous stasis. Longer-term preventative strategies to reduce VTE risk can be considered for patients who have survived a travel-related acute PE event.

**Recommendation-Specific Supportive Text**

1. Outcomes of bed rest versus early ambulation in patients with acute PE, DVT, or both, who are receiving standard anticoagulation treatment were studied in a meta-analysis of 3048 patients from RCTs and prospective registries.<sup>1</sup> The meta-analysis indicated that early ambulation trended toward a lower incidence of new PE and progression of DVT, as well as a lower overall mortality rate, than extended bed rest.<sup>1</sup>
2. A recent Cochrane review of 12 randomized studies comprising 2918 patients found a significant reduction in the risk of asymptomatic DVT among patients who wore compression stockings versus those who did not for long-haul air travel of ≥5 hours. By extension, a reduction in DVT risk is likely to also reduce the risk of acute PE for individuals undergoing long-haul travel.<sup>3</sup>
3. Many patients with a history of PE do not remain on indefinite anticoagulation therapy beyond the initial treatment phase (3-6 months). In those patients who choose not to remain on anticoagulation during the extended phase but who previously experienced a travel- or immobilization-related PE, the use of a 1-time prophylactic-intensity anticoagulant dose is reasonable when traveling long distances (eg, ≥4-h flight) to prevent recurrent PE. This can be achieved either using a 1-time dose of a parenteral LMWH or a DOAC.
4. Patients with acute PE and RV dysfunction consistent with AHA/ACC PE Categories C-E typically require a longer period for recovery of RV function, normalization of pulmonary oxygenation, and resolution of dyspnea. These patients are also at higher risk of 30-day adverse events, including mortality.<sup>4</sup> Increased venous stasis associated with long-duration travel and the stress of

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lower oxygen levels and pressure changes associated with air travel may pose additional risk to patients with acute PE who experienced RV dysfunction or have ongoing PE-related symptoms (eg, dyspnea).

## 5.2. Anticoagulation Therapy by Recurrence Risk

Recommendations for Anticoagulation Therapy by Recurrence Risk Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	LOE	Recommendations
1	A	1. In patients with a first acute PE and no major reversible risk factor, continuing anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase* is beneficial to prevent recurrent VTE. <sup>1-4</sup>
1	B-NR	2. In patients with a first acute PE due to a major reversible risk factor, stopping anticoagulation at the end of the initial treatment phase (3-6 months) is recommended over continuing anticoagulation into the extended treatment phase in order to optimize the net clinical benefit of recurrent VTE versus bleeding. <sup>5</sup>
1	C-LD	3. In patients with a first PE due to a persistent risk factor, continuing anticoagulation at the initial treatment phase (3-6 months) into the extended treatment phase is reasonable in order to prevent recurrent VTE. <sup>6</sup>
1	A	4. For patients with a PE who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, treatment with a DOAC, unless contraindicated, is recommended over a VKA to reduce the risk of bleeding. <sup>7-9</sup>
1	A	5. For patients with a PE and with cancer who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, either a DOAC or LMWH is recommended over VKA to reduce the risk of recurrent VTE. <sup>10-15</sup>
1	B-R	6. For patients with a PE and without cancer offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, but have a contraindication to DOAC, VKA is recommended over aspirin or no therapy to reduce the risk of recurrent VTE. <sup>16-18</sup>
1	A	7. For patients with a PE who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, treatment with half-dose apixaban or rivaroxaban is recommended to reduce the risk of bleeding. <sup>8,9,19,20</sup>
2a	B-NR	8. In patients with a first acute PE due to a minor reversible risk factor, shared decision-making about stopping anticoagulation at the end of the initial treatment phase (3-6 months) versus continuing anticoagulation into the extended treatment phase is reasonable in order to optimize the net clinical benefit of recurrent VTE versus bleeding. <sup>3</sup>
2a	B-R	9. For patients who would be offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, but have a contraindication to or refuse anticoagulation, it is reasonable to choose low-dose aspirin over no therapy to reduce the risk of recurrent VTE. <sup>21,22</sup>

\*Anticoagulation beyond the initial 3 to 6 months without an anticipated stop date.

## Synopsis

The likelihood of recurrent VTE after an initial episode of PE depends on whether risk factors for VTE were present at the time of the initial PE. These factors may be divided into major reversible risk factors, minor reversible risk factors, persistent (chronic) risk factors or, if none are present, the absence of reversible or persistent risk factors (Table 9). The risk of recurrent VTE is low in patients with acute PE and with major reversible risk factors, and anticoagulation may be safely stopped in these individuals. In patients with VTE associated with a minor reversible risk factor or persistent risk factor, decisions to treat beyond an initial treatment period of 3 to 6 months should balance the risk of recurrent VTE versus the risk of bleeding. The risk of recurrent VTE is high in individuals without identifiable risk factors, and these patients should be considered for extended phase anticoagulation.

Treatment of VTE may be divided into several phases: an initiation phase, an initial treatment phase, and an extended treatment phase. When acute VTE is first diagnosed, anticoagulation commences using regimens such as apixaban 10 mg twice daily for 7 days, rivaroxaban 15 mg twice daily for 21 days,  $\geq 5$  days of parenteral anticoagulation before starting dabigatran or edoxaban, or parenteral anticoagulation (eg, with LMWH) along with a VKA until achieving an international normalized ratio  $\geq 2$ . The initial maintenance treatment phase follows the initiation phase and continues for 3 to 6 months. At the end of the initial treatment phase, a decision is made whether to continue anticoagulation into the extended treatment phase, defined as continuation of anticoagulation beyond the initial 3 to 6 months without an anticipated stop date.

## Recommendation-Specific Supportive Text

1. Individuals who develop VTE in the absence of an identifiable risk factor are at high risk of recurrent VTE after anticoagulation is stopped (~30%-40% at 10 years).<sup>1,3</sup> In a study of 281 patients with unprovoked VTE randomized to extended phase anticoagulation (usually warfarin) versus stopping anticoagulation after the initial treatment phase, extended phase anticoagulation was associated with an 80% relative risk reduction of recurrent VTE (2.75 versus 13.54 events per 100 patient-years) with no significant increase in major bleeding.<sup>4</sup> In a meta-analysis of 26 studies (15603 patients) receiving anticoagulation into the extended phase for unprovoked VTE, the incidence of recurrent VTE was 1.41 per 100 person-years.<sup>2</sup> Thus, anticoagulation into the extended phase of anticoagulation significantly reduced the risk of recurrent VTE in patients with no identifiable risk factor.
2. In patients with acute PE and a major reversible risk factor, stopping anticoagulation after the initial treatment phase (3-6 months) is associated with a

**Table 9. Risk Factors for Venous Thromboembolism**

Major Reversible Risk Factor	Minor Reversible Risk Factor	Persistent Risk Factor
Surgery with general anesthesia $\geq$ 30 minutes	Surgery with general anesthesia $<$ 30 minutes	Active cancer with or without ongoing treatment
Hospitalization for acute medical illness $\geq$ 72 hours while confined to hospital bed	Hospitalization for acute medical illness $<$ 72 hours	Autoimmune disease (eg, rheumatoid arthritis, systemic lupus erythematosus)
Cesarean section	Out-of-hospital acute medical illness $\geq$ 72 hours while confined to bed	Inflammatory bowel disease
Lower limb fracture	Estrogen therapy (hormone replacement or contraceptive)	Chronic immobility
	Peripartum period	
	Trauma with decreased mobility $\geq$ 72 hours	

Adapted from Kearon et al.<sup>38</sup> Copyright 2016, with permission from Elsevier.

low risk of recurrent VTE. This is especially true if the PE occurred in the setting of a surgical risk factor (annualized event rate  $<$ 1% per patient-year).<sup>5</sup> The risk of VTE recurrence in patients with a major reversible risk factor is similar whether an individual has received 3 to 6 months of anticoagulation or up to 24 months of anticoagulation, suggesting no benefit of extending anticoagulation beyond 3 to 6 months for these patients.<sup>3</sup>

