Provincial Clinical Knowledge Topic

*Pulmonary Embolism, Adult*

**Emergency**

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Important Information Before You Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Health Now campaign etc.

Within this knowledge topic PICO-D questions or key clinical questions that have been used to guide research using the Population/Problem, Intervention, Comparison, Outcome, Design format. These questions are listed in Appendix A and Appendix B.

Links to PICO questions or Appendices are throughout the document (example: [PICO 1]). Click on the link with your mouse to follow the link. Under the PICO question or Appendix heading you will find a link to return you to your place in the document.
Rationale
Pulmonary embolism (PE) is a risk for a number of patients presenting to the emergency department with dyspnea, tachypnea or tachycardia. They may present with pleuritic chest pain, following syncope, with hemoptysis or a range of other complaints. Key patients at risk for this condition are those with active cancer, recent immobilization, previous venous thromboembolism, and recent surgery.

In Alberta, during the years from 2012 – 2014, Emergency Department (ED) visits for PE among the facilities with an ED Department was 5773. The proportion of admissions amongst these patients was 49%.\(^1\) While relatively uncommon, undiagnosed PE can lead to mortality or severe morbidity due to untreated clot burden leading to pulmonary hypertension. As a result costly and time consuming investigations with some risk to patients in the form of Computerized Tomography (CT) or Lung Ventilation/Perfusion scan (V/Q) scans are being ordered in low risk patients, hoping to avoid a missed PE.\(^2\,^3\)

The goal of this knowledge document is to review the literature and through patient and provider input develop an evidence based standardized approach to improving clinical risk stratification, determining appropriate investigation strategies, optimizing therapeutic protocols, and safely determining outpatient versus inpatient management plans.\(^2\,^3\,^4\)

Goals of Management
1. Airway Breathing Circulation (ABC): Protect airway, prevent aspiration, support ventilation, volume resuscitate as needed
2. Identify unstable PE patients to be able to deliver thrombolysis early in patients without contraindications
3. Based on clinical findings/judgment, apply clinical decision rules, to determine the likelihood of PE for each patient
4. Based on risk stratification determine the most appropriate investigation strategy, including the risk/benefit of initiating treatment pending investigations versus waiting for diagnostic certainty
5. Consider alternate diagnoses including myocardial infarction, congestive heart failure (CHF), pericarditis, pneumothorax, pneumonia and aortic dissection
6. Determine patient risk for anticoagulant therapy including: recent bleeding (e.g. gastrointestinal (GI) tract, epistaxis, recent surgery), previous dangerous bleeds (e.g. intracranial hemorrhage [ICH], GI bleed), or past history of adverse events on anticoagulants (e.g. difficulty maintaining stable international normalized ratio [INR], heparin induced thrombocytopenia [HIT]), medications that will interact with anticoagulants, and renal function
7. Providing a safe and appropriate disposition strategy
Nursing Assessment and Documentation

This section contains specific considerations related to this topic. Standard assessment and documentation practices should still be followed.

1. Triage Assessment/Documentation
   - Vital signs, including a glucose (as indicated)
   - Canadian Emergency Department Information Systems (CEDIS) complaints:
     o chest pain or shortness of breath (SOB) or syncope
   - Canadian Triage and Acuity scale (CTAS) Modifiers:
     o respiratory distress and/or hemodynamic stability are most likely first order modifiers

2. Initial Assessment/Documentation
   - Presenting History: Time of onset, shortness of breath (SOB), pleuritic chest pain, syncope, leg swelling, hemoptysis
   - Brief screening of risk factors:
     o Exogenous hormone therapy used for contraception or postmenopausal indications
     o Surgery within the previous 4 weeks
     o History of immobilization or hospitalization greater than or equal to 72 hours or long distance travel (overseas flights or flights lasting greater than 8 hours)
     o Obesity
     o Active cancer (treatment ongoing, within 6 months, or palliative)
     o Lower extremity trauma
     o Pregnancy
     o Previous deep vein thrombosis (DVT) or pulmonary embolism (PE)
   - Past History: previous clot, family history of clots, renal failure
   - Medications and Allergies: all meds but specifically hormone therapy, warfarin, direct oral anticoagulants (DOACs), antiplatelet agents, and medications that could interact with warfarin
   - Systems review:
     o Respiratory: tachypnea, dyspnea
     o Cardiovascular (CV): tachycardia, signs of dehydration, signs of congestive heart failure (CHF), diaphoresis, pleuritic chest pain
     o Neurological: mental status
     o Gastrointestinal (GI): nausea, vomiting, abdominal pain
     o Extremities: edema, tenderness, redness
Physician Assessment and Documentation

This section contains specific considerations related to this topic. Standard assessment and documentation practices should still be followed.

1. History of Present Illness
   - The dominant presenting complaint (dyspnea, chest pain [generally pleuritic but occasionally central], hemoptysis, syncope, etc.), time of onset (generally sudden), associated symptoms (unilateral leg swelling, fever, syncope, cough, pregnancy, recent long flight (overseas flights or flights lasting greater than 8 hours) and the specific Wells history risk factors listed below (each component is worth 1 point):
     - Clinical signs and symptoms of deep vein thrombosis (DVT)
     - PE is the #1 diagnosis, or equally likely to another diagnosis
     - Heart rate greater than 100
     - Surgery or immobilization within the last 4 weeks
     - Previous deep vein thrombosis (DVT) or pulmonary embolism (PE)
     - Hemoptysis
     - Active malignancy
   - To broaden the differential diagnosis ask about: acute coronary syndrome (ACS) presenting features, possible flash pulmonary edema, signs and symptoms of aortic dissection, pneumonia in the elderly, pneumothorax or pericarditis

2. Medications & Allergies
   - All meds but specifically exogenous hormone therapy used for contraception or postmenopausal indications, warfarin, direct oral anticoagulants (DOACs), antiplatelet agents, and medications that could interact with warfarin

3. Past History
   - Previous Venous thromboembolism (VTE), active cancer (already noted under history of present illness) or any history of thrombophilia ([PICO 1])

4. Review of Systems
   - Specifically looking for limb symptoms that may suggest a DVT and also looking for other potential cause for limb pain or swelling. Look for any evidence of recent bleeds: gastrointestinal bleeding (GIB), intracerebral hemorrhage (ICH), epistaxis

