

# Pulmonary Embolism Diagnosis & Treatment Guideline

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## Last guideline approval: September 2020

**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 September 2020

This 2020 guideline update has only minor differences from the previous (2017) version. The changes are based on the 2019 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism, and include recommendations for the expanded use of direct oral anticoagulants (DOACs) for patients with cancer, recommendations to treat subsegmental and incidental PE in patients with cancer, and options for reduced dosing of DOACs for long-term use for all patients with PE.

## 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 potentially feasible and safe to manage selected low-risk patients in the outpatient setting either entirely or after a short in-hospital observation period.

The 2016 American College of Chest Physicians Guidelines treatment at home or early discharge over standard discharge for patients with low-risk PE (2B recommendation). Many physicians still have concerns regarding the outpatient treatment or early discharge of low-risk PE patients (Singer 2016).

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

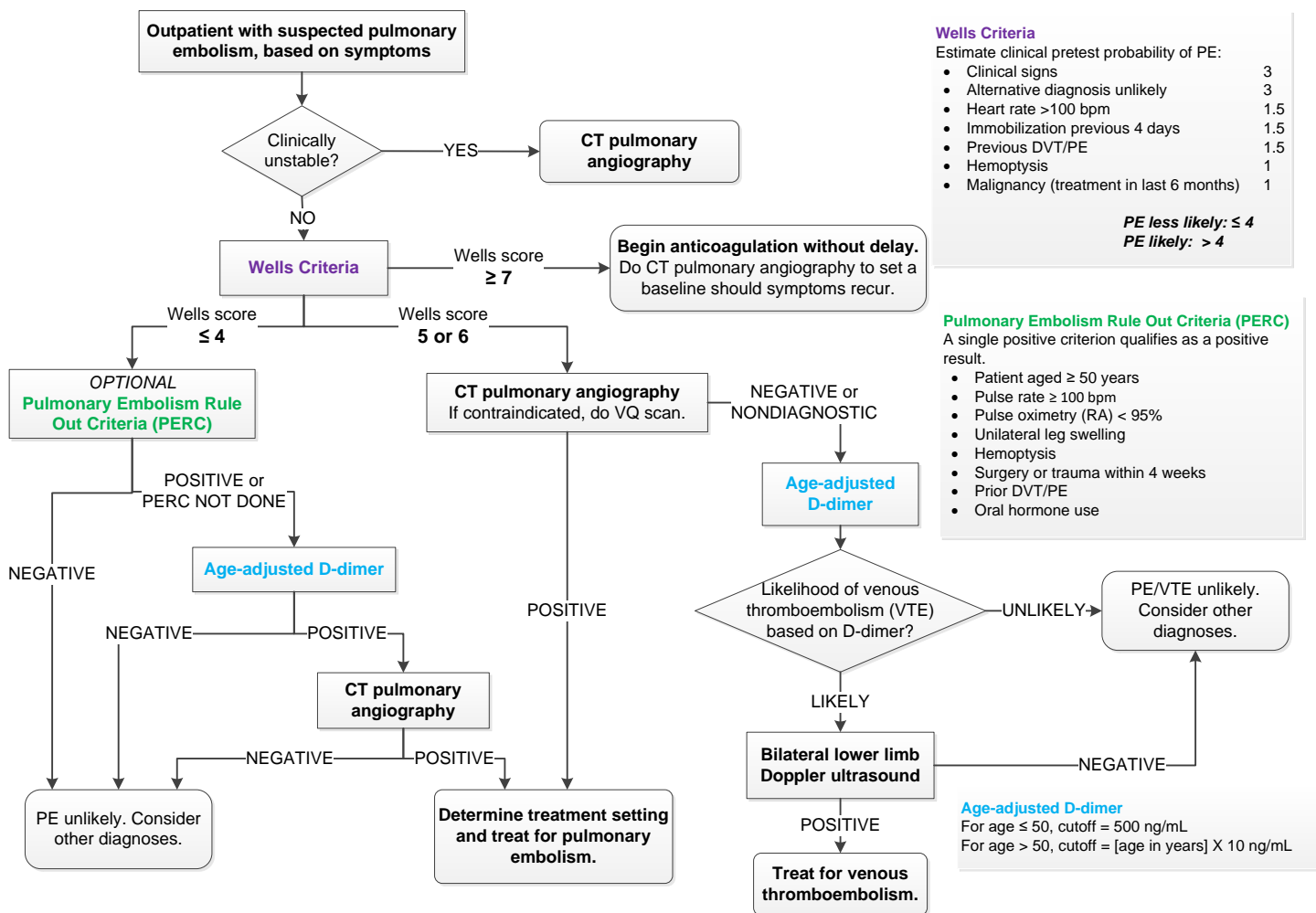
- Pleuritic chest pain
- Shortness of breath
- Dyspnea
- Tachycardia
- Hypoxemia

## Abbreviations

ACCP	American College of Chest Physicians	PERC	Pulmonary Embolism Rule-out Criteria
DOACs	Direct oral anticoagulants	PESI	Pulmonary Embolism Severity Index
DVT	Deep vein thrombosis	SSPE	Subsegmental pulmonary embolism
LMWH	Low molecular weight heparin	UFH	Unfractionated heparin
PE	Pulmonary embolism	VTE	Venous thromboembolism