- Individuals who develop VTE in the presence of persistent risk factors, such as inflammatory bowel disease, autoimmune disorders, and chronic immobility, are at higher risk of both first VTE and recurrent VTE than patients with transient risk factors.<sup>23</sup> For example, patients with autoimmune diseases have a 1.7-times risk of recurrent VTE compared with those without autoimmune diseases.<sup>24</sup> Thus, continuing anticoagulation into the extended phase may be reasonable to reduce the risk of recurrent events in patients with persistent risk factors.<sup>6</sup>
- Multiple randomized trials, observational cohort studies, and meta-analyses have evaluated the efficacy and safety of DOACs compared with placebo, aspirin, or warfarin, in patients who receive anticoagulation beyond the initial 3 to 6 months of the treatment phase in the extended phase. In a randomized trial of  $>$ 4000 patients, dabigatran was superior to placebo and noninferior to warfarin with respect to recurrent or fatal VTE, with no difference in major bleeding between dabigatran, warfarin, and placebo.<sup>25</sup> In a randomized study of  $>$ 1100 patients, rivaroxaban 20 mg daily, when compared with placebo, was associated with significantly lower risk of recurrent VTE with similar risk of major bleeding.<sup>26</sup> In another randomized study of  $>$ 3300 patients, both rivaroxaban 20 mg daily or 10 mg daily, when compared with aspirin 100 mg daily, were associated with significantly lower risk of recurrent VTE, with no difference in major bleeding between the 3 groups.<sup>27</sup> In a randomized study of  $>$ 2400 patients, apixaban 2.5 mg twice daily and apixaban 5 mg twice daily, when compared with placebo, were associated with significantly lower risk of recurrent VTE and
- all-cause mortality, with no difference in major bleeding between the 3 groups.<sup>28</sup> Finally, in an RCT of  $>$ 8200 patients, edoxaban, when compared with warfarin, was associated with a similar risk of recurrent VTE, with a lower risk of clinically relevant bleeding than warfarin.<sup>7</sup> Consequent retrospective studies and a meta-analysis of  $>$ 62000 patients have suggested that risk of bleeding is lower with a DOAC than with warfarin.<sup>8,9</sup>
- Patients with VTE in the setting of active cancer or undergoing treatment for cancer are at high risk of recurrent VTE.<sup>29</sup> In patients with VTE and active cancer, LMWH compared with warfarin is associated with a lower risk of recurrent VTE and a similar risk of major bleeding.<sup>30,31</sup> DOACs (apixaban, rivaroxaban, and edoxaban), when compared with LMWH, are noninferior with respect to recurrent VTE with a similar risk of major bleeding.<sup>12,32–35</sup>
- In 2 randomized trials with  $>$ 500 patients with acute PE, warfarin was associated with significantly lower risk of recurrent VTE compared with placebo, albeit at a higher risk of bleeding.<sup>16,17</sup> In a meta-analysis of  $>$ 22000 patients with acute PE that compared warfarin with aspirin or placebo, VKA was associated with a significantly lower risk of VTE recurrence but at a cost of higher risk of bleeding.<sup>18</sup>
- In a randomized study of 3396 patients receiving rivaroxaban 20 mg daily, rivaroxaban 10 mg daily, or aspirin 100 mg daily for extended anticoagulation, rivaroxaban 10 mg daily was associated with a similar risk of recurrent VTE and major bleeding when compared with rivaroxaban 20 mg daily.<sup>27</sup> In a randomized study of 2486 patients receiving apixaban 2.5 mg twice daily, 5 mg twice daily, or placebo for extended anticoagulation, apixaban 2.5 mg twice daily was associated with a similar risk of recurrent VTE, VTE-related death, and major bleeding, when compared with apixaban 5 mg twice daily.<sup>28</sup> However, these studies were powered to assess whether each dose of rivaroxaban (20 mg daily or 10 mg daily) or apixaban (5 mg twice daily or 2.5 mg twice daily) was superior to aspirin or placebo, respectively, rather than directly comparing

the efficacy and safety of rivaroxaban 20 mg daily versus 10 mg daily, or apixaban 5 mg twice daily to 2.5 mg twice daily. In the RENOVE (Reduced Dose Versus Full-Dose of Direct Oral Anticoagulant After Unprovoked Venous Thromboembolism) trial, 2768 patients with VTE at increased risk of recurrence were randomized to receive either reduced-dose apixaban (2.5 mg twice daily) or rivaroxaban (10 mg daily) or to receive full-dose apixaban (5 mg twice daily) or rivaroxaban (20 mg daily) after an initial 6 to 24 months of initial anticoagulation.<sup>19</sup> The overall rates of VTE were low in all groups (2.2% versus 1.8%; adjusted HR, 1.32 [95% CI, 7.7-12.1] for reduced-dose versus full-dose, respectively).<sup>19</sup> The rate of major or clinically relevant nonmajor bleeding was lower in the reduced-dose DOAC group (9.9%) compared with the full-dose DOAC group (15.2%; adjusted HR, 0.61 [95% CI, 0.48-0.79]).<sup>19</sup> In API-CAT (Apixaban Cancer-Associated Thrombosis Trial), 1766 patients with cancer-associated VTE were randomized to apixaban 2.5 mg or 5 mg twice daily after at least 6 months of treatment.<sup>20</sup> The rate of recurrent VTE was similar in both groups (2.1% versus 2.8%, respectively; HR, 0.76 [95% CI, 0.41-1.41]). The rate of clinically relevant bleeding was 12.1% versus 15.6% (HR, 0.75 [95% CI, 0.58-0.97]), suggesting that half-dose DOAC can be safe and effective even in patients at high risk for VTE recurrence and bleeding.

8. Individuals who develop VTE in the presence of a minor, especially nonsurgical, reversible risk factor, are at risk of recurrent VTE after anticoagulation is stopped (annualized event rate of 4.2%-7.1%).<sup>36</sup> Thus, the decision whether to stop anticoagulation at the end of the treatment phase or to continue anticoagulation into the extended phase should balance the risk of recurrent VTE versus bleeding. Shared decision-making and considering the patient's preference is important. A VTE recurrence risk score (eg, VTE-PREDICT) that considers patient demographics, medical history, index event, presence of reversible risk factors, and comedications may be used to estimate the risk of recurrent 1- or 5-year VTE alongside clinically relevant bleeding to facilitate shared decision-making conversations.<sup>37</sup> However, the VTE-PREDICT score has not been prospectively validated. Additionally, persistent risk factors may vary over time, such as curative management of a cancer. Thus, regular reassessment of necessity to continue extended anticoagulation, weighing the benefits and risks of anticoagulation, is critical.
9. Several randomized trials that have evaluated the role of aspirin in VTE prevention have yielded inconsistent results. In a randomized trial of >400 patients with a history of VTE without an identifiable risk factor, aspirin was associated with a significantly lower risk

of recurrent VTE and no increased risk of bleeding.<sup>21</sup> In another study with a similar population of >822 patients, aspirin was not associated with a reduction in recurrent VTE; however, aspirin discontinuation was common, up to 12% per year, limiting the interpretation of these results.<sup>22</sup>

### 5.2.1. Recurrent Pulmonary Embolism

**Recommendations for Recurrent Pulmonary Embolism**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	C-EO	1. In patients with a history of PE and who present with new symptoms and signs suggestive of recurrent or breakthrough PE, radiographic imaging with a CTPA or V/Q scan is recommended to objectively confirm or exclude the diagnosis.
1	C-LD	2. In patients with a history of PE who have a documented recurrent PE despite being treated with an anticoagulant, an evaluation is recommended to detect clinical and pharmacological factors that may contribute to recurrent PE. <sup>1-3</sup>
2a	C-EO	3. In patients with recurrent PE who are adherent with prescribed therapeutic-intensity anticoagulation, changing therapy to an alternative drug class rather than continuing therapy with the same drug class is reasonable.
2a	C-EO	4. In patients who have documented recurrent acute PE while adherent to anticoagulation with a reduced-dose DOAC, it is reasonable to anticoagulate with a full-dose DOAC within the same class.
2a	B-NR	5. In patients with cancer and a recurrent PE despite being therapeutically anticoagulated with LMWH, dose escalation of LMWH by 20% to 25% is reasonable to prevent future recurrent PE. <sup>4</sup>

### Synopsis

Recurrent PE in patients who are receiving therapeutic anticoagulation is uncommon. There is an increased risk in patients with cancer and those with antiphospholipid antibodies. In patients with suspected recurrent PE while receiving therapeutic anticoagulation, imaging is recommended to confirm a recurrent event. A CTPA is preferable, but a V/Q scan is a reasonable alternative if a baseline comparator V/Q scan is available. In addition, a comprehensive evaluation should be undertaken to determine if there is an identifiable etiology for the recurrence. If anticoagulation was subtherapeutic or there is demonstrable nonadherence to dosing and administration, then changing therapy may not be required. However, recurrent PE in the setting of documented therapeutic anticoagulation is frequently managed by choosing an alternate agent, usually a parenteral drug such as LMWH or fondaparinux.