5. Family History
   - VTE (in 1st degree relative less than 50 years of age), or thrombophilia

6. Social History
   - Financial (health insurance/drug plan) and social supports available, assuming the need for initiation of antithrombotic agents (warfarin requires frequent testing and the ability to regularly access a lab and get INR and dosing monitored; whereas DOACs are expensive without insurance such as Blue Cross as a first line choice), also need to ensure adequate home support if immobile

7. Physical Examination
   - Focused exam looking for diagnosis - tachypnea (greater than 24 breaths/min), hypoxemia, hypotension, unilateral leg swelling with signs suggestive of DVT, bilateral cuff pressure differences suggestive of aortic dissection, fever (temperature greater than 38°C), respiratory exam looking for other causes of dyspnea, congestive heart failure (CHF), pneumonia, chronic obstructive pulmonary disease (COPD), and cardiovascular exam
8. Scoring Tools / Risk Scores
   - Modified Wells Criteria for Pulmonary Embolism (Appendix D)
     o Based on points awarded for each of the history and physical exam-driven
       Wells Criteria, we recommend using the Modified 2 level PE score to assist in
       decision making
       ▪ PE Unlikely equals a score of 4 points or less
       ▪ PE Likely equals a score of more than 4 points
   - PERC Rule for Pulmonary Embolism (Appendix D)
     o The PERC rule has been validated in patients with a low clinical suspicion and
       pretest probability of less than 15%
     o Using the Modified Wells, patients with a score of 2 or less have a very low
       PE probability in a patient population with a PE prevalence of less than 10%
     o Based on this combined knowledge it has been suggested that a negative PERC
       rule (in patients 50 or younger) can rule out PE without the use of D-Dimer
     o If any of the following criteria are present then further work-up is needed:
       ▪ Age greater than or equal to 50
       ▪ Heart rate greater than or equal to 100
       ▪ O2 sat on room air less than 95%
       ▪ Prior history of venous thromboembolism
       ▪ Trauma or surgery within 30 days
       ▪ Hemoptysis
       ▪ Exogenous estrogen therapy
       ▪ Unilateral leg swelling

Initial Decision Making
1. Is the patient pulseless with suspected Pulmonary Embolism (PE)? (Pulseless electrical
   activity [PEA] arrest)? (PICO 2)
   - If yes, initiate standard Advanced Cardiovascular Life Support (ACLS) resuscitation
   - Consider thrombolysis with alteplase in consultation with Critical Care +/- Hematology
     (10 mg bolus via central/peripheral line and 90 mg IV over 2 hours) (PICO 3)

2. Is the patient unstable with suspected PE? (blood pressure less than 90 mmHg for at least
   15 minutes, or requiring inotropic support [not due to causes other than PE], with signs of
   shock)
   - Diagnostic considerations: CT vs transthoracic echocardiogram (TTE) vs
     transesophageal echo (TEE) vs empiric treatment (PICO 4)
   - If yes, consider thrombolysis (after ruling out contraindications and discussions with
     Critical Care +/- Hematology) with alteplase (10 mg bolus via central/peripheral line and
     90 mg IV over 2 hours)
   - Following thrombolysis deliver unfractionated heparin (UFH) or low-molecular-weight
     heparins (LMWH) (PICO 5)
3. Is the patient hemodynamically stable and their presentation consistent with a possible pulmonary embolism (PE)? *(Appendix D)*
   - If yes and based on the risk score/clinical assessment is considered **Likely** for PE *(PICO 6,7)*
     - Option 1: Order a CT angiogram before beginning treatment *(PICO 8)*
     - Option 2: Initiate anticoagulation if there is a delay of greater than 4 hours in obtaining a CT angiogram *(PICO 9)*
   - If yes and based on the risk score/clinical risk is considered **low or Unlikely** for PE *(PICO 10)*
     - For patients younger than 50 and clinically low risk apply the PERC rule and if all answers are **No** clinician can feel fairly confident PE is ruled out
     - If any PERC answer is **Yes** OR clinical concern remains apply the Wells **AND** if **Unlikely** order a D-Dimer. If D-Dimer negative consider PE ruled out *(PICO 11)*
     - If any PERC answer is **Yes** OR Modified Wells **Unlikely AND** D-Dimer is positive, proceed with a CT angiogram or V/Q scan to rule in or rule out a PE
     - We recommend use of V/Q in patients with a normal chest x-ray (CXR), when patient has had prior anaphylactoid reaction to IV contrast, severe renal impairment *(PICO 12)* or in patients with myeloma and paraproteinemia.6

4. Is the patient pregnant?
   - D-Dimer values increase during pregnancy, a negative D-Dimer is still useful in ruling out PE in the **Unlikely** patient *(PICO 13)*
   - For **Likely** patients move directly to DI imaging as below
   - Recommend ordering a CXR and if normal then go to perfusion scan (Q scan). If abnormal CXR then go to CT angiogram. *(PICO 14)*
   - Bilateral venous ultrasounds of the lower limbs prior to radioactive imaging have been recommended by some but this test has a low sensitivity in patients without symptoms. If positive for PE, the ultrasound negates the need for additional testing. It is clearly reasonable to order a unilateral doppler ultrasound in patients with signs of DVT. *(PICO 15)*
Order Set Components
Orders or their components have been added in bold text if recommended as default (e.g. Bedrest). All other orders and components would be selected based on the presentation needs of the patient. Orders that have more than one option for treatment have been entered in square brackets (e.g. Warfarin 5 mg [2, 2.5, 3, 4, 6, 7.5, 10 mg] PO x 1).