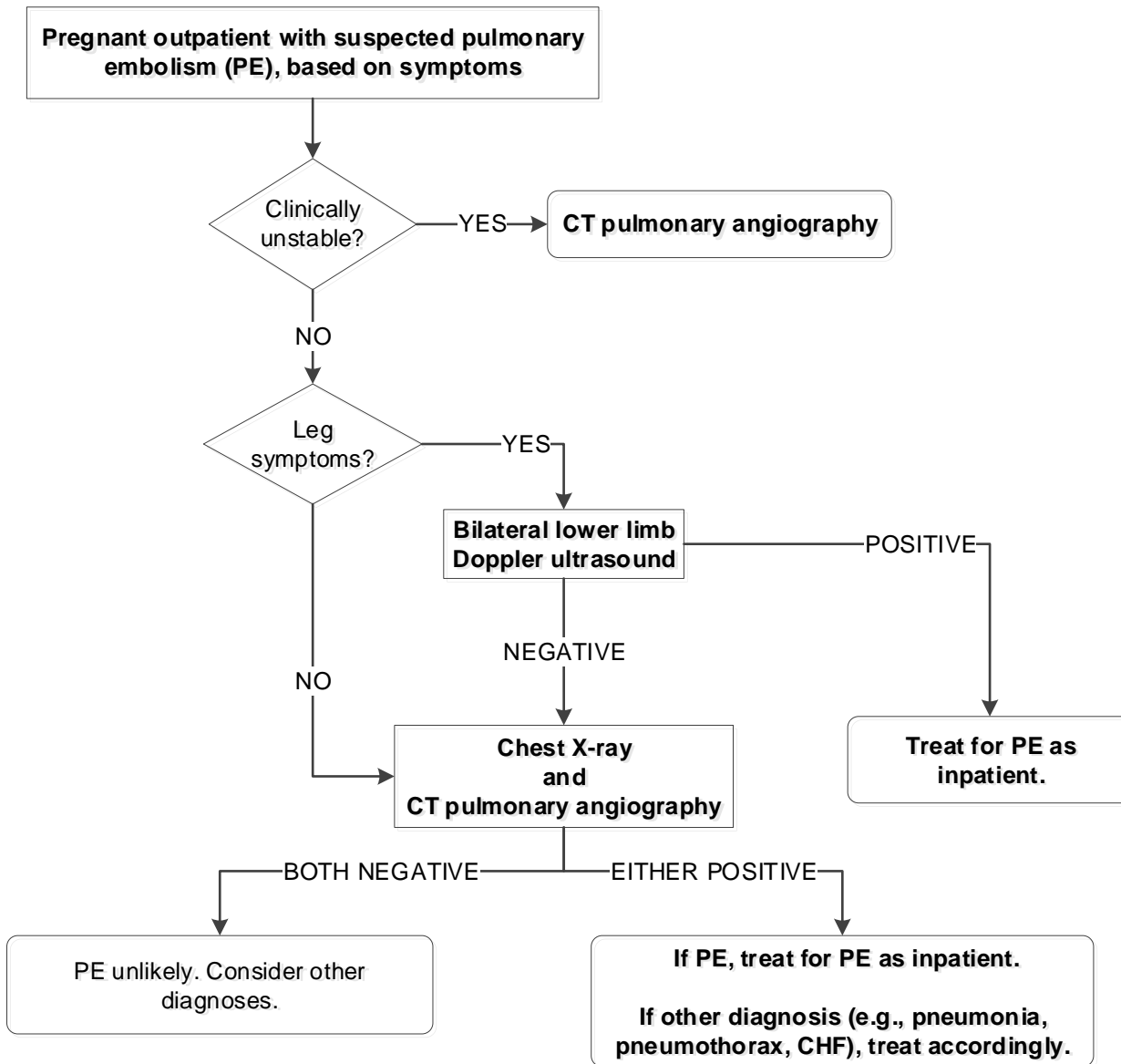
# PE Evaluation and Diagnosis: Non-pregnant Adults Without Cancer

This algorithm is based on ICSI 2013.



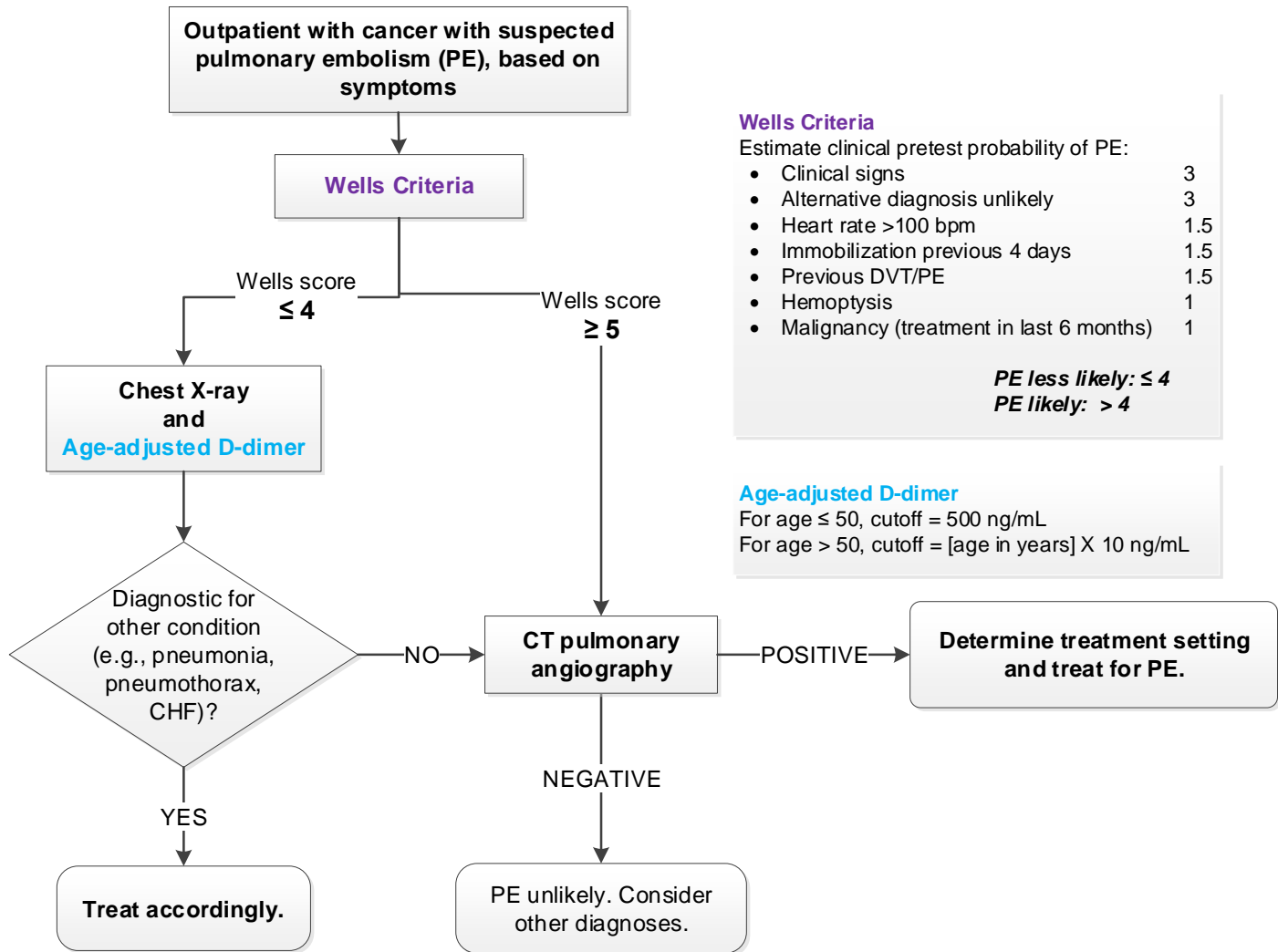
# PE Evaluation and Diagnosis: Pregnant Adults

This algorithm is based on Leung 2012.



# PE Evaluation and Diagnosis: Adults with Cancer

This algorithm is based on NCCN 2016.



