KAISER PERMANENTE®

Pulmonary Embolism Diagnosis & Treatment Guideline

Last guideline approval: November 2022

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

This evidence-based guideline was developed by **Kaiser Permanente Washington (KPWA).**

Changes as of November 2022

- DOACs are now recommended over warfarin as first line treatment for both initial and long-term treatment of PE in adult patients (excluding pregnant women and cancer patients).
- The recommended duration of anticoagulation in adult patients with cancer and VTE has been aligned with the KP National Oncology Drug Treatment Pathway.
- Weight-based limitations on DOAC use were removed due to lack of evidence.
- A follow-up visit 3 months after initiation of treatment is now recommended to assess treatment duration. If treatment is continued beyond 3 months, a follow-up visit at 6 months may be considered to discuss reductions to dosing.

Background

Pulmonary embolism (PE) is a relatively common vascular disease with potentially life-threatening complications in the short term. The accurate incidence of the condition is unknown, but it is estimated that 200,000 to 500,000 patients are diagnosed with PE each year in the United States. Many of these cases are diagnosed in the emergency department (White 2016).

Traditionally, patients with PE are treated in the hospital (usually for 24 hours but up to 5 or 6 days) for initiation of anticoagulation therapy and monitoring for any clinical deterioration. The introduction of low molecular weight heparin (LMWH) and the non-vitamin K–dependent oral anticoagulants, together with the increased ability to accurately stratify patients according to their risk of short-term clinical deterioration, have made it feasible and safe to manage selected low-risk patients in the outpatient setting either entirely or after a short in-hospital observation period.

The 2021 American College of Chest Physicians guidelines (Stevens 2021) recommend treatment at home or early discharge over standard discharge for patients with low-risk PE (strong recommendation, low-certainty evidence).

The purpose of this guideline is five-fold:

- Provide an evidence-based approach to the diagnosis and management of acute pulmonary embolism in clinically stable patients.
- Identify a population of patients newly diagnosed with PE who can be safely managed as outpatients.
- Provide guidance on the preferred anticoagulant for initial and long-term therapy, including the use of direct oral anticoagulants (DOACs).
- Improve patient safety and health outcomes for patients with PE.
- Decrease variation in practice in treating PE.

Target population

The recommendations in this guideline apply to **clinically stable outpatients** who are:

- Adults 18 years or older (non-pregnant) with suspected PE.
- Pregnant adults with suspected PE.
- Adults with malignancy with suspected PE.

Exclusions

This guideline does **not** apply to:

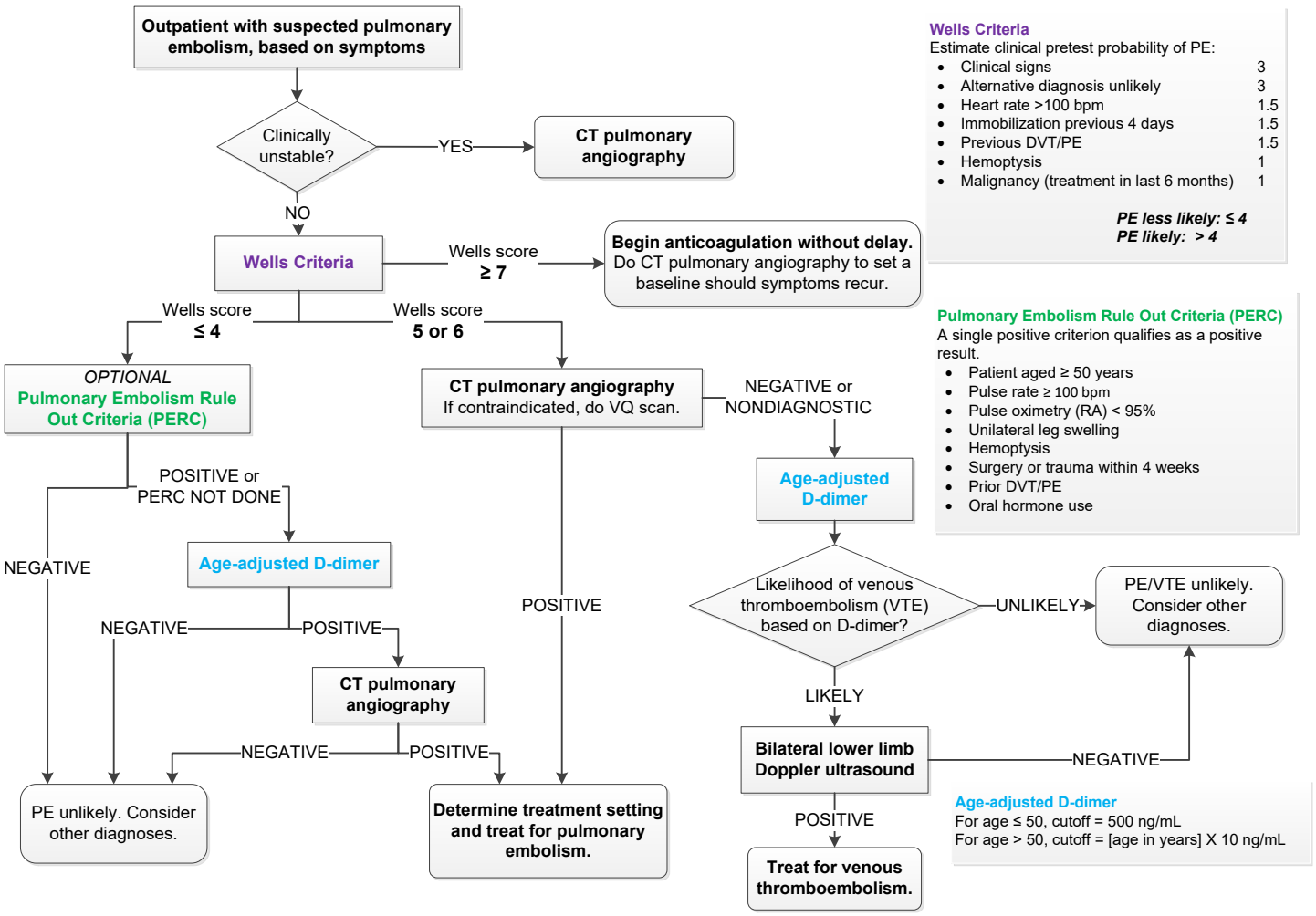
- Clinically unstable patients with suspected PE. These patients should go directly to CT pulmonary angiography.
- Hospitalized patients.
- Patients with established deep vein thrombosis (DVT). These patients may be referred to the KPWA Anticoagulation/Anemia Management Service (AMS).