Order Set Components - General Care
- Goals of Care: utilize appropriate Goal of Care
  - Will be important for unstable patients and admitted patients
  - Use the Resuscitation (R), Medical Management (M), Comfort Measures (C) designations and form
- Precautions and Safety:
  - Consider aids to mobility if needed
- Activity:
  - Bedrest
  - Bedrest - With Bathroom Privileges
  - Ambulate - With Assist
  - Activity as Tolerated
- Diet / Nutrition:
  - NPO
  - NPO: May Have Ice Chips
  - NPO: May Have Sips
  - NPO: May Take Meds
  - Clear Fluids Diet
  - Regular Diet
  - Other Diet: as required

Order Set Components - Patient Care Orders
- Vital Signs: These orders need to be re-evaluated when the patient stabilizes or after 2 hours
  - as per provincial guideline
  - q ______ min(s)
  - q ______ hour(s)
- Cardiovascular Monitoring: Close monitoring in severe dyspnea or hemodynamic instability
- Neurological Vital Signs: These orders need to be re-evaluated when the patient stabilizes or after 2 hours whichever occurs first. Neurological vital signs to include: Glasgow Coma Scale (GCS), and pupillary size and reaction to light with reassessments
  - as per provincial guideline
  - q ______ min(s)
  - q ______ hour(s)
  - Note: the physician should be notified if a patient’s GCS decreases by 2 or more points.
Order Set Components - Respiratory Care

- Suggest starting with ‘oxygen to maintain O2 saturation greater than or equal to 92%, unless otherwise specified’ with O2 rate, O2 device, and O2 Sat options reserved for patients with specific concerns such as COPD. If O2 saturation is already adequate, no supplemental O2 is required.
  - O2 Therapy @______LPM by______(device)____to maintain O2 sat greater than or equal to 92%
  - O2 Therapy – Titrate to Saturation @______LPM to maintain O2 sat greater than or equal to 92%
    - Notify - physician if O2 flow required to be increased by greater than 2 L to maintain the same level of oxygenation of if there is a progressive increase in the work of breathing

Order Set Components - Intravenous Orders

- Intravenous Cannula – Insert
- Options then include:
  - Saline Lock
  - IV bolus or rapid infusion including the following:
    - Amount (e.g. 250 mL, 500 mL, 1000 mL, 2000 mL)
    - Fluid (e.g. 0.9% NaCl infusion, lactated ringers infusion, D5W - 0.9% NaCl infusion)
    - Run time (e.g.15 min, 30 min, 45, min, 60 min)
  - IV maintenance
    - Rate in mL / hour (e.g. 75, 100,125, 150, 200, 250)
    - Fluid (e.g. 0.9% NaCl infusion, lactated ringers infusion)

Order Set Components - Lab Investigations

Laboratory orders appear in **bold** text if recommended as usual default orders. Laboratory orders are **underlined** when needed to assess severity or establish a baseline. All other lab orders (e.g. investigations for possible comorbidities) are to be selected based on the presentation needs of the patient and are in regular font.

- Hematology
  - Complete Blood Count (CBC)
  - D-Dimer (quantitative) - only if Modified Wells score unlikely [4 points or less] (PICO 16, 17, 18)
  - PT INR
- Chemistry
  - Electrolytes (Na, K, Cl, CO2)
  - Creatinine LEVEL
  - Glucose Random LEVEL
  - BNP (NT – ProBNP): Natriuretic Peptide
  - Troponin (I or T)
- HCG Beta
- Urea

- Blood Gases
  - Blood Gas Arterial
  - Blood Gas Venous Mixed

- Urine Tests
  - Urinalysis Random
  - Pregnancy Test, Urine – POCT

Order Set Components - Diagnostic Imaging

- Standard X-rays
  - GR Chest, 2 Projections: Chest X-ray PA and Lateral
  - GR Chest, 1 Projection portable: Chest X-ray Portable

- Advanced Imaging
  - CT Chest For Pulmonary Embolus (PICO 19, 20)
  - V/Q scan (NM Lung Ventilation) (PICO 21)
  - Bilateral or unilateral venous leg doppler ultrasound
    - US Vessels Venous Doppler, Bil
    - US Vessel Venous Doppler, Uni
  - Echo Transesophageal (TEE) (PICO 22)

- Electrocardiogram – 12 Lead

Order Set Components - Medications

** Absolute contraindications to anticoagulation include: active bleeding, recent intracerebral hemorrhage (less than 14 days), uncontrolled severe hypertension, or platelet count - less than 50 x 10^9. In these circumstances consult Hematology for advice.

**Also important to note that for PE likely or D-Dimer positive patient, needing to wait greater than 4 hours for an imaging study, low molecular weight heparin should be initiated. Discharge anticoagulant options are described under Disposition Planning.

1. Low molecular weight heparin (all 3 options can be used for cancer or extensive clot burden patients, but for enoxaparin dosing change suggested)
   - enoxaparin 1.5 mg/kg SUBCUTANEOUSLY daily (consider dosage reduction for glomerular filtration rate [GFR] less than 30 mL/min)
   - OR
   - enoxaparin 1 mg/kg SUBCUTANEOUSLY q12h (preferred for cancer patients or extensive clot burden and consider dosage reduction for GFR less than 30 mL/min)
   - OR
   - dalteparin 200 international units/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min)
OR
- tinzaparin 175 units/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min)

2. Oral anticoagulant (Vitamin K Antagonist)
- warfarin 5 mg [2, 2.5, 3, 4, 6, 7.5, 10 mg] PO x 1 (requires follow up instructions with a target of INR 2 to 3)
  o if initiated in the ED needs INR initially then q2days until achieves therapeutic goal – Internal Medicine, Family Physician, Cardiologist, or anticoagulation management clinic to monitor

3. Direct oral anticoagulants (DOACs) (PICO 23) (Appendix E) (DOACs have been less well studied in active cancer and thrombophilia patients so suggest review with oncology or hematology prior to initiation)¹²
- rivaroxaban 15 mg PO x 1 (a preferred agent for patients over the age of 80 and a GFR of greater than 30 mL/min)
  OR
- apixaban 10 mg PO x 1 (a preferred agent for patients with GFR less than 30 mL/min but greater than 15 mL/min and for patients over the age of 80)

4. Heparin infusion (for massive and submassive PE only)

5. Thrombolysis with alteplase (TPA) 10 mg bolus via central/peripheral line and then alteplase 90 mg IV over 2 hours (in consultation with Critical Care +/- Hematology) (PICO 24)

6. Pain control

Non-opiate Analgesia
- acetaminophen 1000 mg PO once
- acetaminophen 500 to 1000 mg PO q4h PRN for pain (maximum 3000 mg/day)
- acetaminophen ______ mg PO
  **Suggest 500 mg for mild to moderate pain, 1000 mg for moderate to severe pain

Opiate Analgesia
  **For “susceptible patients” defined as elderly, frail, low body mass, systemically unwell, or on medications known to cause sedation or lower blood pressure we recommend decreasing narcotic dosing by 50%.
  - Contact physician or nurse practitioner for reassessment if pain not controlled after administration of maximum dosage.