## PE Treatment: Choice of Setting

### Inpatient setting

- All pregnant women
- 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 ( $< 70,000/\text{mm}^3$ ).
- 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 $\geq 110$ beats per minute	+20
Respiratory rate $\geq 30$ breaths per minute	+20
Temperature $< 36^\circ \text{C}/96.8^\circ \text{F}$	+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 <http://www.mdcalc.com/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:

<b>Advantages and disadvantages of outpatient treatment</b>	
<b>Advantages:</b> <ul style="list-style-type: none"><li>• No or less time in the hospital</li><li>• More mobility</li><li>• Lower cost (avoiding co-pays and out-of-pocket expenses associated with inpatient care)</li><li>• More comfortable in own home</li></ul>	<b>Disadvantages:</b> <ul style="list-style-type: none"><li>• Concern if something happens that requires immediate medical care</li><li>• Possible need for routine lab and blood tests</li><li>• Possible health problems if medication is not taken as prescribed</li></ul>






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. CHEST (2016) recommends considering factors such as hospitalization, reduced mobility, risk factors for VTE (e.g., familial), cardiopulmonary reserve, bleeding risk, and patient preference.

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

- **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.

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.

## 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 <b>and</b> 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 LMWH or fondaparinux in patients with renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m <sup>2</sup> 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) <sup>1</sup>
General adult population	<b>Yes</b> Given <i>concurrently</i> 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.	<b>Yes</b> Rivaroxaban <sup>2</sup> (preferred DOAC). Dabigatran, <i>preceded</i> by at least 5 days of LMWH.
Pregnant adults	No <sup>3</sup>	<b>Yes</b>	No <sup>4</sup>
Adults with cancer	No	<b>Yes</b>	Yes <sup>5</sup>
<sup>1</sup> Additional DOACs are available; contact Pharmacy for more information. DOACs are contraindicated for patients with mechanical heart valves. <sup>2</sup> Prior authorization required. <sup>3</sup> Warfarin can be started immediately post-delivery. <sup>4</sup> DOAC can be started immediately post-delivery <b>if not breastfeeding</b> . <sup>5</sup> Rivaroxaban may be prescribed as an alternative to heparin for patients with most cancers, with the exception of gastrointestinal cancer (due to the increased risk of bleeding). In patients with PE related to gastrointestinal cancer, apixaban (nonformulary DOAC) can be considered.			

## Warfarin Versus DOACs

Comparison: warfarin versus DOACs		
	Warfarin (Coumadin)	DOACs
<b>Years on market</b>	In use for many years. Known long-term side effects. Most common anticoagulant.	Relatively new. Research lacking on <ul style="list-style-type: none"> <li>• Long-term side effects, and</li> <li>• Relative effectiveness of one DOAC against another.</li> </ul>
<b>Dosing</b>	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.
<b>Lab tests/monitoring</b>	Protime/INR blood tests as needed to maintain target range.	Annual labs (CrCl, CBC, LFTs). If indicated, CrCl may be repeated quarterly.
<b>Diet</b>	Requires consistent intake of foods containing vitamin K.	No specific dietary restrictions.
<b>Drug interactions</b>	Interacts with many drugs.	Fewer drug interactions. DOACs should be avoided with P-gp inducers and 3A4 inducers such as carbamazepine and phenytoin.
<b>Intervention to stop dangerous bleeding</b>	Vitamin K.	General measures to control bleeding can be used. Reversal agents are available on a limited basis.
<b>Cost</b>	Low cost, generic available.	More expensive, no generic available.

## 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	“Line”	Drug
General adult population <sup>1</sup>	1st	<p><b>Warfarin</b></p> <p>In patients likely to be warfarin-sensitive, <sup>2</sup> 5 mg initial dose; in patients without sensitivity, 10 mg daily x 2 doses; then dose per AMS.</p> <p><b>and</b></p> <p><b>Concurrent low molecular weight heparin (LMWH)</b> for minimum 5 days:</p> <p><b>Enoxaparin</b> <sup>3</sup> – 1 mg/kg every 12 hours.</p> <p>or</p> <p><b>Dalteparin NF</b> – 200 IU/kg/day once daily.</p> <p>or</p> <p><b>Fondaparinux PA</b></p> <p>If heparin-induced thrombocytopenia (HIT):</p> <p>&lt; 50 kg: 5 mg once daily</p> <p>50–100 kg: 7.5 mg once daily</p> <p>&gt; 100 kg: 10 mg once daily</p> <p><b>and</b></p> <p>Two consecutive <b>INR test results</b> between 2.0 and 3.0.</p> <p><b>or</b></p>
	1st	<p><b>Rivaroxaban PA</b> <sup>4</sup> – 15 mg twice daily with food x 21 days, then 20 mg daily with food. Consider reducing dose to 10 mg once daily after 6 months of treatment.</p>
	2nd	<p><b>Dabigatran</b> <sup>4,5</sup> – 150 mg twice daily <b>Must be preceded</b> by at least 5 days <b>LMWH</b>.</p>
Pregnant adults <sup>6</sup>	1st	<p><b>Low molecular weight heparin</b></p> <p><b>Enoxaparin</b> – 1 mg/kg every 12 hours. Further management by OB.</p>
	2nd	<p><b>Unfractionated subcutaneous heparin (IV)</b> – 80 units/kg bolus followed by 18 units/kg/hour infusion. Adjust dose based on PTT every 12 hours.</p>
Adults with cancer	1st	<p><b>Low molecular weight heparin</b></p> <p><b>Enoxaparin (preferred)</b> – 1 mg/kg every 12 hours.</p> <p>or</p> <p><b>Dalteparin NF</b> – (200 IU/kg/day) once daily.</p> <p><b>or</b></p>
	1st	<p><b>DOAC</b></p> <p><b>Rivaroxaban PA</b> <sup>4</sup> – 15 mg twice daily with food x 21 days, then 20 mg daily with food.</p> <p>or</p> <p><b>Apixaban PA</b> – 10 mg twice daily x 7 days, then 5mg twice daily.</p>
<sup>1</sup>	<p>Weight</p> <ul style="list-style-type: none"> <li>&lt; 50 kg: Avoid all DOACs.</li> <li>&gt; 120 kg: Warfarin preferred</li> </ul>	
<sup>2</sup>	<p>Patients who are sensitive to warfarin include those with malnutrition, malabsorption, decompensated CHF, postoperative major non-cardiac surgery (NPO &gt; 3 days), chronic liver disease, known malignancy, baseline INR &gt; 1.4, and those taking the following medications: amiodarone, fluconazole, metronidazole, propafenone, quinolones, or sulfa-containing medications.</p>	
<sup>3</sup>	<p>Follow dose recommendations for patients with renal impairment:</p> <ul style="list-style-type: none"> <li>CrCl 30–50 mL/min: 0.85 mg/kg every 12 hours.</li> <li>CrCl &lt; 30 mL/min: 1 mg/kg every 24 hours.</li> </ul>	
<sup>4</sup>	<p>CrCl &lt; 30 mL/min: Avoid use.</p>	
<sup>5</sup>	<p>CrCl &lt; 50 mL/min: Avoid use with drug interactions.</p>	
<sup>6</sup>	<p>Doses initially based on pregnancy weight.</p>	

## 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. If indefinite treatment is deemed appropriate, a reduced dose of rivaroxaban or apixaban can be considered after the first 6 months of treatment.