> ***Note:*** While DVT is outside the scope of this guideline, the recommendations for treatment of pulmonary embolism (see p. 10) can also be applied to patients with DVT.

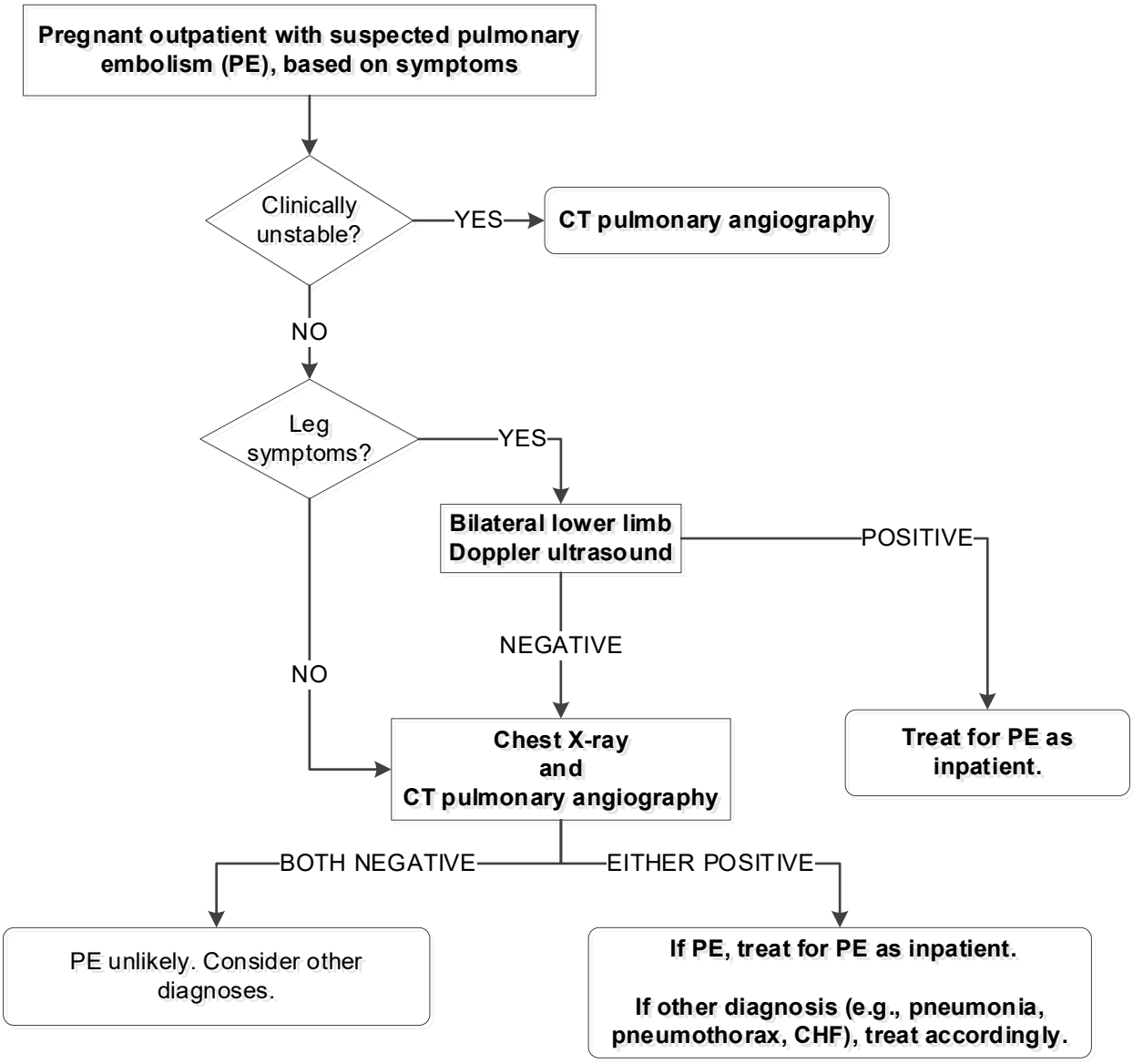
Symptoms of pulmonary embolism

- Pleuritic chest pain
- Shortness of breath
- Dyspnea
- Tachycardia
- Hypoxemia

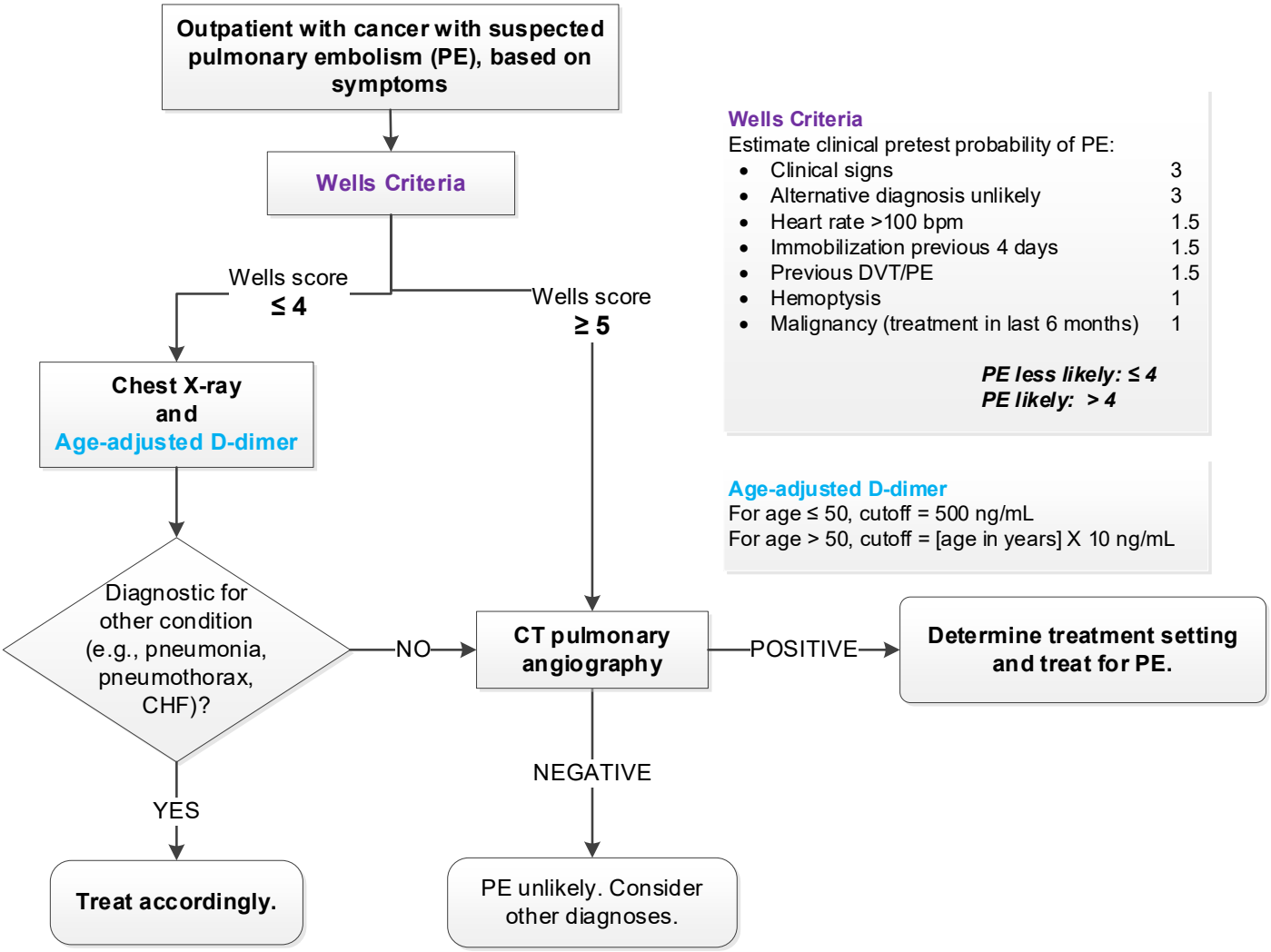
PE Evaluation and Diagnosis: Non-pregnant adults without cancer



PE Evaluation and Diagnosis: Pregnant adults



PE Evaluation and Diagnosis: Adults with active cancer



Wells Criteria

Estimate clinical pretest probability of PE:

• Clinical signs	3
• Alternative diagnosis unlikely	3
• Heart rate >100 bpm	1.5
• Immobilization previous 4 days	1.5
• Previous DVT/PE	1.5
• Hemoptysis	1
• Malignancy (treatment in last 6 months)	1

PE less likely: ≤ 4
PE likely: > 4

Age-adjusted D-dimer

For age ≤ 50, cutoff = 500 ng/mL
For age > 50, cutoff = [age in years] X 10 ng/mL

PE Treatment: Choice of Setting

Inpatient setting
- All pregnant patients
- All patients **not** meeting ACCP criteria
- Patients electing inpatient treatment via shared decision-making

Outpatient setting
Including short-stay observation unit where available.
- Patients meeting ACCP criteria **and** electing outpatient treatment via shared decision-making

Pregnant adults

All pregnant adults with confirmed acute PE should be treated in an **inpatient setting.**

Non-pregnant adults (with or without cancer)

KPWA recommends using the American College of Chest Physicians (ACCP) criteria below to determine which patients with confirmed acute PE are suitable for outpatient treatment and can be safely discharged from urgent care to home. *(Note:* For clinics with short-stay observation units, an additional option is to discharge patients to that unit for shared decision making around choice of treatment setting.)