Oral
- acetaminophen 325 mg/caffeine 15 mg/codeine 30 mg 2 tabs PO once
- acetaminophen 325 mg/caffeine 15 mg/codeine 30 mg 1 to 2 tabs PO q4h PRN for pain
- acetaminophen 325 mg/caffeine 15 mg/codeine 30 mg ______ tabs PO

[Other sections related to pain management]
- oxyCODONE 5 mg/acetaminophen 325 mg 2 tabs PO once
- oxyCODONE 5 mg/acetaminophen 325 mg 1 to 2 tabs PO q4h PRN for pain
- oxyCODONE 5 mg/acetaminophen 325 mg _____ tabs PO ___________________

- HYDROmorphone 1 mg PO once
- HYDROmorphone 1 to 2 mg PO q4h PRN for pain
- HYDROmorphone _____ mg PO ____________________
  **Suggest 1 mg for moderate pain and 2 mg for severe pain**

**Parenteral**

- HYDROmorphone 1 mg IV once
- HYDROmorphone 0.5 to 1 mg q10mins PRN for pain (maximum 3 mg total)
- HYDROmorphone _____ mg IV __________________
  **Suggest 0.5 mg for moderate pain and 1 mg for severe pain**

- morphine 5 mg IV once
- morphine 2.5 to 5 mg IV q10mins PRN for pain (maximum 15 mg total)
- morphine _____ mg IV __________________
  **Suggest 2.5 mg for moderate pain and 5 mg for severe pain**

- fentaNYL 50 mcg IV once
- fentaNYL 25 to 50 mcg IV q5mins PRN for pain (maximum 200 mcg total)
- fentaNYL _____ mcg IV __________________
  **Suggest 25 mcg for moderate pain and 50 mcg for severe pain**

7. Antiemetics

  **Avoid dimenhyDRINATE in patients 65 years of age or older due to increased risk of side effects including delirium**

- dimenhyDRINATE 50 mg PO once
- dimenhyDRINATE 50 mg PO q4h PRN for nausea/vomiting
- dimenhyDRINATE _____ mg PO __________________

- metoclopramide 10 mg IVPB once
- metoclopramide 5 to 10 mg IVPB q6h PRN for nausea/vomiting (use 5 mg dose if CrCl less than 40 mL/min)
- metoclopramide _____ mg IVPB __________________

**4 mg starting dose recommended for IV ondansetron**

- ondansetron 4 mg IV once
- ondansetron 4 mg IV to be repeated once 30 minutes after first dose PRN for nausea/vomiting
- ondansetron 4 mg IV q8h PRN for nausea/vomiting
- ondansetron _____ mg IV __________________

- ondansetron tab 8 mg PO q8h PRN for nausea/vomiting
ondansetron tab _____ mg PO__________________

**Due to high cost, recommend reserving ondansetron DISINTEGRATING tab for actively vomiting patients without an IV**

- ondanestron DISINTEGRATING tab 8 mg PO q8h PRN for nausea/vomiting
- ondanestron DISINTEGRATING tab _____ mg PO__________________
Disposition Planning

1. Considerations for admission (PICO 25)
   - Unstable patient (shock) who received lytics
   - Patients with a total simplified Pulmonary Embolism Severity Index (sPESI) score of 1 or greater (each score component below scores 1 point): (Appendix D)
     - Age greater than 80
     - History of cancer
     - History of CHF or chronic lung disease
     - Heart rate greater than 110
     - Systolic BP less than 100 mmHg
     - Oxygen Saturation less than 90%
   - Patients with signs of elevated right heart pressure
     - Echo indicating right ventricular (RV) hypokinesis or dilation
     - Elevated troponin or BNP level greater than 90 nanograms/L
     - Incomplete or complete right bundle branch block (RBBB)
     - Pulmonary hypertension on ECG (S1Q3T3 or T-Wave Inversion in leads V1-V4)
   - High risk for anticoagulant-related bleeding (active bleeding or recent bleeding episode within 4 weeks, recent surgery or trauma [within 1 week], thrombocytopenia [platelet count less than 100 x 10^9/L], coagulopathy, or advanced cancer with intracranial or intrahepatic metastases or apply REITE risk tool\textsuperscript{13} \textcolor{blue}{http://www.mdcalc.com/riete-score-risk-hemorrhage-pulmonary-embolism-treatment/}
   - Major comorbidities or other factors that warrant inpatient care (including impaired cognitive, self-care or adequate supports to ensure compliance with outpatient care requirements)

2. Considerations for discharge
   - The majority of patients with PE and a total simplified sPESI score of 0 can be safely discharged home, if they can access adequate follow up, are reliable for home care administration of medications and are otherwise healthy
   - The following considerations must be addressed prior to discharge:
     - Anticoagulation method
     - Patients with PE who were started on low molecular weight heparin (LMWH) in the emergency department may be sent home on the LMWH with a bridge to warfarin or dabigatran or can be switched to rivaroxaban or apixaban.
     - For patients with active cancer, pregnancy, iliofemoral DVT, or submissive PE LMWH should be used alone without transition to warfarin/DOACs (Appendix E)
     - Dosing regimens:
       - LMWH x 5 to 10 days + warfarin
         - enoxaparin 1.5 mg/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min)
         \textbf{OR}
         - enoxaparin 1 mg/kg SUBCUTANEOUSLY q12h (preferred for cancer patients or extensive clot burden and consider dosage reduction for GFR less than 30 mL/min)
         \textbf{OR}
         - dalteparin 200 units/kg SUBCUTANEOUSLY daily (dose...
unchanged for cancer patients but consider dosage reduction for GFR less than 30 mL/min)

OR
- tinzaparin 175 units/kg SUBCUTANEOUSLY daily (dose unchanged for cancer patients but consider dosage reduction for GFR less than 30 mL/min)

AND
- warfarin 5, 2.5, 7.5, or 10 mg PO daily with INR 2nd day post discharge from the ED, to be monitored by Internal Medicine, Hematology, Family Medicine or anticoagulation management clinic where available to adjust warfarin dose to achieve an INR of 2 to 3 for 2 days before stopping LMWH

OR
- rivaroxaban 15 mg PO BID x 3 weeks, then 20 mg PO daily (a preferred agent for patients over the age of 80 and a GFR of greater than 30 mL/min)
- Note: Alberta Health publicly funded plans, including Blue Cross, will cover 6 months of therapy with completion of a Special Authorization Form (Appendix F)