**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.

**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			
Population	PE with reversible risk factors	PE with no identifiable risk factors	
		<i>Low risk of bleeding</i>	<i>High risk of bleeding</i>
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 cancer	Indefinite period	Indefinite period	Indefinite period

## Follow-up and Monitoring

### Role of KPWA Anticoagulation/Anemia Management Services (AMS)

- Patients who are discharged from Urgent Care on anticoagulation will be referred to AMS for follow-up. If the AMS referral has not been ordered at discharge, Primary Care will submit the referral order.
- AMS may help patients transition from an injectable agent to an appropriate oral agent via shared decision-making with patient.
- AMS will monitor all patients on anticoagulant medications. In addition to the lab monitoring listed in Table 5, AMS will track patients’ adherence to 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.

**Table 5. Recommended lab monitoring of patients currently receiving anticoagulation treatment**  
 For anticoagulant dose adjustments, see the [AMS Process and Guidelines page](#) on the KPWA staff intranet.

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	<b>Stop</b> 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 <sup>1</sup>	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) <sup>2</sup>	<b>Stop</b> 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	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 months if CrCl is between 30–49 mL/min.	—	<b>Stop</b> dabigatran if CrCl < 30 mL/min. Change to another anticoagulant.
Rivaroxaban	CBC	Annually.	Thrombocytopenia	—
	Serum creatinine	Annually. Check every 3 months if CrCl is between 30–49 mL/min	—	<b>Stop</b> rivaroxaban if CrCl < 30 mL/min. Change to another anticoagulant.
	LFTs	Annually	Hepatic impairment	<b>Stop</b> 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. Check every 3 months for serum creatinine ≥ 1.5 mg/dL	—	If serum creatinine ≥ 1.5 mg/dL <b>and either</b> age ≥ 80 years <b>or</b> body weight ≤ 60 kg, then reduce dose to 2.5 mg twice daily.
	LFTs	Annually	Hepatic impairment	Stop apixaban if severe hepatic impairment (Child-Pugh class C). Use with caution if moderate impairment (Child-Pugh class B).
<sup>1</sup>	<b>Only in special patient populations: severe renal dysfunction (CrCl &lt; 30 mL/min) or pregnancy.</b> Use chromogenic, not clot-based, assays.			
<sup>2</sup>	The manufacturer recommends discontinuation of therapy if platelets are < 100,000/mm <sup>3</sup> .			

**Table 6. Testing to consider in patients with recurrent VTE/suspected thrombophilia**

<b>Eligible population <sup>1</sup></b>	<b>Tests <sup>2</sup></b>
Patients with a recurrent idiopathic thrombosis (more than one event)	All: <ul style="list-style-type: none"><li>• Factor V Leiden</li><li>• Factor II mutation</li><li>• Protein C and S</li><li>• Lupus anticoagulant</li><li>• Antithrombin III</li></ul>
Patients with an unprovoked event and <ul style="list-style-type: none"><li>• Age &lt; 50 years, <b>or</b></li><li>• With a family history of VTE among one or more first-degree relatives</li></ul>	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 <ul style="list-style-type: none"><li>• JAK2 mutation</li></ul>
<sup>1</sup> Consider consult with Hematology for patients with any of these risk factors.	
<sup>2</sup> This testing should be done 3–4 weeks after discontinuation of anticoagulant.	

# 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 guideline

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)?

## External guidelines meeting KPWA criteria for adaptation/adoption

- 2019 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism
- 2016 CHEST Guideline and Expert Panel Report. Antithrombotic Therapy for VTE Disease (Kearon 2016)
- 2016 National Comprehensive Cancer Network (NCCN) Guidelines. Cancer-Associated Venous Thromboembolic Disease version 1.2016 (NCCN 2016)
- 2015 National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Update of 2012 guideline (NICE 2015)
- 2014 Scottish Intercollegiate Guidelines Network (SIGN). Prevention and management of venous thromboembolism: a national clinical guideline.
- 2014 American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. (Lyman 2015)
- 2013 Institute for Clinical Systems Improvement (ICSI) Guideline: Venous Thromboembolism Diagnosis and Treatment. 2013. Retired January 2017. (ICSI 2013)
- 2012 American Thoracic Society documents: an official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline—Evaluation of Suspected Pulmonary Embolism in Pregnancy (Leung 2012)
- 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. (Kearon 2012)



## Initial and long-term management of PE

### **Key question 1: What is the optimal initial and long-term management of acute PE in adult patients, excluding pregnant women and cancer patients?**

The recent studies on the management of acute PE in adult patients mainly evaluated the use of direct oral anticoagulants (DOACs, formerly known as novel non–vitamin K-dependent oral anticoagulant agents, or NOACs)—rivaroxaban, apixaban, dabigatran, and edoxaban—in the management of VTE. The pivotal trials and a number of systematic reviews and meta-analyses were reviewed in the updated 2016 CHEST Guideline and Expert Panel Report (AT10). The panel concluded that the quality of evidence was moderate or high for efficacy and safety when comparisons were made between one of the DOACs versus vitamin K antagonists (VKAs) for the initial and long-term treatment of VTE. Based on the lesser bleeding risk with DOACs and greater convenience for patients, the guideline expert panel suggested that DOACs are preferred over VKAs for the initial and long-term treatment of VTE in patients without cancer. The choice of anticoagulant should be individualized and based on several factors and comorbidities, including cancer, pregnancy, liver disease, coagulopathy, renal disease and creatinine clearance, coronary artery disease (CAD), dyspepsia, history of gastrointestinal bleeding, compliance, use of parenteral therapy, need for thrombolytic therapy, and need for a reversal agent, as well as cost, coverage, and licensing.

The literature search for more recent studies and meta-analyses published after the last CHEST guideline panel review did not identify any randomized controlled trials (RCTs) that directly compared the different DOAC agents head-to-head to determine whether they differ in terms of efficacy, safety, tolerability, and/or compliance. The search revealed a number of meta-analyses and network meta-analyses that directly and indirectly compared different anticoagulation therapies and/or drugs used for the initial and long-term treatment of VTE (Robertson 2015 and 2017, Dentali 2015, Gomez-Outes 2014 and 2015, Cohen 2015, Mantha 2015, Sindet-Pederson 2015, Chatterjee 2014, Rollins 2014). The literature search also identified a number of systematic reviews and meta-analyses that were not included in the CHEST guideline (e.g., Kakkos 2014, Robertson 2015). These, however, mainly pooled the results of the same large pivotal trials and would not change the overall conclusion of the CHEST guideline.