ACCP criteria for outpatient treatment of acute PE

- Patient is clinically stable with good cardiopulmonary reserve.
- Patient has no contraindications, such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (< 70,000/mm^3).
- Patient has none of the following: right ventricular dysfunction shown on echocardiogram, or signs of right heart strain on CTPA, or increased cardiac biomarkers (troponin or brain natriuretic peptide) levels.
- Patient is expected to be compliant with treatment.
- Patient feels well enough to be treated at home.
- Patient has a **Pulmonary Embolism Severity Index (PESI)** score of < 85:

Pulmonary Embolism Severity Index (PESI)	
Predictor	**Points**
Age	+1 per year
Male sex	+10
Heart failure	+10
Chronic lung disease	+10
Arterial oxygen saturation < 90%	+20
Pulse ≥ 110 beats per minute	+20
Respiratory rate ≥ 30 breaths per minute	+20
Temperature < 36° C/96.8° F	+20
Cancer	+30
Systolic blood pressure < 100 mm Hg	+30
Altered mental status	+60

The PESI is a validated, accurate, easy-to-use tool that can be used at no cost**.** It can be accessed at https://www.mdcalc.com/calc/1304/pulmonary-embolism-severity-index-pesi

Risk classification based on PESI score			
Risk	**PESI score**	**30-day mortality**	**Recommendation**
Class I: Very low risk Class II: Low risk	< 65 66–85	0.1 to 1.6% 1.7 to 3.5%	Offer outpatient treatment to patients in Classes I and II. Discuss the benefits and risks of outpatient treatment.
Class III: Intermediate risk Class IV: High risk Class V: Very high risk	86–105 106–125 > 125	3.2 to 7.1% 4.0 to 11.4% 10.0 to 24.5%	Provide inpatient treatment for patients in Classes III–V.