### Recommendation-Specific Supportive Text

1. Approximately 2% of patients treated for VTE will suffer a recurrent event while on anticoagulation. In an analysis of contemporary trials comparing DOACs to VKA, recurrence rates were 2.4% in patients treated

with DOACs compared with 2.6% with VKA.<sup>5</sup> In patients suspected of having a recurrent PE and who are being treated with an anticoagulant, imaging should be obtained to document the recurrence. CTPA is preferred to V/Q scan unless there is a baseline V/Q scan for comparison. Imaging should be compared with previous imaging, and a diagnosis of a recurrent PE should be based on inclusion of a previously uninvolved vessel or segment. A negative or normal D-dimer may be used to support the exclusion of suspected recurrent PE in patients currently on anticoagulation.<sup>6</sup> However, elevated D-dimer levels should not be used as a stand-alone diagnostic criteria for recurrent PE.

2. Recurrent PE in patients who are currently anticoagulated presents a diagnostic challenge and a therapeutic conundrum. Investigation into clinical and pharmacological conditions that may be associated with recurrent VTE while on anticoagulation should be pursued.<sup>2</sup> Although the etiology of recurrent PE in anticoagulated patients is not well studied, cancer and antiphospholipid antibodies have been identified as clinical risks associated with recurrent PE while on anticoagulation.<sup>3</sup> Nonadherence to the prescribed drug regimen can be difficult to assess in patients taking DOACs and LMWH. Review of the prescribing and dispensing records may be helpful. For patients on a VKA, assessing time in therapeutic range and recent monitoring records may reveal subtherapeutic dosing as the etiology. Off-label subtherapeutic DOAC dosing is also associated with increased risk of adverse events, including recurrent thromboembolism and bleeding.<sup>7,8</sup> Drug-drug and food-drug interactions are well recognized with VKA. However, these interactions may be overcome or managed by more frequent monitoring and dose adjustment. Patients prescribed DOACs along with concomitant p-glycoprotein and CYP-3A4 inducers may have reduced DOAC plasma concentrations.<sup>9</sup> Although there are few DOAC-related food-drug interactions, adequate absorption of rivaroxaban (15 mg and 20 mg doses) requires that it be taken with a meal.<sup>10</sup> In addition, a history of gastrointestinal surgery may affect DOAC absorption.<sup>11</sup> Other conditions described that may be associated with recurrent PE in patients who are currently anticoagulated include: vasculitis, inflammatory conditions, paroxysmal nocturnal hemoglobinuria, pregnancy, and vascular compression or other vascular abnormalities.<sup>2</sup> In patients receiving LMWH or UFH for anticoagulation who have recurrent PE, evaluation for heparin-induced thrombocytopenia, antithrombin deficiency, or subtherapeutic drug levels should be considered.<sup>12</sup>
3. If patients who develop recurrent PE despite anticoagulation are found to have been nonadherent to therapy, subtherapeutic within several weeks

of the recurrent event, or taking the anticoagulant medication improperly, then changing to an alternative anticoagulant may not be required. Patient education and increased frequency of monitoring may suffice as an intervention despite the recurrent event. However, for patients with documented recurrent PE despite therapeutic anticoagulation, changing therapy to an alternative drug class is common practice and may be a reasonable course of action.<sup>13</sup>

4. When patients have documented recurrent PE while using reduced dose DOAC (rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily) in the extended phase of anticoagulant therapy, it is reasonable to resume full therapeutic dosing within the same drug class.
5. Patients with cancer and recurrent PE represent a unique population. A recent meta-analysis did not find a significant difference regarding recurrent PE among the anticoagulation strategies evaluated.<sup>14</sup> It is recognized that patients with cancer have a higher risk for recurrent PE during anticoagulation than the 2% recurrence identified in unselected populations.<sup>5,15</sup> In 1 clinical trial, patients with cancer and recurrent VTE who were receiving therapeutic LMWH were managed with dose escalation of the weight-based dose by 20% to 25%. Notably, 3 of 15 patients in the cohort managed by dose escalation developed recurrent VTE.<sup>4</sup>

## 6. COMPLICATIONS AND SEQUELAE

### 6.1. Persistently Symptomatic Patients After Acute PE

**Recommendations for Persistently Symptomatic Patients After Acute PE**  
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
<b>Evaluation</b>		
<b>1</b>	<b>B-NR</b>	1. In patients with ongoing dyspnea and/or functional impairment after $\geq 3$ months of therapeutic anticoagulation after an acute PE, a diagnostic evaluation is recommended to assess for CTEPD. <sup>1-3</sup>
<b>2a</b>	<b>B-NR</b>	2. For patients undergoing a diagnostic evaluation for CTEPD, it is reasonable to obtain both a transthoracic echocardiogram (TTE)* and a lung perfusion scan (planar V/Q, or V/Q single-photon emission CT [SPECT], SPECT/CT) over an echocardiogram alone to exclude CTEPD or determine if additional diagnostic testing is needed. <sup>1,4,5</sup>
<b>2a</b>	<b>B-NR</b>	3. For patients undergoing a diagnostic evaluation for CTEPD, cardiopulmonary exercise testing (CPET) is reasonable to exclude CTEPD. <sup>4,6-10</sup>
<b>3: No benefit</b>	<b>B-NR</b>	4. In patients with a history of acute PE, who have resolution of symptoms and low suspicion for CTEPD, a follow-up CTPA or lung perfusion scan (planar V/Q, V/Q SPECT, SPECT/CT) is not beneficial to assess for the degree of thrombosis resolution. <sup>11,12</sup>

Recommendations for Persistently Symptomatic Patients After Acute PE (Continued)		
COR	LOE	Recommendations
<b>Management</b>		
1	B-NR	5. Patients being evaluated for CTEPD should continue anticoagulation until the evaluation is completed to prevent recurrent VTE and/or CTEPD progression unless contraindicated due to high bleeding risk. <sup>13</sup>
1	B-R	6. For patients in whom CTEPD has been excluded but who have ongoing dyspnea and/or functional impairment despite ≥3 months of therapeutic anticoagulation after an acute PE, a pulmonary rehabilitation program is reasonable to improve symptoms and exercise tolerance. <sup>14–16</sup>
1	C-LD	7. For patients with a diagnosis of CTEPD with PH, referral to a center with expertise in managing CTEPD is recommended to optimize evaluation and management. <sup>17–19</sup>
2a	C-LD	8. For select patients with a diagnosis of CTEPD without PH, referral to a center with expertise can be beneficial in managing CTEPD. <sup>17–19</sup>

\*In a patient with normal echocardiogram at the time of acute PE, a repeated echocardiogram at 3 to 6 months is low yield and may be omitted.