### **Conclusion**

- There is fair evidence that low molecular weight heparin (LMWH) is associated with significantly lower rates of recurrent thrombotic complications and major hemorrhage, but with no difference in overall mortality when compared to unfractionated heparin (UFH) for the initial anticoagulation of acute VTE. The difference between the two therapies for PE did not reach a significant level, which may be attributed to the smaller number of patients with PE enrolled in the trials.
- There is moderate- to high-quality evidence indicating that the four DOACs studied were noninferior in efficacy compared to the conventional treatment of VTE. In terms of safety, major bleeding was significantly lower than with conventional treatment in the apixaban trial (Agnelli 2013) and the rivaroxaban PE study (Prins 2013). In terms of clinically relevant bleeding, edoxaban and dabigatran were safer than conventional treatment.
- There is insufficient direct evidence to determine that one of the DOACs is superior to the others. The indirect comparison, with its limitations, suggests that there is no significant difference between the different DOACs in terms of their efficacy in reducing VTE recurrence and related deaths. Apixaban appears to be associated with less major bleeding compared to dabigatran and edoxaban, as well as lower risk of composite endpoint of major or clinically relevant nonmajor bleeding when compared to any of the three other agents. It is to be noted, however, that patients randomized to dabigatran or edoxaban receive an initial heparin treatment, while those receiving rivaroxaban or apixaban do not receive heparin, which would bias the results.
- There is insufficient evidence to determine the long-term safety and efficacy of the DOACs. The duration of treatment in the published trials ranged from 6 to 12 months.
- There is evidence that aspirin used for extended treatment may reduce the risk of VTE recurrence by ~40% (Marik 2015), which is lower than the > 80% reduction observed with the VKAs or DOACs.
- There is insufficient evidence to determine whether aspirin should be used for extended treatment of patients with unprovoked VTE who are at low risk of recurrence.
- There is insufficient evidence to determine the optimal duration of aspirin therapy for patients at moderate risk of recurrence.
- A number of meta-analyses and one RCT investigated the extended treatment of VTE with DOACs, warfarin, and aspirin (Marik 2015, Sobieraj 2015, Weitz 2017). The overall results showed a significant reduction in the risk of recurrent VTE, but the risk of bleeding associated with the individual treatments differed across meta-analyses, which could be explained by the different inclusion/exclusion criteria of the meta-analyses.

- The results of the published studies and meta-analyses may not be generalizable to all patients due to several factors including, but not limited to:
  - The published studies were heterogeneous, with differences in study design, baseline patient characteristics and risk factors, and the regimens used with regard to doses, duration of therapy, dose adjustment, use of heparin lead, comparator used, duration of follow-up, and definitions of outcomes.
  - DOAC trials included a small proportion of patients aged > 75 years and/or with extreme body weight and excluded patients with severe renal impairment or liver failure.
  - All studies were conducted under controlled environments, which may differ from the real world.
  - The meta-analyses that pooled the results of the DOAC trials assumed that they have a class effect, and that the studies were homogeneous.
  - The majority of the studies combined the results for patients with either deep vein thrombosis (DVT) or PE, **and did not perform subgroup analyses.**

## **Key question 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 risk of recurrent VTE after treatment discontinuation is estimated at 1–5% at 1 year and 3–15% at 5 years in patients with provoked VTE, and at 10% and 30% at 1 and 5 years respectively in patients with unprovoked VTE (Sobieraj 2015). Despite the high recurrence risk associated with unprovoked VTE, extended anticoagulation remains controversial, and there is uncertainty about the optimal long-term duration of anticoagulation. There are no published RCTs to date that randomized patients with VTE to stop or continue anticoagulation and then followed them indefinitely (for ≥ 10 years). The follow-up duration in published trials ranges from 6 months to 3 years.

In a 2015 meta-analysis, Marik and colleagues calculated that the annualized rate of events after discontinuation of treatment was 6.5% in the active treatment group and 4.4% in the control group. This rate was calculated from the results of three trials in which patients received extended anticoagulation for periods ranging between 6 months and 3 years; this does not allow for any recommendation to be made on the benefits and harms of indefinite anticoagulation therapy.

The published guidelines recommend that long-term anticoagulation using VKAs or other oral anticoagulants should take into account patients' individual characteristics, risk factors for recurrence, bleeding risk (i.e., risk benefit ratio), and personal preference.

The 2016 ACCP CHEST guideline suggests extending anticoagulation therapy (with no scheduled stop date) for patients with unprovoked VTE and a low to moderate risk of bleeding.

More recent meta-analyses (Prandoni 2017, Bova 2016), an earlier Cochrane systematic review (Middeldrop 2014), and the PADIS-PE trial (Couturaud 2015) were reviewed to determine whether they would provide additional evidence on the optimal duration of anticoagulation therapy.

## **Conclusion**

- The published literature does not provide sufficient evidence to determine the optimal duration of anticoagulation after the initial treatment of unprovoked PE. There are no published RCTs to date that compared long-term outcomes of patients with VTE who stopped treatment with the outcomes of those who continued anticoagulation treatment indefinitely (for ≥ 10 years).
- There is evidence that prolonged treatment with VKAs reduces the risk of recurrent VTE as long as they are used and that their effects do not last after their discontinuation. One meta-analysis (Middeldorp 2014) showed that the efficacy of VKAs during continuing treatment decreases with time.
- There is evidence that bleeding risk increases with the extended use of VKAs.
- Moderate-quality evidence shows that the extended use of VKAs may not significantly reduce mortality.
- It is to be noted that all conclusions and recommendations were based on research from RCTs with strict inclusion/exclusion criteria and may not be representative of the general population with VTE. Thus, the results may not be applied to the sicker, older, or frail populations that were excluded from the trials.

### **Key question 3: What is the optimal initial and long-term management of acute PE in pregnant women?**

The literature search did not identify any more recent studies that would add to or change the recommendations of the external guidelines reviewed on the management of acute PE in pregnant women.