OR
- apixaban 10 mg PO BID x 7 days, then 5mg PO BID (recommended DOAC for patients with a GFR of less than 30 mL/min but greater than 15 mL/min and for patients over the age of 80) Note: Alberta Health publicly funded plans, including Blue Cross, will cover 6 months of therapy with completion of a Special Authorization Form

OR
- LMWH x 7 days, then start dabigatran
  - enoxaparin 1.5 mg/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min)

OR
- enoxaparin 1 mg/kg SUBCUTANEOUSLY q12h (preferred for cancer patients or extensive clot burden and consider dosage reduction for GFR less than 30 mL/min)

OR
- dalteparin 200 units/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min)

OR
- tinzaparin 175 units/kg SUBCUTANEOUSLY daily (consider dosage reduction for GFR less than 30 mL/min

THEN
- dabigatran 150 mg PO BID/twice daily (*** dabigatran is not covered by Alberta Health publicly funded plans) [Appendix F]
  - To be started only after treatment with a parenteral
anticoagulant for 5-10 days and the length of therapy may vary based on individual patient assessments and bleeding risk.

- For treatment or prevention of DVT/PE, recommended dose adjustments are as follows:
  - General patient population: 150 mg twice daily
  - For moderate renal impairment (eCrCl 30 to 50 mL/min): 110 mg twice daily
  - For elderly patients older than 80 years or patients at higher risk of bleeding (age older than 75 years with more than 1 risk factor for bleeding): 110 mg twice daily
  - For more information please access the drug monograph (Page 29 and Table 16):

- Risk and benefit of different anticoagulants:
  - DOACs: do not require blood tests but antidotes/reversible agents are not as established as warfarin reversal
  - Warfarin: requires frequent blood tests but does have established reversal agents it required for severe bleeding or pre operatively for emergency surgery

- Reasons to return the ED
  - New onset CNS symptoms: seizures, headache, syncope, speech problems, focal weakness
  - Increasing symptoms of worsening chest pain, shortness of breath or hemoptysis
  - Fever

- Reversal of bleeding on DOACs ([Appendix E](#))

3. Outpatient follow-up
   - Follow up with your family doctor / internal medicine / hematology / anticoagulation management clinic
     - within 48 hours regarding INR follow-up and warfarin dosing if not started on DOAC
     - Within 1 week, any patient ruled out for PE but ongoing symptoms
     - Any new symptoms of bleeding

4. Patient education / discharge instructions ([Appendix C](#))
   - a. Pulmonary Embolism: After Your Visit
   - b. How to Give a Heparin Shot: After Your Visit
   - c. Taking Blood Thinners Other Than Warfarin: After Your Visit
   - d. Taking Warfarin Safely: After Your Visit
Rural Considerations
The major challenges and considerations from a rural perspective are:
- Capability of treating unstable patients with a possible PE
- Timely access to appropriate lab and DI tests
- Inpatient facilities and/or ability to transfer patients suitable for admission
- Timely outpatient follow-up for patients in whom anti-coagulation has been initiated

Patient Experience and Expectations
Based on a meeting with 8 patient advisors in Calgary January 25, 2015, we received the following feedback and general recommendations regarding approaches to communication, care and patient expectations in the emergency department (ED):

1. They hoped we would be able to improve care consistency among ED providers.
   
   Patient quote: “Every time I presented to the emergency department with the same condition (atrial fibrillation), each doctor provided a different treatment approach.”

2. They were supporters of care pathways, checklists, protocols, etc. wherever appropriate.
   
   Patient quote: “I am a strong supporter of care pathways as whenever I/my family member receive treatment using a pathway the care seems clearer and more consistent”

3. While none of the patients liked long waits, they could accept them better if there was clearer communication and reassessments as required.
   
   Patient quote: “Nobody likes to wait and I understand that sicker patients take priority, however, there needs to be improved communication and reassessments for those patients who are waiting”

4. They pointed out the importance of having a patient advocate accompany a sick person, but also allowing the advocate to be with the patient at decision critical points (e.g. initial assessment, treatment decision making, receiving bad news, etc.) was considered paramount.
   
   Patient quote: “When I accompany my family member to the ED I am often not permitted to join them when they are moved into a treatment space. I am often told this is ‘policy’.”

5. They believe that improving follow up, especially for patients being discharged from the ED and being referred to a specialist is important. This was recognized as a key safety risk for patients; having to rely on faxed referrals and a call back from the consultant’s office can lead to dangerous delays or failed connections to the detriment of the patient’s health and well-being.
   
   Patient quote: “The current health care system is poorly coordinated with lots of gaps and delays, especially with referrals from one physician to another.”
Preparation for Analytics

1. Key Outcomes
   - Clinical Outcomes
     - Appropriate risk stratification of suspected PE patients
     - Few missed or delayed PE diagnoses
     - Effective outpatient management of stable PE patients
   - Process Outcomes
     - Broad use of standardized risk scoring
     - Improved access to anticoagulation clinics for long term planning
   - Patient Experience
     - Patient and family kept informed of clinical suspicions and management plan
     - Effectively engaged in their own ‘informed’ decision making
     - Disposition plan clear and met the patient’s needs and expectations

2. Data Elements for Capture
   - Patient demographics
   - CEDIS presenting complaint and CTAS score
   - ED time markers (triage to physician, physician to consult and then to admission or physician to discharge) and outcome markers (identified as CDU patient, consulted for admission, admitted to ICU or ward, died)
   - ED diagnoses ICD 10 for PE, aortic dissection, ACS
   - Site and zone identifiers
   - Date and time of use of PE order set use
   - Date and time of ED LMWH injection
   - Date and time of D-Dimer ordering
   - Date and time of CT or V/Q ordering
   - D-Dimer and CT results
   - Discharge instructions provided
   - Time and location of next physician/clinic follow up
   - Discharge medications (using PIN [Pharmaceutical Information Network])
References

1. Data provided by Data Integration and Management Resources (DIMR) March 2015
Appendix A - PICO-D Questions (Key Clinical Questions)

For information regarding PICO-D Methodology and GRADE Terminology please see Appendix B

**PICO 1: Are there clinical indicators in patients with a new diagnosis of venous thromboembolism (VTE) which should prompt investigation or consultation to look for genetic hypercoagulable risk factors to determine length of anticoagulation?**