Outpatient treatment of PE: eligibility and shared decision-making

Outpatient treatment is recommended only for Class I or II patients who have a good understanding of the risks and benefits as well as adequate social support. Studies show that patients with Class I and II PESI scores have similar clinical outcomes when treated with warfarin as either outpatients or inpatients.

All patients eligible for outpatient care should receive shared decision-making about care setting (inpatient versus outpatient) and choice of anticoagulant (warfarin versus DOAC). Patients should receive appropriate education based on their choices.

The following SmartPhrase—**.petreatment**—is available in KP HealthConnect (Epic) to support and document the shared decision making process:

.petreatment

We talked about medication and treatment options for your pulmonary embolism. We reviewed the risks and benefits of the medications and talked about the advantages and disadvantages of outpatient treatment.

You agreed to understanding the risks and benefits and have decided to do {NEW LIST: outpatient/inpatient} treatment.

Here's a summary of what we talked about for treatment during your visit:

Advantages and disadvantages of outpatient treatment	
Advantages: • No or less time in the hospital • More mobility • Lower cost (avoiding co-pays and out-of-pocket expenses associated with inpatient care) • More comfortable in own home	**Disadvantages:** • Concern if something happens that requires immediate medical care • Possible need for routine lab and blood tests • Possible health problems if medication is not taken as prescribed

Additional points to consider when discussing treatment setting with the patient:

- Advantage: Avoiding a hospital stay lowers the risk of hospital-acquired infections or injuries.
- Disadvantage: Possible discomfort with using medications that are administered by self-injection.
- Disadvantage: Potential noncompliance with treatment or lack of reliable follow-up.

Subsegmental and Incidental PE: Treatment Versus Surveillance

There is no high-quality evidence to support a recommendation **for or against** anticoagulation treatment versus clinical surveillance for patients with subsegmental pulmonary embolism.

In patients with subsegmental pulmonary embolism (PE with no involvement of more proximal pulmonary arteries) **and** no proximal DVT in the legs, CHEST (Stevens 2021) suggests:

- Considering factors such as hospitalization, reduced mobility, risk factors for VTE (e.g., familial), cardiopulmonary reserve, bleeding risk, and patient preference,
- Clinical surveillance over anticoagulation for those with a **low risk** of recurrent VTE, and
- Anticoagulation over clinical surveillance for those with a **high risk** of recurrent VTE, including patients with cancer.

However, evidence from CHEST and other external guidelines is weak, with low certainty, and there is no overall consensus on whether subsegmental PE should be treated with anticoagulation or observed. Shared decision-making and clinical judgment can be helpful in this setting.

In patients with cancer, an incidental finding of PE on CT of the chest should be treated the same way as symptomatic PE. In patients without cancer, there is insufficient evidence to recommend treatment of incidental PE.

PE Treatment: Anticoagulant Medications

Note: Treatment recommendations apply to both PE and DVT.

Role of KPWA Anticoagulation/Anemia Management Services (AMS)

- Regardless of anticoagulant chosen, **all** patients with PE should be referred to AMS.
- AMS may help patients transition from an injectable agent to an appropriate oral agent via shared decision-making with patient.
- AMS will monitor patients on oral anticoagulant medications and long-term enoxaparin (e.g., adjusting warfarin to target INR range and DOACs per changes in renal function, drug-drug interactions). AMS will also track adherence to DOAC anticoagulants.
- The referring provider will set a discontinuation date for anticoagulation. AMS will check in with the provider to confirm that the PE has resolved before discontinuing the medication.

Testing prior to choosing and initiating anticoagulant medications

Table 1. Testing recommended prior to choosing and initiating anticoagulant medications

Test(s)	Looking for:	Interpretation/considerations
Complete blood count (hemoglobin/hematocrit, platelets, and white blood cells [WBC])	Myeloproliferative disorder (e.g., polycythemia vera, essential thrombocythemia)	Elevations in hematocrit or platelet count, especially in patients with splenomegaly, should lead to consideration of myeloproliferative disorders. These disorders predispose patients to venous **and** arterial thrombotic events, particularly when the abnormalities are not controlled by therapy.
	Occult neoplasm	Secondary polycythemia or reactive thrombocytosis may suggest underlying malignancy.
	Paroxysmal nocturnal hemoglobinuria	Anemia, leukopenia, and thrombocytopenia are often found in paroxysmal nocturnal hemoglobinuria.
Partial thromboplastin time (PTT)	Antiphospholipid syndrome	If PTT results are abnormal, screen for antiphospholipid antibodies (e.g., anticardiolipin antibody and lupus anticoagulant).
Creatinine/eGFR	Chronic kidney disease	Do not use low molecular weight heparin (LMWH) or fondaparinux in patients with renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 or creatinine clearance < 30 mL/min).
Prothrombin time/ international normalized ratio (PT/INR)	Purpose is to establish baseline before initiating anticoagulation.	