## Synopsis

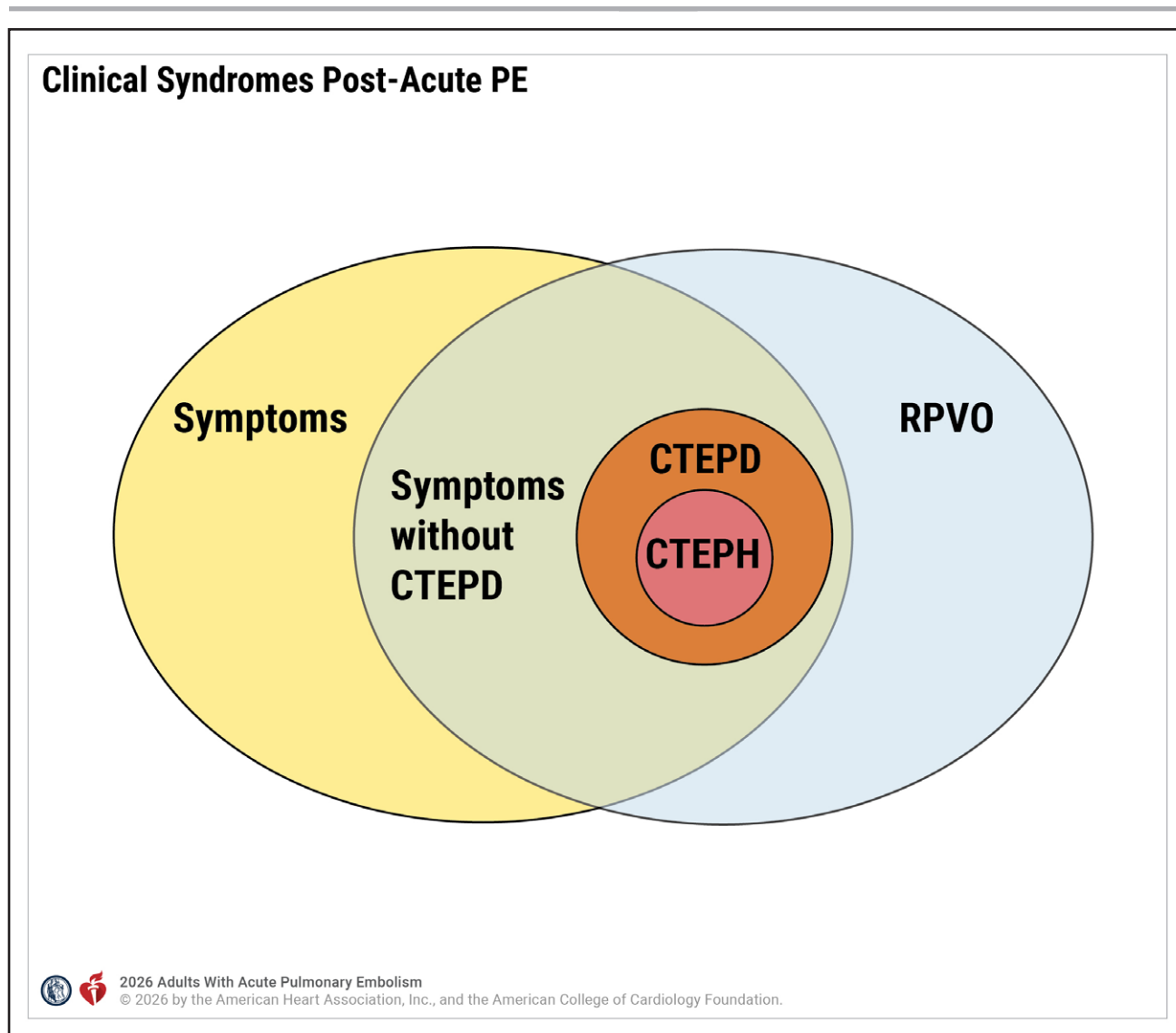
The constellation of clinical symptoms after acute PE are reviewed in Section 3.1.1, “Clinical Assessment.” Up to half of patients after an acute PE will have ongoing dyspnea and/or functional impairment despite 3 months of therapeutic anticoagulation.<sup>1</sup> Similarly, about half of patients with acute PE have persistent perfusion defects on imaging, termed residual pulmonary vascular obstruction (RPVO), many of whom are asymptomatic.<sup>20,21</sup> CTEPD encompasses patients who had a PE and have persistent symptoms, RPVO, and pulmonary vascular disease-related exercise limitation, both without and with resting PH<sup>19</sup> (Figure 7). The prevalence of CTEPD with PH, also called chronic thromboembolic pulmonary hypertension (CTEPH), after acute PE is approximately 3%, while the prevalence of CTEPD without PH is unknown but is felt to be at least as prevalent.<sup>22,23</sup> The objective of diagnostic testing in symptomatic patients with persistent symptoms ≥3 months after an acute PE is to determine the etiology of symptoms and whether or not CTEPD is the cause. The diagnosis of CTEPD requires evaluation for pulmonary vascular disease-related exercise limitation, defined as resting or precapillary PH and/or thrombus-related abnormally elevated alveolar dead space. A diagnostic algorithm to aid in the evaluation of patients with ongoing symptoms after the acute period of PE is illustrated in Figure 8.

## Recommendation-Specific Supportive Text

1. Three large prospective studies demonstrated that a diagnostic evaluation performed in patients with persistent symptoms at 3 months after acute PE reduces

the time to diagnosis of CTEPD. The InShape II (Non-invasive Early Exclusion of Chronic Thromboembolic Pulmonary Hypertension After Acute Pulmonary Embolism) study, a multicenter, single-arm study combining a clinical prediction score, electrocardiography, and NT-proBNP in symptomatic patients 3 months post-PE, found that most patients with CTEPD with PH can be diagnosed within 4 months of their acute PE. In the FOCUS (Follow Up After Acute Pulmonary Embolism) study, a multicenter observational cohort study utilizing a standardized assessment plan at 3, 12, and 24 months in 880 patients after acute PE, the median time to CTEPD with PH diagnosis was 129 days. Another systematic study found that a mean of 4 months follow-up post-PE in a PE specialty clinic reduced the time to diagnosis of CTEPD with PH.<sup>3</sup> Diagnostic evaluation at the 3-month time point after acute PE is also supported by the finding that vascular obstruction after acute PE does not change after 3 months; therefore, waiting longer only delays the diagnosis.<sup>8,9</sup>

2. TTE alone is insufficient to include or exclude a diagnosis of CTEPD. In a retrospective study of 42 patients with confirmed CTEPD with PH, one-third had normal TTEs.<sup>4</sup> Similarly, in a prospective study of 400 unselected patients after an acute PE, about 40% diagnosed with CTEPD had no signs of PH on TTE but had CTEPD findings suspicious for abnormal pulmonary perfusion.<sup>23</sup> Conversely, many patients with persistently abnormal TTEs after acute PE do not develop CTEPD. The 2 largest studies performed in patients after an acute PE found a low incidence of CTEPD with PH (1.6%–3.2%) but greater than 30% to 50% of patients had persistently abnormal TTEs.<sup>15</sup> The negative predictive value of planar V/Q to exclude a diagnosis of CTEPD approaches 100%.<sup>10,24</sup> Both SPECT perfusion imaging combined with low-dose non-contrast CT (SPECT/CT) and V/Q SPECT have similar diagnostic performance to planar V/Q in the diagnosis of CTEPD with PH.<sup>25,26</sup> Although normal lung perfusion imaging (planar V/Q, SPECT/CT, or V/Q SPECT) is sufficient to exclude CTEPD, RPVO is common after acute PE and may not correlate with symptoms. Therefore, TTE is a useful adjunctive test to determine the likelihood of PH and aids in the evaluation of dyspnea. Clinicians may perform lung perfusion imaging without a TTE in patients who had a normal baseline TTE at the time of acute PE.
3. Dyspnea and exercise limitation in CTEPD can be attributed to the reduced ability to augment stroke volume with exercise due to increased RV afterload and/or increased alveolar dead space related to pulmonary artery obstruction.<sup>27</sup> Therefore, findings suggestive of CTEPD on noninvasive CPET may include a reduced peak oxygen consumption,