*Population, Patient or Problem:* Emergency department patients with newly diagnosed Venous Thromboembolism (VTE)

*Intervention, Prognostic Factor, Exposure:* Selective screening for hypercoagulability

*Comparison:* Random screening for hypercoagulability

*Outcome:* Sensitivity, specificity, cost effectiveness, safety

*Design:* Systematic reviews of RCT’s or observational studies

*Search Strategy:* Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were searched

*Clinical Recommendation:* There is insufficient evidence to make a firm recommendation regarding which patients should be considered for thrombophilia testing in the emergency department prior to initiating anticoagulation.12,3 We have included the criteria and link to the “Thrombophilia testing” policy and procedure guideline for the Calgary Zone published January 2010 which stated thrombophilia testing should be considered in the following situations.4

1. All patients with first episode of idiopathic VTE.
2. Patients with recurrent VTE irrespective of the presence of risk factors.
3. Patients with VTE at unusual sites such as cerebral venous sinus, retinal vein thrombosis, upper extremity thrombosis, mesenteric or hepatic vein thrombosis. Screening is not routinely recommended in portal or splenic vein thrombosis or arterial thrombosis.
4. Women of child bearing age with prior idiopathic VTE or transient provocative factor such as oral contraceptives therapy, estrogen replacement therapy or pregnancy.
5. Women with two or more consecutive miscarriages during the first trimester, or one miscarriage after first trimester, or three non-consecutive miscarriages at any gestational age.
6. Women with prior severe or recurrent pre-eclampsia or unexplained fetal death after 20th week gestational age.
7. Asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia including protein C or S deficiency, antithrombin III deficiency, Factor V Leiden, Prothrombin G202210A. APLA should be tested in female relatives of child bearing age.
8. Testing should only be offered after counseling on potential implications.
9. Testing for antithrombin III should not be done in the setting of acute thrombosis or while on heparin products.
10. Testing for Protein C and Protein S should not be done in the setting of acute thrombosis or while on warfarin.
11. Testing for Protein S should not be done during pregnancy or on hormone therapy.

**Quality of Evidence:** Low, GRADE C. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Strength of Recommendation:** Insufficient evidence

**References:**

**PICO 2:** In adult patients presenting to the ED pulseless with PEA are there clinical criteria to help identify patients with possible massive/saddle pulmonary emboli to guide thrombolysis?

**Return to Table of Contents**
**Return to Initial Decision Making**

**Population, Patient or Problem:** Adults presenting in PEA

**Intervention, Prognostic Factor, Exposure:** Clinical history directed thrombolysis

**Comparison:** Indiscriminate thrombolysis all/any PEA patient

**Outcomes:** Return of spontaneous circulation, PE diagnosis, admission to ICU, survival

**Design:** Prospective or Cohort studies (using Reference standard +/- Retrospective Observational Studies [ROS] curves) / meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** There is insufficient evidence and lack of consensus to make a recommendation regarding whether there are clinical criteria to help identify patients with possible massive/saddle pulmonary emboli to guide thrombolysis. The American Heart Association in their 2011 scientific Statement on the management of massive and submassive pulmonary embolism...
stated “fibrinolysis is not recommended for undifferentiated cardiac arrest”, however, did state “fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications” (Class IIa; Level of Evidence B).\(^1\)

The Canadian pre hospital RCT showed no benefit to TPA over placebo for PEA cardiac arrest but the study lacked the power to definitively rule out effectiveness.\(^2\) A European RCT comparing thrombolysis to placebo in out of hospital cardiac arrest also found no benefit and the trial was terminated for futility after 1050 patients were enrolled.\(^3\) One prospective study examined whether PE was responsible for patients with sudden cardiac arrest as a results of PEA.\(^4\) The study examined patients in a level 1 trauma center. The study found that 8 out of 25 patients with PEA also had pulmonary embolism. The study concluded that the rate of pulmonary embolism was high among patients with PEA; however the sample size of the study was considerable small.\(^4\) No recommendations on thrombolysis were made.

Another retrospective study\(^5\) examined whether PE was a predictor of sudden death in patients with PEA and witnessed cardiac arrest. The study examined the medical charts of adults presenting to the ED with sudden death. The study found patients with witnessed cardiac arrest and PEA had a high probability of massive pulmonary embolism. No recommendations on thrombolysis were made.

A review article in 2000 looked at nine case reports totalling 67 patients who were thrombolysed during cardiac arrest with known or suspected pulmonary embolism and reported an overall survival rate of 75%.\(^6\) New evidence on this topic is unlikely to come forward. It does seem reasonable that for patients with pre-existing VTE or high risk for VTE, who have a witnessed arrest, a short down time, and present in PEA, early thrombolysis could be justified.

**Quality of Evidence:** Low, GRADE C. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Strength of Recommendation:** Insufficient evidence

**References:**


**PICO 3:** In adult patients presenting to the ED pulseless with PEA and suspected massive/saddle PE is alteplase superior to tenecteplase (TNK)?

**Population, Patient or Problem:** Adults presenting in PEA with suspected PE  
**Intervention, Prognostic Factor, Exposure:** Alteplase  
**Comparison:** Tenecteplase (TNK)  
**Outcomes:** Return of spontaneous circulation, ICU admission, bleeding complications, survival  
**Design:** Randomized Controlled Trials (RCTs)/meta-analysis of RCTs

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** There is insufficient evidence and lack of consensus to make a recommendation regarding whether there are clinical criteria to help identify patients with possible massive/saddle pulmonary emboli to guide thrombolysis, however, whichever thrombolytic is chosen bolus dosing, not slow infusion is required.

The American Heart Association in their 2011 scientific Statement on the management of massive and submassive pulmonary embolism notes that alteplase is currently approved for use in PE patients but TNK has not yet been approved for this role, however, noted that 2 trials TOPCOAT and PEITHO were looking at tenecteplase in submassive PEs. In addition the Canadian RCT used t-PA and the European study used tenecteplase, both of which can and were given as bolus dosing which is a requirement in a cardiac arrest situation. The results appeared to show some trending towards favourable outcomes, with increased bleeding risk, especially in patients over 65 years of age. The studies were not powered to show a clear benefit.

No studies examining Alteplase vs. TNK in patients with PEA with suspected PE were available.