The overall recommendations may be summarized as follows:

- Weight-adjusted–dose LMWH is the recommended therapy for acute VTE in pregnant women without shock or hypotension.
- LMWH is preferred over UFH for the treatment of acute VTE in pregnant women based on extrapolation of efficacy data from trials in non-pregnant patients where LMWH was found to be more effective than UFH and associated with lower risk of bleeding and mortality.
- UFH does not cross the placenta and may be considered as an alternative if LMWH cannot be used or when UFH is considered more advantageous (e.g., in women with high risk of bleeding or severe renal impairment). UFH should also be used as an initial therapy for women with confirmed PE and hemodynamic compromise who are candidates for thrombolysis, until a definitive treatment decision is made (European Society of Cardiology 2019).
- After delivery, heparin treatment may be replaced by anticoagulation with VKA.
- Fondaparinux should not be used in pregnancy due to a lack of data.
- VKAs cross the placenta and are associated with embryopathy during the first trimester, and with fetal and neonatal hemorrhage as well as placental abruption if used in the third trimester.
- Warfarin may be associated with CNS anomalies throughout pregnancy.
- DOACs may cross the placenta and are contraindicated in pregnant women. They can be used postnatally if the woman is not breastfeeding.
- There is insufficient evidence to determine the optimal duration of anticoagulation after an unprovoked PE in pregnant women. There are no published studies to date that addressed the optimal duration of anticoagulation therapies for VTE in pregnant women.
- The ACCP 2012 recommends that pregnant women with VTE be treated with LMWH for a minimum total duration of 3 months, including at least 6 weeks following delivery.

### **Key question 4: What is the optimal initial and long-term management of acute PE in adult patients with cancer?**

The 2016 CHEST Guideline and Expert Panel Report suggests treating patients with VTE and active cancer with LMWH for the first 3 months. The guideline panel suggested that:

- In patients with VTE and cancer, the risk reduction for recurrent VTE appears to be greater with LMWH than with VKA therapy.
- The risk reduction for recurrent VTE with all the DOACs appears to be similar to the risk reduction with VKA, including in patients with cancer.
- The risk reduction for recurrent VTE with the DOACs compared to LMWH has not been assessed but, based on indirect comparisons; LMWH may be more effective than DOACs in patients with VTE and cancer.

Additional evidence on the initial therapy (Robertson 2017, Aki 2014 CD006649) as well as the extended therapy in cancer patients with PE (Aki 2014 CD006650, Lee 2015) were identified and reviewed. The evidence review also included meta-analyses (Donadini 2014, Van Der Hulle 2015) and an analysis of registry data (Peris 2016) on the treatment of incidentally detected PE (IPE) on CT scan, also known as clinically unsuspected PE (CUPE or UPE).

### **Conclusion**

- The literature indicates that LMWH is preferred over UFH for the initial therapy of adult patients with cancer and acute VTE.
- There is insufficient evidence to determine that one LMWH agent is preferred over the others.
- There is insufficient evidence to support the routine use of fondaparinux for initial treatment of acute VTE in patients with cancer.
- There is insufficient evidence to support the routine use of DOACs for initial treatment of acute VTE in patients with cancer.
- There is insufficient published evidence to determine the comparative efficacy and safety of LMWH with newer oral agents for initial anticoagulation in cancer patients.
- There is insufficient published evidence to determine the comparative efficacy and safety of VKAs and DOACs in the extended treatment of VTE in cancer patients.

- The published evidence on the treatment of incidentally detected PE on CT scan is conflicting and insufficient in quality and quantity to support making a recommendation for or against treatment. It appears, however, that incidental VTE may have the same risk of recurrence and bleeding and mortality as symptomatic VTE.

## Outpatient treatment of PE

### **Key question 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?**

The most extensively studied and validated prognostic models are the Pulmonary Embolism Severity Index (PESI), its simplified form sPESI, and the Geneva Prognostic Score (GPS).

Other clinical prediction rules include Aujesky, Davies, the European Society of Cardiology (ESC) prognostic model, Global Registry of Acute Coronary Events (GRACE), and Uresandi. These rules, however, have not been evaluated extensively and/or have not been externally validated.

There is no consensus on the criteria to use for stratifying patients with PE into low- and high-risk categories.

Several systematic reviews and meta-analyses (including Elias 2016, Kohn 2015, Squizzato 2012, Zhou 2012) were performed to review and synthesize the evidence for existing prognostic models in acute PE and determine how valid and useful they are for identifying low-risk patients with PE and/or predicting patient outcomes.

### **Conclusion**

- Several clinical prediction rules have been introduced for identifying low-risk patients who may be suitable for outpatient treatment or early discharge from the hospital. Few tools were validated, and there is no consensus on which one to apply.
- The Pulmonary Embolism Severity Index (PESI) and its simplified version sPESI are the tools that have been most widely validated and updated.
- The PESI and Geneva prognostic rules are clinical scores, based on vital signs and comorbid conditions. Both are influenced by the presence of malignancy and preexisting cardiopulmonary disease, which may predict all-cause mortality, but may not be associated with the PE-related mortality that clinicians are intending to estimate before discharging a patient early from the hospital (White 2016).
- PESI is the only tool that has been assessed in a completed randomized controlled trial (Aujesky 2011).
- There is fair evidence that the PESI clinical prediction rules can accurately identify low-risk patients with hemodynamically stable acute PE.
- PESI is a validated score that is easier to use and may be more accurate in predicting low-risk patients compared to other prediction rules, such as the Geneva prediction score. However, PESI has not been compared to other more recent prognostic tools that incorporate other factors such as biomarkers and imaging findings (Jimenez 2007).
- External validation and comparison of PESI and Geneva prognostic scores suggest that PESI has a higher discriminatory power for predicting 30-day mortality than the Geneva score.

### **Key question 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?**

There is a lack of published randomized controlled trials (RCTs) comparing the effectiveness and safety of outpatient versus inpatient treatment of acute PE. The literature search revealed only two RCTs that compared outpatient versus inpatient management of low-risk PE patients (Aujesky 2011, Otero 2010). The other empirical studies identified by the literature search were all observational prospective or retrospective studies with no control or comparison groups. There were a number of systematic reviews with or without meta-analyses that included selected published RCTs and observational studies. A Cochrane review (Yoo 2014), which limited the search to RCTs, included the OTPE study (Aujesky 2011). Two other meta-analyses (Piran 2013, Zondag 2013) pooled the results of randomized and observational studies.

The Outpatient Treatment of Pulmonary Embolism (OTPE) study (Aujesky 2011) provides the best published evidence. This was a multinational, open-label, randomized controlled, non-inferiority study that compared the outpatient versus inpatient treatment of low-risk patients with acute PE. The study included adult patients (> 18 years)

with acute symptomatic and objectively verified PE who were at low risk of death according to the PESI score. The authors did not evaluate right ventricular dysfunction or myocardial injury. Patients at moderate to high risk were excluded, as were those fulfilling 14 other exclusion criteria including hypoxia, high risk of bleeding, and chest pain that required opiates. 339 patients (PESI risk Classes I or II) were randomly assigned in a 1:1 ratio to an outpatient or inpatient group. (30% of the patients screened met the low-risk eligibility with PESI.) Both groups received subcutaneous LMWH (enoxaparin 1 mg twice a day) for > 5 days followed by oral anticoagulation with a vitamin K antagonist for at least 90 days. Those in the outpatient group were discharged from the emergency department within 24 hours of randomization after they were trained on self-injection. After discharge, they were managed by their primary care physician or the hospital anticoagulation staff (17 patients were excluded from the study due to their primary care physician's opposition to outpatient treatment). All patients were followed for 90 days; they were contacted daily for the first week, then at 14, 30, 60, and 90 days to ask about any bleeding, symptoms of recurrent VTE, and the use of health resources.