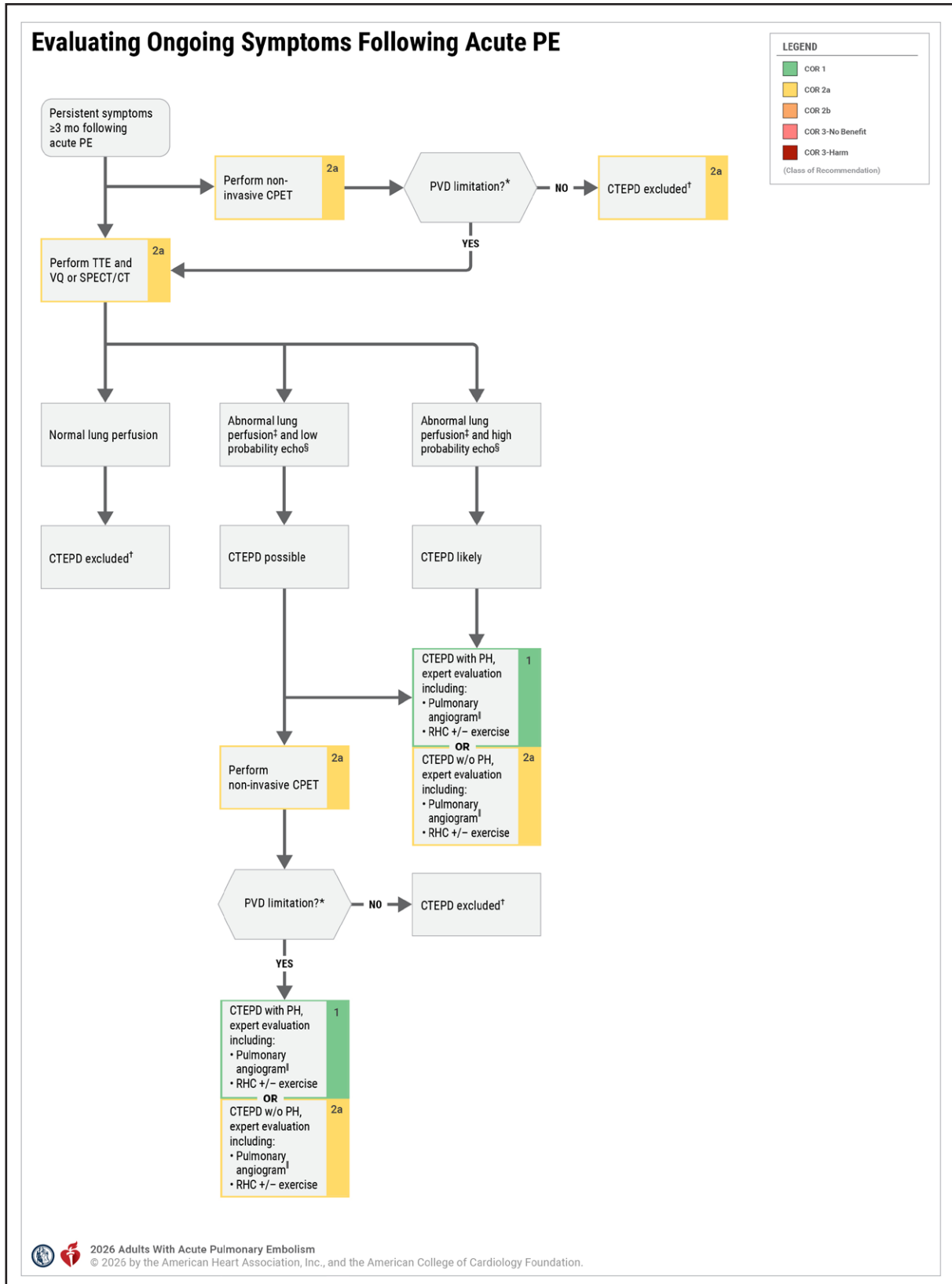


**Figure 7. Clinical Syndromes Post-Acute PE.**

CTEPD indicates chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; and RPVO, residual pulmonary vascular obstruction.

impairments in stroke volume (estimated using oxygen pulse or stroke volume reserve), and ventilatory inefficiency (increased  $V_E/VCO_2$ ) related to increased alveolar dead space (VD/VT). CPET is highly sensitive at detecting underlying cardiopulmonary impairments, is noninvasive, and does not require radiation. Despite this, the precise diagnostic performance of CPET to diagnose or exclude CTEPD with or without PH is not established. A study of 400 patients with acute PE utilized CPET and TTE in symptomatic patients and found rates of CTEPD without PH of 5.75% and with PH of 5.25%.<sup>23</sup> A significant number of patients were diagnosed with CTEPD via an abnormal CPET, despite no echocardiographic signs of PH.<sup>23</sup> Studies of patients with CTEPD with and without PH have found a correlation of ventilatory

inefficiency and reduced oxygen pulse on noninvasive CPET with abnormal hemodynamics on exercise right heart catheterization.<sup>6,7</sup> Important caveats include: cardiovascular and ventilatory abnormalities on CPET are not specific to CTEPD; peak oxygen consumption alone is not a reliable screening metric for CTEPD; and CPET parameter thresholds to exclude CTEPD have not been clearly defined.<sup>27</sup> Most studies have used abnormalities in ventilatory efficiency ( $VE/VCO_2$ ) as a surrogate for VD/VT to define exercise limitation in patients with CTEPD; however, the determination of VD/VT requires the measurement of arterial  $PCO_2$ , which is not available in many CPET labs. Despite the low specificity for  $VE/VCO_2$  to predict elevated VD/VT, its high sensitivity suggests  $VE/VCO_2$  is a reasonable surrogate for alveolar dead



**Figure 8. Evaluating Ongoing Symptoms Following Acute PE.**

\*PVD limitation defined by circulatory impairment with abnormalities in stroke volume (oxygen pulse) and VD/VT and/or VE/VCO<sub>2</sub>. †While CTEPD is excluded, evaluation for other etiologies of symptoms is warranted. ‡Positive V/Q or SPECT/CT scan refers to any mismatched perfusion defects. §Low-probability echocardiogram is defined as a TRV ≤2.8 m/s and absence of echocardiographic PH signs (Table 10). Higher probability echocardiogram is defined as a TRV ≥2.8 m/s and presence of echocardiographic PH signs (Table 10). (Continued)

**Figure 8 Continued.** High-risk echocardiogram refers to intermediate- or high-probability echocardiography criteria per 2022 European Respiratory Society guidelines, while low-risk echocardiogram refers to low-probability echocardiography criteria.<sup>40</sup> IPulmonary angiography may be CT or invasive pulmonary angiogram depending on clinician choice as evaluation will differ based on center experience. CPET indicates cardiopulmonary exercise testing; CT, computed tomography; CTPED, chronic thromboembolic pulmonary disease; PH, pulmonary hypertension; PVD, pulmonary vascular disease; RPVO, residual pulmonary vascular obstruction; RHC, right heart catheterization; SPECT, single-photon emission computed tomography; TRV, tricuspid regurgitation velocity; TTE, transthoracic echocardiography; VE/VCO<sub>2</sub>, ventilatory inefficiency; and V/Q, ventilation-perfusion. Adapted from Pugliese et al<sup>30</sup> and from the American Thoracic Society. Copyright © 2019 American Thoracic Society. All rights reserved. *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.

space, assuming patients with VE/VCO<sub>2</sub> abnormalities get more definitive testing, such as exercise right heart catheterization.<sup>28</sup>

- Several cohort studies and meta-analyses have demonstrated no correlation between RPVO on CTPA 6 to 12 months after the diagnosis of PE and various clinical outcomes during follow-up. These outcomes include functional impairment, dyspnea, the RV/LV ratio, CTEPH, and recurrent PE.<sup>11,12,29</sup> Abnormal V/Q scans during follow-up for acute PE are not predictive of exercise limitation at 12 months, limiting their value in asymptomatic patients.<sup>11</sup> Therefore, the utility of CTPA for follow-up purposes is limited. Exceptions include patients with new symptoms requiring exclusion of recurrent PE or patients with persistent symptoms in which V/Q or SPECT/CT is not available. CTPA is not indicated for determining the duration of anticoagulation therapy.
- Because of the risk of recurrent VTE and/or progression of CTEPD, continued anticoagulation is recommended, even in patients with apparent transient provoking risk factors until the evaluation is

complete unless contraindicated due to increased bleeding risk.<sup>13,30</sup>

- There are limited data related to efficacy and safety of physical exercise and rehabilitation after acute PE. One RCT included 211 patients with persistent dyspnea 6 to 72 months after an acute PE who were randomized to usual care versus 8 weeks of home supervised exercise program and found that the latter improved exercise capacity and quality of life.<sup>31</sup> However, 2 other RCTs comparing a supervised exercise program in patients within 3 months of an acute PE found no significant between-group difference in exercise capacity or quality of life, but sample size and methodologic consideration were limited.<sup>15,16</sup> These trials may suggest the benefit of rehabilitation is limited to patients with persistent symptoms after the acute phase of PE (after 3 months).
- There are no randomized data comparing outcomes in patients with CTEPH treated in a center specializing in CTEPD versus those treated in a nonspecialized center. Balloon pulmonary angioplasty (BPA) and/or pulmonary thromboendarterectomy (PTE) surgery, which have been shown to be superior to medical therapy alone in patients with CTEPH, are often restricted to specialty centers.<sup>32–34</sup> Center experience with both BPA and PTE surgery are tied to outcomes. Among 64 PTE centers in the United States, the odds of mortality declined with increasing annual case volume.<sup>18</sup> Mortality and other outcomes improve at high-volume referral centers over time and with increased patient numbers.<sup>17,35</sup> One study demonstrated that among 184 patients with inoperable CTEPH undergoing 1006 BPA sessions, complication rates decreased from 13.3% in the initial half of treated patients to 5.9% in the second half of patients ( $P < 0.001$ ).<sup>19</sup>
- Data for outcomes in the management of patients with CTEPD without PH are limited to small case series involving highly selected patients treated with BPA or PTE. These studies demonstrate improvements in exercise capacity, functional class, and hemodynamics.<sup>7,36–38</sup> Therefore, some patients may benefit from a referral to a center experienced in the management of CTEPD. However, many patients with mild disease do not benefit from procedural/surgical management.<sup>7,36,37</sup> Therefore, referral to a CTEPD specialty center may not be needed for all patients with CTEPD without PH, especially those with mild disease who may have a benign prognosis.<sup>39</sup>

**Table 10. Echocardiographic Signs Suggestive of Pulmonary Hypertension**

Echocardiographic Signs Suggestive of Pulmonary Hypertension*		
A: Ventricles	B: Pulmonary Artery	C: Inferior Vena Cava and RA
RV/LV basal diameter/area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the intraventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm <sup>2</sup>
TAPSE/sPAP ratio <0.55 mm/mm Hg	PA diameter >AR diameter PA diameter >25 mm	

\*Signs from at least 2 categories (A/B/C) must be present to alter the level of echocardiographic probability of PH. Adapted with permission from Humbert et al.<sup>40</sup> © 2025 European Society of Cardiology & European Respiratory Society.