**Quality of Evidence:** Very Low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Strength of Recommendation:** Insufficient evidence

**References:**


**PICO 4: In hemodynamically unstable adult patients presenting to the ED with a suspected PE what diagnostic test is most appropriate?**

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Return to Initial Decision Making

**Population, Patient or Problem:** Hemodynamically unstable adults presenting with suspected PE

**Intervention, Prognostic Factor, Exposure:** CT

**Comparison:** Transthoracic echocardiogram (TTE) and transesophageal echo (TEE)

**Outcomes:** Diagnostic accuracy, patient safety, patient tolerance/ability to cooperate, time to test completion,

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that spiral CT and TEE both have high sensitivity and specificity in diagnosing PE in hemodynamically unstable patients.

The European society of cardiology\(^1\) states that TEE has diagnostic value in hemodynamically unstable patients due to the high prevalence of bilateral central pulmonary emboli in most cases. Pruszczynk found TEE had high sensitivity and specificity.\(^2\) A study comparing TEE vs. spiral CT found that both tests were similarly effective in regards to their high sensitivity and specificity in diagnosing PE.\(^3,4\)

**Quality of Evidence:** Low, GRADE C. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. A very limited number of
studies comparing diagnostic tests for hemodynamically unstable patients with suspected PE

**Strength of Recommendation:** GRADE 2, Weak

**References:**

**PICO 5:** In hemodynamically unstable adult patients presenting to the ED with a suspected PE and treated with thrombolysis, what is the preferred heparin choice?

**Population, Patient or Problem:** Hemodynamically unstable adults presenting with suspected PE  
**Intervention, Prognostic Factor, Exposure:** Low molecular weight heparin (LMWH)  
**Comparison:** Unfractionated heparin (UFH)  
**Outcomes:** Patient safety, bleeding events, morbidity, mortality  
**Design:** Randomized Controlled Trials (RCTs)/meta-analysis of RCTs  

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that unfractionated heparin (UFH) is preferred for patients likely to receive primary reperfusion based on the short half life, ability to monitor the anticoagulant effects and ability to rapidly reverse in the face of uncontrolled bleeding.\(^1\,^2\) UFH can be switched to LMWH several hours after completion of thrombolysis once it is confirmed that bleeding has not occurred. While there is evidence to suggest that LMWH and unfractionated heparin are similar in regards to their effect on mortality and re-bleeding, the results may not be applicable to hemodynamically unstable patients.

A 2004 meta-analysis compared LMWH vs. unfractionated heparin to treat symptomatic pulmonary embolism in adults. The study included 14 RCTs which included patients with symptomatic
proximal DVT, symptomatic PE, symptomatic VTE, and symptomatic DVT with PE. Results from a meta-analysis found LMWH to be similar to unfractionated heparin in mortality, bleeding, and recurrent symptomatic venous thromboembolism.\(^3\) A recent 2014 retrospective study found mortality rates to be similar in patients receiving LMWH or unfractionated heparin in patients with PE.\(^4\) Another Cochrane review found that patients receiving LMWH had reduced mortality and haemorrhagic episodes than patients receiving unfractionated heparin.\(^5\)

**Quality of Evidence:** Very Low, GRADE D. We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

**Strength of Recommendation:** Weak, GRADE 2

**References:**

**PICO 6:** In hemodynamically stable patients presenting to the ED with a possible PE, does applying a structured risk stratification criteria (through decision rules) improve risk stratification estimates?

**Population, Patient or Problem:** In a broad spectrum of patients with suspected pulmonary embolism

**Intervention, Prognostic Factor, Exposure:** Does the application of structured risk stratification criteria (through decision rules)

**Comparison:** Compared to an unstructured approach or clinical gestalt

**Outcome:** Improve risk stratification estimates
Design: Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

Search Strategy: Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

Clinical Recommendation: We suggest that application of clinical prediction rules allow for reproducible predictability of pre-test probably for patients suspected of having a PE. Both the 2 and 3-level Wells rules and the revised and simplified Geneva rule categorize patients into similar risk categories.\(^1,2,3\) Wells original study of 930 ED patients with suspected PE stratified them into low, moderate and high risk of PE with rates of 1.3%, 16.2%, and 37.5% respectively.\(^4\) Using the 2-level modified Wells a score of \(\leq 4\) (unlikely) and a negative D-dimer they found a PE rate of 2.2% (95% CI = 1.0% to 4.0%) in the derivation set and 1.7% (95% CI = 0.3% to 8.0%) in the validation set.\(^5\)

In populations with a PE prevalence of 7% or less (equivalent to Wells score of less than 2), the PERC rule can be applied to patients presenting to ED with suspected PE, in conjunction with clinical judgment, to identify patients with a prevalence of PE that is below the 1.8% test threshold proposed by Kline et al.\(^6,7\)

Quality of Evidence: Low, GRADE C. Our confidence in the effect estimate is limited.

Strength of Recommendation: Weak, GRADE 2

References:
6. Rehnberg JV. BET 3: Pulmonary embolism rule-out criteria (PERC) for excluding pulmonary


**PICO 7: In hemodynamically stable adult patients presenting to the ED with a possible PE is one risk score superior to the others?**

**Population, Patient or Problem:** Hemodynamically stable adults presenting with possible PE  
**Intervention, Prognostic Factor, Exposure:** Wells criteria  
**Comparison:** Revised Geneva / Charlotte  
**Outcomes:** diagnostic accuracy, role of D-dimer, patient safety  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that the Wells score and Geneva, and Charlotte rules are similarly accurate; however the rules differ in regards to their specificity and sensitivity. For simplicity and based on its derivation within a Canadian emergency department population the 2-level modified Wells rule be the preferred choice.\(^1\),\(^2\) It is recommended that none of the rules are sensitive enough to be used alone to exclude PE, but rather, should be used in conjunction with D-Dimer testing.