Medication options by population

Table 2. Anticoagulant medication options by population

Population	Warfarin	Low molecular weight heparin (LMWH)	Direct oral anticoagulants (DOACs) [1]
General adult population	**Yes** Given *concurrently* with LMWH for first 5 days until two consecutive INR test results between 2.0 and 3.0.	Only if contraindications to warfarin and DOACs.	**Yes** Rivaroxaban [2] OR Dabigatran, *preceded* by at least 5 days of LMWH
Pregnant adults	No [3]	**Yes**	No [4]
Adults with active cancer	No	**Yes**	Yes [5]
CrCl < 30 ml/min	**Yes**	Shared decision-making [6]	No [5]

1 DOACs are contraindicated for patients with mechanical heart valves.
2 Prior authorization required.
3 Warfarin can be started immediately post-delivery.
4 DOAC can be started immediately post-delivery **if not breastfeeding.**
5 Rivaroxaban should be avoided in gastrointestinal and genitourinary cancers, high bleeding risk situations, and active brain metastasis, or when chemotherapy will cause significant thrombocytopenia. Apixaban (nonformulary DOAC) can be considered in cancer-associated VTE patients with CrCl < 30 mL/min. Dabigatran has not been adequately studied in cancer-associated VTE.
6 Shared decision-making: Hospitalization with heparin may be preferred treatment if CrCl < 15 mL/min.

Warfarin Versus DOACs

Comparison: warfarin versus DOACs		
	Warfarin (Coumadin)	**DOACs**
Years on market	In use for many years. Known long-term side effects. Most common anticoagulant.	Research lacking on • Long-term side effects, and • Relative effectiveness of one DOAC against another.
Dosing	Taken once a day in the evening. Dose might change based on lab test results.	Taken one or two times per day. Dose might change based on lab test results.
Lab tests/monitoring	Protime/INR blood tests as needed to maintain target range.	Annual labs (CrCl, CBC, LFTs). If indicated, CrCl may be repeated quarterly.
Diet	Requires consistent intake of foods containing vitamin K.	No specific dietary restrictions.
Drug interactions	Interacts with many drugs.	Fewer drug interactions. DOACs should be avoided with P-gp inducers and 3A4 inducers such as carbamazepine and phenytoin.
Use in patients with reduced renal function	Can be used no matter what the renal function.	DOACs have only been studied in patients with CrCl > 30.
Intervention to stop dangerous bleeding	Vitamin K.	General measures to control bleeding can be used. Reversal agents are available on a limited basis.
Cost	Low cost; generic available.	More expensive; dabigatran generic is anticipated in 2023.

Aspirin

For patients who are **unable or unwilling to use warfarin, heparin, or DOACs,** aspirin may be considered for long-term anticoagulation.

Anticoagulant medication dosing for pulmonary embolism

Table 3. Anticoagulant medication dosing for pulmonary embolism

Population	Drug
General adult population	**DOAC – *preferred class*** **Rivaroxaban** [3] **– *PA required*** 15 mg twice daily with food x 21 days, then 20 mg daily with food. Can consider reducing dose to 10 mg once daily after 6 months of treatment. **OR** **Dabigatran** [3,4] – 150 mg twice daily. ***Must be preceded*** by at least 5 days **low molecular weight heparin (LMWH).** **2nd line - Warfarin** In patients likely to be warfarin-sensitive, [1] 5 mg initial dose; in patients without sensitivity, 10 mg daily x 2 doses; then dose per AMS. **and** ***Concurrent* LMWH** for minimum 5 days: **Enoxaparin** [2] – 1 mg/kg every 12 hours. **and** Two consecutive **INR test results** between 2.0 and 3.0.
Pregnant adults [5]	**1st Line - Low molecular weight heparin** **Enoxaparin** – 1 mg/kg every 12 hours. Further management by OB. **2nd Line - Unfractionated subcutaneous heparin (IV)** – 80 units/kg bolus followed by 18 units/kg/hour infusion. Adjust dose based on PTT every 12 hours.
Adults with active cancer	**Low molecular weight heparin** [6] **Enoxaparin (preferred)** [7] – 1 mg/kg every 12 hours. **OR** **DOAC** **Rivaroxaban PA** [3] – 15 mg twice daily with food x 21 days, then 20 mg daily with food. ***or*** **Apixaban NF** [8] – 10 mg twice daily with food x 7 days, then 5 mg twice daily

1 Patients who are sensitive to warfarin include those with malnutrition, malabsorption, decompensated CHF, postoperative major non-cardiac surgery (NPO > 3 days), chronic liver disease, known malignancy, baseline INR > 1.4, and those taking the following medications: amiodarone, fluconazole, metronidazole, propafenone, quinolones, or sulfa-containing medications.

2 Follow dose recommendations enoxaparin for patients with renal impairment:
- CrCl 30–50 mL/min: 0.85 mg/kg every 12 hours.
- CrCl < 30 mL/min: 1 mg/kg every 24 hours.

3 CrCl < 30 mL/min: Avoid use.

4 CrCl < 50 mL/min: Avoid use if clinically significant drug interactions.

5 Doses initially based on pregnancy weight.

6 If GFR < 15 mL/min, use heparin IV then bridge to warfarin PO. *Note:* To convert GFR to CrCl, use .CRCL.

7 If patient with BMI > 40 kg/m^2, consider enoxaparin 0.8 mg/kg SQ BID.

8 Use if CrCl < 30 mL/min or per KP National Oncology Drug Treatment Pathway.

Duration of anticoagulation treatment

Most PE patients require a minimum of 3 months of anticoagulation, with some patients requiring treatment for 6 to 12 months or indefinitely. Extending the duration of anticoagulation treatment reduces the risk of recurrent PE, but at the same time, increases the risk of bleeding. The patients most likely to benefit from indefinite treatment are those with a high risk of recurrence and a low risk of bleeding. For patients with a higher bleeding risk, a reduced dose of rivaroxaban or apixaban can be considered after the first 6 months of treatment.