AR indicates aortic root; IVC, inferior vena cava; LV, left ventricle; LVEI, left ventricle eccentricity index; m, meters; PA, pulmonary artery; PH, pulmonary hypertension; RA, right atrium; RV, right ventricle; RVOT AT, right ventricular out-flow tract acceleration time; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity, and s, second.

**Table 11. Evidence Gaps and Future Direction in the Management of Acute PE**

Category	Evidence Gaps and Future Directions
Risk Stratification and Scoring Systems	<p>Validation of the AHA/ACC Acute PE Clinical Categories</p> <p>Determination of the utility of generic risk scores (eg, NEWS2) in predicting outcomes</p> <p>Better characterization of the impact of genetic and acquired thrombophilia testing on patient-relevant outcomes in acute PE</p> <p>Determination of whether the degree of RV enlargement relative to the LV may be more predictive than a binary normal/abnormal assessment</p> <p>Development of risk scores that can identify patients who will have better outcomes with advanced therapies</p> <p>Assessment of the role of thrombus burden in key subpopulations and the impact of acute intervention to reduce thrombus burden on patient-relevant outcomes</p>
Anticoagulation/Thrombolytic Therapy	<p>Development of new anticoagulants with lower bleeding risk</p> <p>Evaluation of how D-dimer–based strategies perform in patients on therapeutic anticoagulation</p> <p>Assessment of the impact of compression therapy and anticoagulation to reduce PE risk for short- and long-haul travel</p> <p>Safety and efficacy of short-term LMWH versus DOAC following acute PE intervention</p>
Advanced Therapies	<p>Creation of algorithms for when to use each interventional tool for advanced therapy of PE</p> <p>Assessment of efficacy and safety of various dosing regimens of thrombolytic agents to treat acute PE</p> <p>Assessment of the efficacy and safety of interventional and postinterventional procedure anticoagulant therapy</p> <p>Evaluation of the efficacy and safety of catheter-based interventions versus anticoagulation alone among AHA/ACC PE Categories C-D patients for acute and long-term outcomes</p> <p>Evaluation of the efficacy and safety of surgical embolectomy in a randomized trial</p> <p>Determination of the role for isolated RV support devices in AHA/ACC PE Category E patients</p> <p>Evaluation of the efficacy and safety of catheter-based interventions versus systemic thrombolysis among AHA/ACC PE Category E patients for acute and long-term outcomes</p>
Chronic Conditions and Long-Term Outcomes	<p>Better characterization of subtypes of CTEPD and their clinical consequences</p> <p>Assessment of novel biomarkers, clinical characteristics, and imaging findings for risks of developing chronic thromboembolism</p>
Special Populations and Personalized Medicine	<p>Evaluation of diagnostic and treatment strategies in rural populations with limited access to care</p> <p>Determine the efficacy of anticoagulation therapy on patients with a history of PE who require long-term estrogen-containing hormone therapy</p> <p>Determination of the safety of direct oral anticoagulants in patients who are pregnant or breastfeeding</p>
Technology and Innovation	<p>Use of AI in the diagnosis and risk stratification of patients with acute PE</p> <p>Radiomics for aging of thrombus PE and risk stratification</p>

## 7. EVIDENCE GAPS AND FUTURE DIRECTIONS

The management of acute PE continues to evolve, yet significant evidence gaps persist across multiple domains of care (Table 11). Current challenges include refining risk stratification tools—such as validating the AHA/ACC clinical categories and integrating novel predictors like thrombus burden and RV enlargement metrics—to better guide therapeutic decisions. For anticoagulation and thrombolytic therapy, there is a need for safer agents, improved strategies for patients on existing treatments, and clearer guidance for travel-related prophylaxis. Advanced therapies require robust algorithms and comparative effectiveness data, particularly for catheter-based interventions and surgical embolectomy in high-risk populations. Long-term outcomes remain poorly understood, especially in chronic thromboembolic disease and special populations such as rural patients, those requiring hormone therapy, and pregnant individuals. Finally, emerging technologies such as artificial intelligence and radiomics offer promising avenues for enhancing diagnosis and personalization of care but require further validation. Addressing

these gaps is essential to optimize outcomes and tailor treatment strategies for diverse patient populations.

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### ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee and the American Heart Association Science Advisory and Coordinating Committee in October 2025, the American College of Cardiology Science and Quality Committee in November 2025, and the American Heart Association Executive Committee in December 2025.

Supplemental materials are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001415>

This article has been copublished in the *Journal of the American College of Cardiology*.

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**Appendix 1. Author Relationships With Industry and Other Entities—2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mark Creager (Chair)	Dartmouth Hitchcock Medical Center—Professor of Medicine and Surgery	None	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • Elsevier • UpToDate*	None
Geoffrey D. Barnes (Vice Chair)	University of Michigan Health—Associate Professor	NOT RELEVANT • Anthos RELEVANT • Bayer* • Bristol Myers Squibb* • Janssen Biotech • Pfizer	None	None	None	NOT RELEVANT • Anticoagulation Forum (Board of Directors)† RELEVANT • Boston Scientific*	None
Jay S. Giri (Vice Chair)	Penn Medicine—Associate Professor of Medicine; Director, Cardiovascular Catheterization Laboratories	NOT RELEVANT • Endovascular Engineering RELEVANT • Boston Scientific* • Inari Medical*	None	NOT RELEVANT • Endovascular Engineering	None	RELEVANT • Boston Scientific* • Inari Medical*	None
William Schuyler Jones (JCCPG liaison)	Duke University School of Medicine—Associate Professor of Medicine	None	None	None	None	RELEVANT • Bayer* • Boehringer Ingelheim* • Merck* • Novartis*	None
Debabrata Mukherjee (JCCPG liaison)	Texas Tech University Health Sciences Center—Professor and Chair, Department of Internal Medicine	None	None	None	None	None	None
Allison Burnett (ACCP rep)	University of New Mexico Hospital—Lead Pharmacist, Inpatient Antithrombosis Stewardship Program	None	None	NOT RELEVANT • UpToDate	None	NOT RELEVANT • Anticoagulation Forum (Board of Directors)† • NCBAP (Board of Directors)† RELEVANT • Bristol Myers Squibb/Pfizer Alliance	None
Teresa Carman	University Hospitals Cleveland Medical Center—Director, Vascular Medicine	None	None	None	None	NOT RELEVANT • Alliance for Physician Certification and Advancement • ABVLM (Board of Directors)† • APCA† • Icon† • Vascular Medicine	None
Ana I. Casanegra	Mayo Clinic—Internist, Vascular Medicine Specialist	None	None	None	None	• Society for Vascular Medicine	None