The primary outcome of the OTPE study was the recurrence of objectively confirmed VTE within 90 days; secondary outcomes included major bleeding and all-cause mortality. Overall patient satisfaction and treatment preference were also assessed. Outcomes were confirmed by clinical experts blinded to the treatment assignment. The study was a non-inferiority trial and its results showed that outpatient management was non-inferior to inpatient management of low-risk PE patients both in safety and effectiveness, except for bleeding at 90 days, which did not reach non-inferiority level. The mean length of hospital stay was shorter by 3.4 days, and the duration of LMWH use was longer by 2.6 days in the outpatient management group. 14% of outpatients versus 6% of inpatients received home nursing visits for enoxaparin injection (n = 348 versus 105 home visits). There were no significant differences between the two groups in hospital readmission rates, emergency department visits, or primary care visits. The results also show that outpatient care was well accepted by patients (satisfaction rate 92% versus 95% for inpatients).

## Conclusion

- There is weak evidence from one published open-label randomized controlled trial (OTPE) and a number of observational studies and systematic reviews with meta-analyses of published studies (mainly observational) that early discharge and outpatient treatment of carefully selected, hemodynamically stable, low-risk patients with acute PE may not be inferior to inpatient management in terms of efficacy and safety.
- Large high-quality randomized controlled trials on outpatient treatment of PE patients are needed to provide strong evidence for recommending for or against outpatient treatment of PE.
- There is insufficient evidence to determine the safety of initiating anticoagulation therapy in the outpatient setting in patients with cancer and acute PE.

## Management of subsegmental PE

### **Key question 7: What is the appropriate management strategy for patients with isolated or incidental subsegmental pulmonary embolism (SSPE)?**

There is insufficient published evidence to recommend for or against the use of anticoagulation treatment for patients with isolated or incidental subsegmental pulmonary embolism (SSPE).

The 2016 American College of Chest Physicians Antithrombotic Therapy for VTE Guideline and Expert Panel report suggests the following:

1. Clinical surveillance over anticoagulation for patients with subsegmental PE (no involvement of more proximal pulmonary artery) and no proximal DVT in the legs who have low risk of recurrent VTE.
2. Anticoagulation over clinical surveillance for patients with subsegmental PE (no involvement of more proximal pulmonary artery) and no proximal DVT in the legs who have high risk of recurrent VTE.

The AT10 panel noted that

- If no anticoagulant therapy is an option, patients with subsegmental PE should have bilateral ultrasound examination to exclude proximal DVT in the legs. Proximal DVT should also be excluded from other high-risk locations. Anticoagulation is required if any DVT is detected. If no DVT is detected, there is uncertainty about whether the patient should be anticoagulated. If not anticoagulated, the patient should undergo serial testing for proximal DVT.
- Other factors should be considered, including hospitalization, reduced mobility, active cancer, risk factors for VTE, cardiopulmonary reserve, risk of bleeding, and patient preference.

There is uncertainty about whether patients with subsegmental PE should be anticoagulated because:

- The abnormalities are small, and the diagnosis is more likely to be a false positive finding.
- A true SSPE will have likely resulted from a small DVT, and the risk of progressive or recurrent VTE without treatment is expected to be lower than in patients with a large PE.
- There are no published RCTs in patients with SSPE.
- The evidence on larger PE is expected to apply to SSPE; however, the risk of progressive or recurrent VTE in subsegmental SSPE is uncertain.

The 2019 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism recommend that the treatment of incidentally detected PE in cancer patients, including those in segmental or subsegmental arteries, should be considered, based on the unclear and limited knowledge on the significance of incidentally discovered PE with the widespread use of CT. The guidelines recommend that these incidental PEs be treated as symptomatic PEs.

A Cochrane review and meta-analysis (Yoo 2016) aimed to evaluate the effectiveness and safety of anticoagulation therapy versus no intervention in patients with isolated SSPE or incidental SSPE. The authors did not identify any RCT that met their inclusion criteria, and concluded that they could not draw any conclusion on the effectiveness and safety of anticoagulation therapy versus no intervention in patients with isolated or incidental SSPE.

## **Conclusion**

There is insufficient published evidence to recommend for or against the use of anticoagulation treatment for patients without cancer who have isolated or incidental subsegmental pulmonary embolism (SSPE).

- It is suggested that cancer patients with PE—even those in segmental or subsegmental arteries—be treated similarly to patients with symptomatic PE.

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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 September 2020.

## Team

Clinician lead: [Angie Sparks, MD](#), Medical Director, Clinical Knowledge Development & Support

Guideline coordinator: [Avra Cohen, MN, RN](#), Clinical Improvement & Prevention

Jamie Andrews, MHA, Director, Clinical Value Improvement

Eric Chen, MD, Hematology/Oncology

Jaron Christianson, MD, Emergency Medicine

Stephanie Cooper, MD, Emergency Medicine

Tim Dewhurst, MD, Cardiology

Scott Ekin, MD, Urgent Care

Gail Elliott, PharmD, Manager, Anticoagulation/Anemia Management Service

Eric Feldman, MD, Hematology/Oncology

Tina Ghia, MD, Cardiology

Jeffrey Halpern, MD, Consultative Internal Medicine

Melissa Hull, PharmD, Clinical Programs Coordinator

Megan Kavanagh, Patient Engagement Team, Clinical Improvement & Prevention

Dave McCulloch, MD, Medical Director, Clinical Improvement

Michael Nevins, MD, Pulmonary Medicine

Nadia Salama, MD, MPH, PhD, Clinical Epidemiologist, Clinical Improvement & Prevention

Jonathan Scheffer, MD, Emergency Medicine

Ann Stedronsky, Clinical Publications, Clinical Improvement & Prevention

## Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care-related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Pulmonary Embolism Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.

## Appendix 1. Shared decision-making for choosing anticoagulant medication

### **For AVS:** .peanticoagulantoptions

We spoke today about treatment options for your {pulmonary embolism or VTE: 23142}. We decided to start you on \*\*\*. The information about medicines and treatments we talked about during your visit is below.

If you have any questions or concerns about your medicine, please call \*\*\*.

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### **Anticoagulants: Understanding your options**

Below are answers to common questions that can help you understand the different options for anticoagulant medicines. After reading this information, you and your doctor should talk about any concerns you have and decide which option is right for you.