- A check-back visit 3 months after initiation of treatment is recommended to assess treatment duration.
- If treatment is continued beyond 3 months, a check-back visit at 6 months may be considered to discuss reductions to dosing.

PE with reversible risk factors (formerly called "provoked" PE) is PE caused by a known event, such as surgery, hospital admission, malignancy, pregnancy, or reduced mobility. **PE with no identifiable risk factors** (formerly called "unprovoked" PE) is PE with no identifiable cause.

The risk of a recurrent PE in the first year is higher for patients with no identifiable risk factors than for patients with reversible risk factors (10% versus 1%) and higher after the second episode of PE than the first (15% versus 5%). The risk of recurrence declines by 50% after the first year. Based on moderate evidence, the risk of a recurrent PE is about 10% higher in men than women (Khan 2019).

Bleeding risk factors include

- Active bleeding
- Acquired bleeding disorder
- Thrombocytopenia
- Lumbar puncture/epidural/spinal anesthesia within the previous 4 hours or expected within the next 12 hours
- Active stroke
- Current use of anticoagulants
- Uncontrolled systolic hypertension (> 230/120 mm Hg)
- Untreated inherited bleeding disorders such as hemophilia or von Willebrand disease
- High fall risk

Anticoagulation treatment duration by population

Note: Repeat imaging is not required before stopping anticoagulation unless the patient is symptomatic.

Table 4. Anticoagulation treatment duration by population
Note: Use shared decision-making with the patient to determine the treatment duration.

Population	PE with reversible risk factors	PE with no identifiable risk factors	
		Low risk of bleeding	*High risk of bleeding*
General adult population	3 months	Indefinite period	3 months
Pregnant adults	At least 3 months total, including at least 6 weeks post-delivery	At least 3 months total, including at least 6 weeks post-delivery	At least 3 months total, including at least 6 weeks post-delivery
Adults with active cancer	Indefinite period	Indefinite period	Indefinite period

Follow-up and Monitoring

For anticoagulant dose adjustments, see the AMS Process and Guidelines SharePoint.

Table 5. Recommended lab monitoring of patients currently receiving anticoagulation treatment

Anticoagulant	Test(s)	Frequency	Condition/ complication	Interpretation/next steps
LMWH	CBC	Every 2–3 days from days 6 to 14, then every 1–3 months thereafter.	Thrombocytopenia	**Stop** LMWH. Consider direct thrombin inhibitor treatment.
	Serum creatinine	Every 1–3 months or change in renal function or bleeding suspected or confirmed.	—	Adjust enoxaparin dose if needed.
	Patient weight	Every 1–3 months.	—	Adjust enoxaparin dose if needed.
	Anti-Xa [1]	Measure peak 4 hours after dose after a minimum of 3 doses, then again if adjustment is needed.	—	Target anti-Xa levels. Every 12 hours dosing: 0.5–1.0 units/mL.
Heparin	CBC	Every 2–3 days from days 6 to 14, then every 1–3 months thereafter.	Heparin-induced thrombocytopenia (HIT) [2]	**Stop** heparin. Consider direct thrombin inhibitor treatment.
	Serum creatinine	Every 1–3 months or change in renal function or bleeding suspected or confirmed.	—	Adjust heparin dose if needed.
Warfarin	CBC	Annually.	Thrombocytopenia	—
	PT/INR	Every 1–3 days until INR is in range for 2 consecutive measurements, then gradually extend per AMS protocol up to maximum of 12 weeks between tests.	Warfarin-induced hypercoagulation or hypocoagulation	Adjust dose per warfarin dosing calculator or per AMS.
Dabigatran	CBC	Annually.	Thrombocytopenia	—
	Serum creatinine	Annually. Check every 3–6 months if CrCl is between 30–49 mL/min.	—	**Stop** dabigatran if CrCl < 30 mL/min. Change to another anticoagulant.
Rivaroxaban	CBC	Annually.	Thrombocytopenia	—
	Serum creatinine	Annually. Check every 3–6 months if CrCl is between 30–49 mL/min	—	**Stop** rivaroxaban if CrCl < 15–30 mL/min. Change to another anticoagulant.
	LFTs	Annually.	Hepatic impairment	**Stop** rivaroxaban if moderate to severe hepatic impairment (Child-Pugh class B or C) or any hepatic disease associated with coagulopathy.
Apixaban	CBC	Annually.	Thrombocytopenia	—
	Serum creatinine	Annually.	—	
	LFTs	Annually.	Hepatic impairment	Stop apixaban if severe hepatic impairment (Child-Pugh class C). Use with caution if moderate impairment (Child-Pugh class B).

[1] **Only in special patient populations: severe renal dysfunction (CrCl < 30 mL/min) or pregnancy.** Use chromogenic, not clot-based, assays.

[2] The manufacturer recommends discontinuation of therapy if platelets are < 100,000/mm³.

Table 6. Testing to consider in patients with recurrent VTE/suspected thrombophilia	
Eligible population [1]	**Tests** [2]
Patients with a recurrent idiopathic thrombosis (more than one event)	All: • Factor V Leiden • Factor II mutation • Protein C and S • Lupus anticoagulant • Antithrombin III
Patients with an unprovoked event and • Age < 50 years, **or** • With a family history of VTE among one or more first-degree relatives	All of the above
Patients with a massive VTE or VTE in unusual location (portal, hepatic, mesenteric, or cerebral vein)	All of the above and • JAK2 mutation

[1] Consider consult with Hematology for patients with any of these risk factors. Thrombophilia testing should generally be avoided during acute phase of VTE.

[2] For patients on warfarin, this testing should be done 3–4 weeks after discontinuation of treatment. For patients on a DOAC, this testing can be done during treatment.