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## Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Lana Castellucci	Ottawa Hospital—Scientist, Clinical Epidemiology Program; University of Ottawa—Associate Professor, Medicine	RELEVANT • Bayer	NOT RELEVANT • LEO Pharma RELEVANT • Inari Medical	None	None	NOT RELEVANT • Medscape	None
Sherrell Clark (Patient rep)	Smithfield Foods—Associate Diversity Culture and Engagement Specialist	None	None	None	None	None	None
Mary Cushman	University of Vermont—Professor of Medicine; Professor of Pathology & Laboratory Medicine	None	None	None	None	NOT RELEVANT • ISTH (Governance Committee)† • NIH*	None
Kerstin de Wit	Queen's University—Professor; Research Director, Department of Emergency Medicine, Faculty of Health Sciences  Division of Emergency Medicine, Department of Medicine, Faculty of Health Sciences, McMaster University	NOT RELEVANT • Committee to Evaluate Drugs	None	None	NOT RELEVANT • Canadian Institutes of Health Research (PI)*	NOT RELEVANT • CanVECTOR  	NOT RELEVANT • Defendant, misdiagnosed PE, 2024
Jennifer Eaves‡	AHA/ACC—Science & Health Advisor, Guidelines	None	None	None	None	None	None
Margaret Fang (SHM rep)	University of California, San Francisco—Professor of Medicine	None	None	None	None	NOT RELEVANT • Anticoagulation Forum† • National Blood Clot Alliance (Medical and Scientific Advisory Board)† • North American Thrombosis Forum (Medical and Scientific Advisory Board)†	None
Joshua Goldberg	Weill Cornell Medicine—Associate Professor, Cardiothoracic Surgery	RELEVANT • AngioDynamics	None	None	None	None	None
Stanislav Henkin	Mayo Clinic—Senior Associate Consultant	None	None	None	None	None	None

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**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Hillary Johnston-Cox	Zucker School of Medicine at Hofstra/Northwell—Assistant Professor of Cardiology and Director of Peripheral Interventions; Northwell Health—Interventional Cardiologist, Vascular Medicine	None	None	None	None	None	None
Daniella Kadian-Dodov	Icahn School of Medicine, Mount Sinai—Associate Professor, Medicine	RELEVANT • Boston Scientific	RELEVANT • Abbott Fund	None	RELEVANT • Philips*	NOT RELEVANT • JACC† • CLI Global Society (Board of Directors)† • McGraw-Hill Companies • Medscape* • SVM (Board of Trustees)† • <i>Vascular Medicine</i> • Women As One • Zevra Therapeutics	None
Sabeeda Kadavath (JCPM liaison)	St. Bernards Healthcare—Interventional Cardiologist, St Mary's—Interventional Cardiologist	None	None	None	None	None 	None
William Brent Keeling	Emory University—Associate Professor	NOT RELEVANT • Dexcom RELEVANT • AngioDynamics • Penumbra	None	NOT RELEVANT • Viz.ai	None	None	None
Andrew J. Klein (SCA rep)	Piedmont Heart Interventional Cardiology—Cardiologist	None	None	None	None	NOT RELEVANT • Amgen§ • AngioDynamics§ • AstraZeneca§ • Boston Scientific§ • Edwards Lifesciences§ • Janssen§ • Kestra Medical Technology§ • Medtronic§ • Novartis§ • Shockwave§	None
Jun Li	University Hospitals Harrington Heart & Vascular Institute—Interventional Cardiologist; Endovascular Specialist	RELEVANT • Abbott Vascular • Boston Scientific* • Inari Medical • Medtronic*	None	None	None	None	None

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**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Michael C. McDaniel	Emory University School of Medicine—Associate Professor, Medicine, Division of Cardiology	None	None	None	NOT RELEVANT • Imperative Care	NOT RELEVANT • ACCF* • Boston Scientific • Georgia Department of Public Health* • Inari Medical • Penumbra (DSMB) • PERT Consortium†	NOT RELEVANT • Defendant, air embolism during coronary angiography, 2024* • Defendant, chest pain and sudden death in the ED, 2023 • Defendant, complication from ablation procedure in patient with AF, 2023 • Defendant, patient with endocarditis, 2023 • Defendant, delayed revascularization after MI, 2023* • Defendant, delayed revascularization after acute MI, 2023 • Defendant, death in ED after cardiac complaint, 2024 • Defendant, undertreated cardiac condition, 2024 • Defendant, complication during cardiac catheterization and intervention, 2024 • Defendant, hospitalization for acute MI, 2024 • Defendant, acute PE, 2024 • Defendant, fall leading to hospitalization and acute PE, 2024 • Plaintiff, dislodged catheter during cardiac catheterization, 2024 • Defendant, acute cardiac event, 2024 • Defendant, cardiac catheterization complication, 2024 • Defendant, PCI complication, 2024
Lisa K. Moores <i>(CHEST rep)</i>	Uniformed Services University—Associate Dean for Assessment and Professional Development	None	None	None	None	None	None
Gregory Piazza	Brigham and Women’s Hospital and Harvard Medical School—Director, Vascular Medicine Section, Division of Cardiovascular Medicine and Associate Professor, Medicine	RELEVANT • Boston Scientific* • Bristol Myers Squibb* • Merck • Penumbra • Pfizer • Regeneron Pharmaceuticals	None	None	NOT RELEVANT • Esperion* • NAMSA (DSMB)	NOT RELEVANT • Alexion Pharmaceuticals* • Georgia Department of Public Health RELEVANT • Amgen • Bayer • Boston Scientific • Boston Scientific (spouse) • Bristol Myers Squibb • Janssen	None

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**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Karen S. Prenger (SVN rep)	Ohio State University Medical Center—Clinical Nurse Specialist	None	None	None	None	NOT RELEVANT • American Nurses Association	None
Steven C. Pugliese	PennMedicine and Hospital University of Pennsylvania—Associate Professor of Clinical Medicine and Director, Pulmonary Embolism Response Team	NOT RELEVANT • iSchemaView	None	None	RELEVANT • Janssen Biotech	NOT RELEVANT • PERT Consortium (Board of Directors)	NOT RELEVANT • Plaintiff, patient developed PPES, 2023 • Plaintiff, patient with suspected PE, 2024
Mona B. Ranade (SIR rep)	UCLA Health—Health Sciences Assistant Clinical Professor, Radiological Sciences	RELEVANT • AngioDynamics • Boston Scientific* • Inari Medical • Medtronic • Terumo	None	None	RELEVANT • AngioDynamics*	RELEVANT • Penumbra*	None
Rachel P. Rosovsky	Massachusetts General Hospital—Hematologist	NOT RELEVANT • Arbor Biotechnologies • Pulmonary Embolism Response Team Consortium RELEVANT • Boston Scientific • Inari Medical • Inquis Medical • Janssen Pharmaceuticals • Penumbra • Thrombolex†	None	None	None	NOT RELEVANT • PERT Consortium (Board of Directors- Immediate Past President)† RELEVANT • AngioDynamics • Janssen • Penumbra 	None
Farla Russo (Patient rep)	Retired	None	None	None	None	None	None
Eric A. Secemsky	Beth Israel Deaconess Medical Center—Director, Vascular Intervention and Interventional Cardiologist	NOT RELEVANT • Infrar • Rampart • RapidAI • Zoll Medical RELEVANT • Abbott Vascular* • AngioDynamics • Bard Peripheral Vascular* • Bayer • Boston Scientific* • Bristol Myers Squibb* • Cardiovascular Systems • Cook* • Inari Medical • Janssen • Medtronic* • Penumbra • Philips* • Shockwave Medical* • Siemens • Terumo* • Thrombolex • VentureMed Group* • WL Gore & Associates	None	NOT RELEVANT • Endovascular Engineering RELEVANT • Innova RELEVANT • Inquis Medical • Thrombolex	None	RELEVANT • Thrombolex	None

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**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Akhilesh K. Sista	Weill Cornell Medicine—Professor of Radiology, Radiologist	None	None	None	None	NOT RELEVANT • NHLBI (PI)*	None
Leben Tefera	Cleveland Clinic—Physician, Vascular Medicine	None	None	None	None	None	None
Ido Weinberg (SVM rep)	Massachusetts General Hospital—Physician and Business Development, VasCore	NOT RELEVANT • Arenal Medical RELEVANT • Daiichi Sankyo • Magneto Thrombectomy • Penumbra*	None	None	None	None	None
Lauren M. Westafer (ACEP rep)	Baystate Health—Assistant Professor, Emergency Medicine	None	None	None	NOT RELEVANT • Baystate Health* • NHLBI*	None	None
Michael N. Young	Dartmouth Hitchcock Medical Center—Associate Professor of Medicine; Director, Cardiac Catheterization Laboratories	RELEVANT • Boston Scientific*	None	None	None	RELEVANT • Boston Scientific* • Edwards Lifesciences*	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥\$5 000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Significant relationship.

†No financial benefit.

‡Niya Jones is an AHA/ACC joint staff member and acts as the Science and Health Advisor for the AHA/ACC Guideline for Acute Pulmonary Embolism. No relevant relationships to report. Nonvoting author on recommendations and not included/counted in the RWI balance for this writing committee.