#### **What are anticoagulants?**

Anticoagulants are medicines used to keep blood clots from forming. Sometimes anticoagulants are called blood-thinners, but they don't actually make your blood thinner. They work by lowering your blood's ability to clot, which reduces your risk of stroke or other blood vessel blockage.

#### **What anticoagulant medicines are available?**

There are currently a few anticoagulant medicines to choose from including:

- Warfarin (Coumadin®)
- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Rivaroxaban (Xarelto®)
- Edoxaban (Savaysa®)

Warfarin has been used the longest and we know its long-term side effects. It's also low cost. Studies show that the newer anticoagulants (apixaban, dabigatran, rivaroxaban, and edoxaban) work just as well as warfarin, but there hasn't been enough research to say if one is more effective than the others.

#### **What are the side effects of taking anticoagulants?**

There is a risk of bleeding problems with all anticoagulants. Bleeding problems can include bruising easily as well as bleeding in the brain and stomach. There is also a risk of skin rash and upset stomach with some anticoagulants. And even though anticoagulants lower your risk of having a stroke, there is still a chance of stroke when taking these medicines.

With the newer anticoagulants, the risk of bleeding might be lower than with warfarin. However, if warfarin levels are well controlled, bleeding rates might be similar. Newer anticoagulants can increase the risk of bleeding problems for people with kidney problems and for people older than 75 years of age.

#### **Call immediately for medical help if you have any of the signs of bleeding, such as:**

- Pain or swelling
- Nosebleeds, bleeding gums, or bleeding from a cut that doesn't stop
- Bleeding or bruising without knowing the cause
- Coughing up or vomiting blood, or vomit that looks like coffee grounds
- Stronger than normal menstrual flow or vaginal bleeding
- Pink, red, or dark brown urine
- Red or tarry black bowel movements
- Headache, dizziness, or weakness

**For medical concerns after hours, Kaiser Permanente members can call the Consulting Nurse Service 24 hours a day, 7 days a week at 1-800-297-6877.**

#### **What is the treatment for bleeding problems?**

Doctors are able to reverse the effects of warfarin with vitamin K if a dangerous bleeding problem does happen.

Dabigatran, rivaroxaban and apixaban have a remedy that can be used in an emergency to reverse its anti-clotting effects. Edoxaban currently does not have an approved remedy if a dangerous bleeding problem happens. However, other general measures can be used to help control the bleeding.

#### **What are other things to think about when considering anticoagulants?**

##### **Blood tests**

With warfarin, you need to have blood tests regularly to make sure you're taking the right dose and that it's working for you. Depending on your test results, you may need to adjust your dose.

Newer anticoagulants are more convenient because they don't require you to have as many blood tests or make as many changes in your dose.

##### **Diet**

When taking warfarin you'll need to be careful about your diet. Foods high in vitamin K, such as some vegetables, affect how well warfarin works. Eating a diet that contains small but consistent amounts of these foods is best.

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Newer anticoagulants aren't affected by how much vitamin K you get.

**Drug interactions**

Many other prescription and over-the-counter medicines can affect how well warfarin works. Some of them make it harder for warfarin to work, which can increase your risk of a blood clot. Some medicines make warfarin work better and that increases your risk for bleeding problems.

You can manage this by closely monitoring all of your medicines and adjusting your warfarin dose as needed.

The newer anticoagulants have fewer drug interactions than warfarin.

Make sure your doctor and pharmacist know about all the medicines you're taking, including over-the-counter medicines and supplements.

Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine. If you're not sure, ask your doctor or pharmacist for a list of your current medicines.

**Dosing**

You only need to take warfarin once a day.

You would take a newer anticoagulant one or 2 times a day.

**Cost**

Warfarin is available as a generic medicine and costs most people less than \$20 for a one-month supply.

The newer anticoagulants are only available as brand name drugs and are much more expensive than warfarin. The cost to a patient can range widely depending on a person's prescription drug coverage.

**Anticoagulants: Comparing your options**

The following chart can help you compare your anticoagulant choices.

	Warfarin (Coumadin)	Apixaban (Eliquis )	Dabigatran (Pradaxa )	Rivaroxaban (Xarelto )	Edoxaban(Savaysa)
When and how much	Dose is adjusted based on lab results. Taken once a day in the evening.	Dose is between 2.5 and 10 mg twice a day. Dose might be adjusted based on kidney function.	Dose is between 75 and 150 mg twice a day. Dose might be adjusted based on kidney function.	Dose is between 10 and 20 mg once a day or 15 mg twice a day. Dose might be adjusted based on kidney function.	Dose is between 30 and 60 mg once a day.
How to take it	Tablets are scored, and can be broken, crushed or chewed.	Tablets can be crushed.	Capsules must be swallowed whole and cannot be broken, crushed or chewed.	Tablets are taken with food and can be crushed.	Tablets can be taken with or without food.
Lab tests	A blood test (prothrombin time/protime/INR) is generally required once a month and sometimes more often.	A blood test is required before you start treatment and then at least once every year after that.	A blood test is required before you start treatment and then at least once every year after that.	A blood test is required before you start treatment and then at least once every year after that.	A blood test is required before you start treatment and then at least once every year after that.
Diet	Requires a consistent intake of foods that contain vitamin K.	No special considerations.	No special considerations.	No special considerations.	No special considerations.
Drug interactions	Interacts with many medicines and might require changing dose based on blood test to prevent complications.	Interacts with some medicines. Tell your doctor and pharmacist about all your medicines.	Interacts with some medicines. Tell your doctor and pharmacist about all your medicines.	Interacts with some medicines. Tell your doctor and pharmacist about all your medicines.	Interacts with some medicines. Tell your doctor and pharmacist about all your medicines.
Remedy to stop dangerous bleeding	Vitamin K	Andexanet alfa (AndexXa)	Idarucizumab (Praxbind)	Andexanet alfa (AndexXa)	None available, but general measures to control bleeding can be used
Cost	Low cost - available as a generic.	Only available as brand name. Patient cost share can be much higher than that of warfarin and preferred DOACs	Only available as brand name. Patient cost share can be much higher than that of warfarin.	Only available as brand name. Patient cost share can be much higher than that of warfarin.	Only available as brand name. Patient cost share can be much higher than that of warfarin.

**For questions about coverage:**

If you have questions about your benefit plan or coverage for these medications, please call Member Services toll-free 1-888-901-4636 between 8am and 5pm Monday through Friday. For TTY Relay (hearing impaired), call 711 or toll-free 1-800-833-6388.

**For more information and help in making your decision:**

Atrial Fibrillation: Which Anticoagulant Should I Take to Prevent Stroke?

<https://member.ghc.org/kbase/topic.html?docId=abl2009>