Evidence Summary

The Pulmonary Embolism Diagnosis & Treatment Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

Key questions addressed in the KPWA evidence review

1. What is the optimal initial and long-term management of acute pulmonary embolism (PE) in adult patients, excluding pregnant women and cancer patients?
2. What is the optimal duration of anticoagulation after a first episode of acute PE in adult patients, excluding pregnant women and cancer patients?
3. What is the optimal initial and long-term management of acute PE in pregnant women?
4. What is the optimal initial and long-term management of acute PE in adult patients with cancer?
5. What are the most accurate and validated evidence-based criteria or risk stratification tools for identifying patients with acute PE who can be safely and effectively treated as outpatients?
6. Does the early discharge and outpatient treatment of selected patients with acute PE have outcomes equivalent or non-inferior to inpatient treatment in terms of mortality, bleeding, recurrence of PE, and patient satisfaction?
7. What is the appropriate management strategy for patients with isolated or incidental subsegmental pulmonary embolism (SSPE)?
8. Is the Wells score more effective (diagnostic accuracy) than the Geneva score or the revised Geneva score in discriminating PE in suspected patients?
9. What is the validity of predictive scores for the diagnosis of PE in hospitalized COVID-19 patients?
10. Are there racial disparities in PE management/outcomes?

External guidelines meeting KPWA criteria for adaptation/adoption

2021 CHEST Guideline and Expert Panel Report. Antithrombotic Therapy for VTE Disease Second Update. (Stevens 2021)

2020 American Society of Hematology (ASH) 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. (Ortel 2020)

2020 National Institute for Health and Care Excellence (NICE).Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. (NICE 2020)

2019 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. (Konstantinides 2019)

1. What is the optimal initial and long-term management of acute PE in adult patients, excluding pregnant women and cancer patients?

The 2016 CHEST guidelines (Kearon 2016) recommend DOAC over vitamin K agonists (VKAs) for initial and long-term (3 months) management and extended anticoagulant. These recommendations did not change in 2021. The 2020 ASH guidelines (Ortel 2020) also recommend DOAC over VKA for initial and long-term treatment of VTE.

A number of studies were identified from a search conducted from 2021 to July 2022. The studies compared thrombolytic versus heparin (Zuo 2021), or VKA versus DOAC (Alhousani 2021). The studies were of low quality and did not change the recommendations of the 2021 CHEST guidelines or the 2020 ASH guidelines. Another study (Su 2022) assessed the comparative efficacy and safety of the different DOACs, but the evidence is insufficient to make a firm recommendation regarding the most effective and safest DOAC.

For aspirin versus anticoagulant therapy, or anticoagulant therapy versus no anticoagulant in patients with incidentally diagnosed asymptomatic acute pulmonary embolism, or anticoagulant therapy versus no anticoagulant therapy in patients with isolated distal DVT, no high-quality studies challenge the 2021 CHEST guidelines (Stevens 2021).

2. What is the optimal duration of anticoagulation after a first episode of acute PE in adult patients, excluding pregnant women and cancer patients?

The 2021 CHEST guidelines and 2020 ASH guidelines should be adopted.

3. What is the optimal initial and long-term management of acute PE in pregnant women?

No new high-quality studies add or change the current KPWA evidence review recommendations/2019 ESC guidelines (Konstantinides 2019). Prophylaxis: The quality of evidence is very low to support the benefits and harms of VTE thromboprophylaxis in women at increased risk of VTE during pregnancy and the early postnatal period.

4. What is the optimal initial and long-term management of acute PE in adult patients with cancer?

The 2021 CHEST guidelines and 2020 ASH guidelines should be adopted. Please refer to recommendations above.

In addition to the above guidelines, two systematic reviews (Alexander 2021, Song 2021) (not reviewed comprehensively) suggest that patients with cancer and VTE are candidates for indefinite anticoagulation and that DOACs are more effective than LMWH in the treatment phase (3 months).

The 2021 CHEST guidelines differ from the 2020 ASH guidelines on the initial phase of PE anticoagulation therapy. A meta-analysis (of the four major RCTs comparing DOACs and LMWH) performed in the RCT (Planquette 2022) evaluated DOACs and LMWH (dalteparin) for the treatment of acute CAT reported a significantly lower risk of recurrent VTE for DOACs and a comparable risk of major bleeding between the two medications. These findings indicate that DOACs are effective in the acute phase and comparable to LMWH in terms of major bleeding.

For incidental VTE, a meta-analysis (Caiano 2021) of RCTs indicated a significantly lower rate of recurrent VTE in patients with incidental VTE compared to those with symptomatic VTE (RR 0.62 [0.44–0.87]). There was no difference in the risk of major bleeding between the two groups (RR 1.47 [0.99–2.20]). No difference was reported in terms of mortality between the groups.

5. What are the most accurate and validated evidence-based criteria or risk stratification tools for identifying patients with acute PE who can be safely and effectively treated as outpatients?

Current guidelines (refer to above) suggest a stratification approach or criteria for the suitability of outpatient treatment in patients with PE. Each guideline above defines its criteria, but there are similarities among them. The 2020 NICE guideline recommends the pulmonary embolism rule-out criteria (PERC) and the 2-level PE Wells score when offering outpatient treatment to people with suspected PE. The supporting evidence of the PERC is very low to low. The 2019 ESC guideline recommends the PESI or sPESI or the HESTIA criteria; regarding the assessment of clinical (pre-test)

probability, the revised Geneva rule and the Wells rule are the most frequently used prediction rules. KPWA currently uses the American College of Chest Physicians (ACCP) rule, which contains PESI < 85 as a criterion for outpatient management. According to the 2017 KPWA evidence review, PESI is one of the most validated and studied scores for outpatient management of PE patients, and there is fair evidence that the PESI clinical prediction rules can accurately identify low-risk patients with hemodynamically stable acute PE.