§The Centers for Medicare & Medicaid Services reported food and beverage payments from Amgen, AngioDynamics, AstraZeneca, Boston Scientific, Edwards Lifesciences, Janssen, Kestra Medical Technology, Medtronic, Novartis, and Shockwave in 2023. Dr. Menon disputes these payments.

ABVLM indicates American Board of Venous and Lymphatic Medicine; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; ACEP, American College of Emergency Physicians; AF, atrial fibrillation; AHA, American Heart Association; APCA, Alliance for Physician Certification and Advancement; CanVECTOR, Canadian Venous Thromboembolism Research Network; CHEST, American College of Chest Physicians; EC, emergency department; ISTH, International Society on Thrombosis and Haemostasis; JACC, *Journal of the American College of Cardiology*; MI, myocardial infarction; NAMS, North American Science Associates; NCBAP, National Certification Board for Anticoagulation Providers; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PERT, Pulmonary Embolism Response Team; PPES, post-pulmonary embolism syndrome; SCAI, Society for Cardiovascular Angiography & Interventions; SHM, Society of Hospital Medicine; SIR, Society of Interventional Radiology; SVM, Society for Vascular Medicine; SVN, Society for Vascular Nursing; and VasCore, Vascular Imaging Core Laboratory.

**Appendix 2. Reviewer Relationships With Industry and Other Entities—2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults**

Reviewer	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Joaquin Cigarroa, Co-Chair	OHSU—Professor of Medicine, Division of Cardiovascular Medicine; School of Medicine, Head of the Division of Cardiovascular Medicine	• US FDA†	None	None	None	• ACC† • SCAI (Board of Trustees)† • Wiley*	None
Scott C. Woller, Co-Chair	University of Utah School of Medicine—Professor of Medicine; Intermountain Medical Center—Chair of Medicine	None	None	None	• Janssen Pharmaceuticals*	None	None
Melver Anderson (SHM rep)	University of Colorado Anschutz Medical Campus—Professor of Medicine; Rocky Mountain Regional VA Medical Center—National Program Director, VHA Hospital Medicine	None	None	None	None	None	None
Supreeti Behuria	Donald and Barbara Zucker School of Medicine at Hofstra/Northwell—Assistant Professor; Northwell Health—Director of Nuclear Cardiology; Staten Island University Hospital—Director, The Hypertension Center	• Medtronic	None	None	None	None	None
Behnood Bikdeli	Brigham and Women's Hospital—Associate Physician, Cardiovascular Medicine Division	• International Consulting Associates	None	None	• AHA* • Brigham and Women's Hospital*	• <i>Journal of the American College of Cardiology</i> † • NHLBI (DSMB) • <i>New England Journal of Medicine</i> • <i>Thrombosis Research</i> • Vasculearn Network	None
Julie C. Bulman (SIR rep)	Harvard Medical School—Instructor in Radiology	• Argon Medical Devices* • Endovascular Engineering	None	None	• Endovascular Engineering (PI)	None	None
Mark Carrier	University of Ottawa—Professor of Medicine; Ottawa Hospital Research Institute—Senior Scientist; Ottawa Hospital—Chief, Division of Hematology, Department of Medicine	• Anthos Pharmaceuticals† • Pfizer† • Regeneron	None	None	None	• LEO Pharma • Pfizer*	None
Saurav Chatterjee	Zucker School of Medicine at Hofstra—Clinical Assistant Professor of Medicine/Cardiology	None	None	None	None	• AHA	None
Maya Chilbert (ACCP rep)	University at Buffalo School of Pharmacy and Pharmaceutical Sciences—Clinical Assistant Professor	• AACME	None	None	None	• ACCF* • New York State Council of Health-Systems Pharmacy	None
Antoinette S. Gomes	David Geffen School of Medicine at UCLA—Professor, Departments of Medicine and Radiology	None	None	• Abbott Laboratories*	None	None	None
Matthew Hartwig	Duke University School of Medicine—Professor of Surgery	• CSL Behring* • Intuitive Surgical*	None	None	• BioMedInnovations*	None	None
Brittany R. Messer	Marshall Health—Clinical Pharmacist	None	None	None	None	None	None
Julie Partridge (patient rep)	Southern Illinois University—Professor and Interim Director, School of Human Sciences	None	None	None	None	• National Blood Clot Alliance (Board of Directors)	None

(Continued)

## Appendix 2. Continued

Reviewer	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Crystal Preston-Lloyd (SVN rep)	Family Medical Clinic—Nurse Practitioner	None	None	None	None	• SVN	None
Parth Rali (CHEST rep)	Lewis Katz School of Medicine at Temple University—Associate Professor, Thoracic Medicine and Surgery	<ul style="list-style-type: none"> <li>• Inari Medical*</li> <li>• Penumbra</li> <li>• ThinkSono</li> <li>• Thrombolex*</li> <li>• Viz.ai*</li> </ul>	<ul style="list-style-type: none"> <li>• Janssen Pharmaceuticals*</li> </ul>	None	None	None	None
Kenneth Rosenfield (SCAI rep)	Massachusetts General Hospital—Section Head, Vascular Medicine and Intervention	<ul style="list-style-type: none"> <li>• Abbott Vascular*</li> <li>• Akura Medical†</li> <li>• AngioDynamics*</li> <li>• Becton, Dickinson and Company*</li> <li>• Boston Scientific*</li> <li>• Contego Medical*</li> <li>• Innova Vascular†</li> <li>• Johnson &amp; Johnson Health Care Systems*</li> <li>• Medtronic Vascular*</li> <li>• Philips*</li> <li>• Surmodics*</li> </ul>	None	<ul style="list-style-type: none"> <li>• Contego Medical*</li> <li>• Imperative Care*</li> <li>• Neptune Medical†</li> </ul>	None	None	None
Jennifer Rymer (SVN rep)	Duke University—Associate Professor of Medicine	None	None	None	<ul style="list-style-type: none"> <li>• Abiomed (PI)*</li> <li>• AHA (PI)*</li> <li>• Chiesi USA (PI)*</li> <li>• Idorsia (PI)*</li> <li>• NIH*</li> </ul>	<ul style="list-style-type: none"> <li>• Idorsia</li> </ul>	None
Maanasi Samant	Northwestern University Feinberg School of Medicine—Assistant Professor	<ul style="list-style-type: none"> <li>• Johnson and Johnson</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• United Therapeutics</li> </ul>	<ul style="list-style-type: none"> <li>• American Heart Association.</li> </ul>	None
Richard D. Shih (ACEP rep)	Florida Atlantic University Schmidt College of Medicine—Professor of Emergency Medicine	None	None	None	None	None	None
Edwin Takahashi	Mayo Clinic—Physician	None	None	None	None	None	None
Jeffrey I. Weitz	McMaster University—Professor of Medicine and Biochemistry and Biomedical Sciences	<ul style="list-style-type: none"> <li>• Alnylam Pharmaceutical†</li> <li>• Anthost</li> <li>• Bayer†</li> <li>• Boehringer Ingelheim†</li> <li>• Bristol Myers Squibb†</li> <li>• Daiichi Sankyo†</li> <li>• Ionis Pharmaceutical†</li> <li>• Janssen Global Services†</li> <li>• Merck Company Foundation†</li> <li>• Novartis†</li> <li>• Pfizer†</li> <li>• Regeneron†</li> <li>• Servier†</li> <li>• VarmX Pharmaceutical†</li> </ul>	None	None	None	None	None

This table represents all reviewers' relationships with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity or ownership of ≥\$5000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to <http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Significant relationship.

†No financial benefit.

AACME indicates American Academy of Continuing Medical Education; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; ACEP, American College of Emergency Physicians; AHA, American Heart Association; CHEST, American College of Chest Physicians; CME, continuing medical education; DSMB, data and safety monitoring board; FDA, Food and Drug Administration; FMMJUA, Florida Medical Malpractice Joint Underwriting Association; NHLBI, National of Heart, Lung and Blood Institute; OHSU, Oregon Health & Science University; PE, pulmonary embolism; PI, principal investigator; SCAI, Society of Cardiovascular Angiography & Interventions; SHM, Society of Hospital Medicine; SIR, Society of Interventional Radiology; SVM, Society for Vascular Medicine; SVN, Society for Vascular Nursing; UCLA, University of California, Los Angeles; VA, Veterans Affairs; and VHA, Veterans Health Administration.