In addition to the external guidelines, a non-inferiority RCT (Roy 2021) reported both strategies, sPESI and Hestia, are effective and that the Hestia criteria are non-inferior to the sPESI with regard to the 30-day composite complication rate.

No new studies challenge the PESI/sPESI or Hestia, which are recommended by the 2019 ESC guideline. This guideline should be adopted.

6. Does the early discharge and outpatient treatment of selected patients with acute PE have outcomes equivalent or non-inferior to inpatient treatment in terms of mortality, bleeding, recurrence of PE, and patient satisfaction?

Both the 2021 CHEST and 2020 ASH guidelines recommend outpatient treatment over hospitalization in low-risk patients with PE. Their recommendations are based on low-quality evidence.

A systematic review and meta-analysis of two RCTs (Yoo 2022), from Cochrane, indicates no difference in treatment effect for recurrence of PE, major bleeding, and mortality.

7. What is the appropriate management strategy for patients with isolated or incidental subsegmental pulmonary embolism (SSPE)?

The 2021 CHEST guidelines suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) in patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have low risk for recurrent VTE. However, in patients who have high risk for recurrent VTE, anticoagulation over clinical surveillance is recommended (weak recommendation, low-certainty evidence).

For incidental asymptomatic acute PE, the 2021 CHEST guidelines suggest similar treatment as for patients with symptomatic PE (weak recommendation, moderate-certainty evidence).

In patients with cancer and incidental PE, the 2020 ASH guidelines suggest short-term anticoagulation over observation (very low-certainty evidence).

A systematic review from Cochrane (Yoo 2020) reported no evidence from RCTs to assess the efficacy and safety of anticoagulants in this population. The 2021 CHEST and 2020 AHS guidelines should be adopted.

8. Is the Wells score more effective (diagnostic accuracy) than the Geneva score or the revised Geneva score in discriminating PE in suspected patients?

Seven studies including a systematic review and meta-analysis (Shen 2016) and six observational studies—two prospective (Coelho 2020, Di Marca 2015) and four retrospective (Gruettner 2015, Girardi 2020, Ma 2016, Simon 2021) were reviewed. The studies were all of low quality and the findings from two studies (Coelho 2020, Gruettner 2015) suggested a comparable performance (accuracy) between the two prediction rules. However, the remaining five studies found the Wells score to be more accurate in discriminating PE than the revised Geneva score. The discriminating power was assessed by the area under the receiving operating characteristic (ROC) curve (AUC).

9. What is the validity of predictive scores for the diagnosis of PE in hospitalized COVID-19 patients?

The 2019 ESC suggests algorithms combining pre-test probability assessments and D-dimer tests can be used in case of suspected acute PE.

The Wells score and the revised Geneva score are the most studied. The evidence is either insufficient in quality, or the predictive scores are not good predictors of PE in COVID-19 patients, or the findings are mixed (one study found that the revised Geneva score is superior to the Wells score). Further studies are needed. The available evidence shows unsatisfactory or low diagnostic accuracy.

A systematic review (Rindi 2022) of prospective and retrospective studies shows an AUC of 0.54 for Wells score when used alone and AUC of 0.727 (95% CI, 0.525–0.929) for the revised Geneva score. The diagnostic accuracies of the following three scores— CHADS2, CHA2DS2-VASc, and the M-CHA2DS2VASc—were unsatisfactory (AUC 0.497, 0.490, and 0.541, respectively).

A retrospective study (Silva 2021) reported that none of the prediction rules (Wells, revised Geneva, YEARS, PEGeD) are good predictors of PE in COVID-19 patients. Wells and Geneva scores showed no predictive value for PE occurrence, irrespective of standard or age-adjusted D-dimer cut-off (OR 1.084; 95% CI, 0.841–1.396, p = 0.533; OR 1.023, 95% CI 0.869–1.205, p = 0.784, respectively). AUCs ranged from 0.52 to 0.58, indicative of unsatisfactory discriminative power.

A longitudinal study (Quezada-Feijoo 2021) reported that the revised Geneva score is superior to the Wells score for classifying elderly patients with COVID-19 and suspected PE (AUC 0.74 vs 0.65). The combination of high D-dimer value (> 4.3 mg/mL) and clinical scores increases specificity.

10. Are there racial disparities in PE management/outcomes?

Several studies suggest the existence of racial disparities in PE.

In one study (Martin 2020),the rates of PE hospitalization were higher among non-Hispanic Black men and women than non-Hispanic white men and women in all age groups (14.5 and 16.5 versus 8.8 and 9.3 per 10,000 population, respectively). In younger patients (< 65 years), racial disparities were obvious because the rate of hospitalization among non-Hispanic Black patients was twice that of non-Hispanic white patients (Rate Ratio 1.9, 95% CI, 1.5–2.3).

A study (Sanaiha 2018) using data from the Nationwide Inpatient Sample showed disparities in incidence of PE among adult colectomy patients. The incidence of PE was significantly higher in Black patients than white patients (1.5% vs 0.9%, p < 0.001) and Hispanics (1.5% vs 0.8%, p < 0.001).

One retrospective study (Phillips 2021) showed an association between Black race and higher PE severity after matching on age and sex (OR, 1.08 [1.03–1.14]) and controlling for clinical and socio-economic characteristics. There was also an association between Black race and low risk of receiving any intervention, especially among participants with intermediate and high-severity PE. There was no association between race and in-hospital mortality.

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Guideline Development Process and Team

Development process

To develop the Pulmonary Embolism Diagnosis & Treatment Guideline, the guideline team adapted recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards. Additionally, the team used an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in November 2022.

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