The European Society of Cardiology (ESC) 2014 guidelines states that the Wells rule and the revised Geneva rule are both validated rules, which have also been changed from 3 risk groups down to 2 (likely versus unlikely).\(^3\)

A systematic review\(^4\) examined the accuracy of various clinical prediction rules. The review included 29 studies. The review found that the 2 and 3 level Wells scores, Geneva and revised Geneva scores, and the Charlotte rule to be the most extensively validated rules. The review concluded that the Wells score, Geneva score, and Charlotte rule overall were similar in regards to accuracy, however the choice of score should depend on the local prevalence of PE, type of patients, and type of D-Dimer test used. For example, the Wells score has been validated for use on outpatient and hospitalized patients, while the Geneva and Charlotte rule have only been validated in the outpatient population. The results of this review are similar to another meta-analysis\(^5\) which found that using either Gestalt, Wells2, Geneva, or revised Geneva scores had similar sensitivity for detecting PE; however neither was sensitive enough on its own to exclude PE. The review concluded that using either Gestalt or Wells or Geneva scores, in addition to D-Dimer testing, was a safe method for excluding PE.
A small non-randomized prospective study compared the effectiveness of ECG, Wells, Geneva, and Miniati scores to diagnosis PE in adult patients. The Wells and Miniati scores were found to be better and predicting a diagnosis of PE than ECG and Geneva clinical scoring. Another study found the Wells score to be more accurate in diagnosing acute PE than the modified Geneva score.

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: While studies were primarily prospective or retrospective non-randomized studies, two systematic reviews with similar outcomes were published comparing the accuracy of clinical prediction rules.

**Strength of Recommendation:** Strong, GRADE 1

**References:**

**PICO 8:** In hemodynamically stable adult ED patients identified as ‘high risk’ for PE does the result of a D-Dimer influence diagnostic imaging testing?

**Population, Patient or Problem:** Hemodynamically stable adult ED patient at high risk for PE
**Intervention, Prognostic Factor, Exposure:** Wells criteria/ clinical judgment alone

**Comparison:** Wells criteria/clinical judgment plus negative D-Dimer

**Outcomes:** diagnostic accuracy, frequency of high risk having a negative D-Dimer, safety of withholding DI imaging with a negative D-Dimer

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that D-Dimer should not be measured in patients with a high risk (likely) for PE, due to the low negative predictive value of the high-risk population.

The ESC 2014 guideline, National Institute for Health and Care Excellence (NICE) guideline and Scottish Intercollegiate Guidelines Network (SIGN) guideline all recommend against measuring D-Dimer in patients considered high risk for PE, due to the low negative predictive value of this population and the need for definitive diagnostic imaging to be able to rule out a PE. Righini recommends that D-Dimer should only be measured in patients with low/intermediate risk for PE.

The ESC 2014 guideline recommends that patients at high risk for PE should receive a CT angiography to confirm whether or not they have a PE.

**Quality of Evidence:** Moderate, GRADE B. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Strength of Recommendation:** Strong, GRADE 1

**References:**

**PICO 9:** In hemodynamically stable adult ED patients at risk for PE (low/intermediate/high),
what is the risk of a single dose of heparin prior to imaging if there is a delay in obtaining DI?

Population, Patient or Problem: Hemodynamically stable adult ED patient
Intervention, Prognostic Factor, Exposure: Single dose of heparin
Comparison: No heparin until definitive diagnosis
Outcome: Complications of heparin (HITT, bleeding) vs. risk of delaying heparin if PE does exist
Design: Randomized Controlled Trials (RCTs)/meta-analysis of RCTs

Search Strategy: Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

Clinical Recommendation: There is insufficient evidence and lack of consensus to make a recommendation regarding the risk of providing a patient with single dose of heparin prior to imaging if there is a delaying in obtaining DI, however, all the major guidelines recommend anticoagulation (generally LMWH) be provided to patients if there is to be a delay (NICE says beyond 4 hours) in getting definitive diagnostic imaging.1,2,3

A retrospective cohort study found that some physicians did provide heparin to a small sample of patients prior to a confirmed diagnosis.4 The patients tended to be acutely ill with a high probability of PE. The study did not note any differences in outcomes between patients that did or did not receive early heparin, and few complications were identified. A non-systematic report conducted an estimate of mortality rate in patients with suspected PE receiving heparin before confirmation based on previously published data in studies.5 The paper searched for studies in which diagnosis confirmation was delayed by either one or two days, or one week. The study estimates that mortality in patients receiving heparin is 25% in patients with LMWH, and 30% unfractionated heparin and does not recommend providing outpatients with heparin while waiting for a definitive diagnosis.

Quality of Evidence: Very Low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Strength of Recommendation: Insufficient evidence

References:


**PICO 10: In hemodynamically stable adult ED patients at low risk (less than 15%) for PE, do negative PERC criteria rule out at PE?**

**Population, Patient or Problem:** Hemodynamically stable adult ED patient at low risk for PE

**Intervention, Prognostic Factor, Exposure:** PERC criteria negative (NO to all questions)

**Comparison:** Usual care (including D-Dimer +/- other diagnostic testing)

**Outcomes:** Diagnostic accuracy, optimizing diagnostic test ordering, low enough estimate of probability to cease further testing

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest the PERC criteria could be used to effectively exclude PE in patients with low risk for PE. PERC was developed and prospectively tested in 2004 in a low risk group of 1427 patients (PE prevalence 8%) yielding a sensitivity of 96% and a PE prevalence among the PERC rule out group of 1.4% (95% CI 0.5-3.0%).

This result was confirmed in a validation study on 1952 PERC negative, low risk patients showing a sensitivity of 95.7% (95% CI 93.6–97.2%), and a false negative rate of 1.3% (95% CI 0.8–1.9%).

A systematic review was identified which examined the accuracy of the PERC rule to diagnose PE included 13 non-randomized studies. Overall, the review found to be effective in ruling out PE in patients with low risk. The sensitivity and specificity positive likelihood ratio was (0.97 95% CI: 0.96 to 0.98; and 0.22 95% CI: 0.22 to 0.23 respectively, while the sensitivity and specificity negative likelihood ratio was (1.22 95% CI: 1.16 to 1.29 and 0.17 95% CI: 0.13 to 0.23) respectively. The miss rate of the PERC rule was 0.3% when used alone, and 0.296% when used in combination with clinical gestalt. The review suggested that the PERC rule could rule out PE without the need for additional testing. Interestingly, another systematic review that examined various clinical
decision rules (including Wells, Geneva, and the PERC rule) stated that none of the decisions rules were sensitive enough to exclude PE on their own, and required an additional D-Dimer test to exclude PE. This review only identified 3 studies which examined the PERC rule compared to the 13 identified in the Singh 2013 review.

A study completed in 2014 examined the rate of PE diagnosis after D-Dimer testing in patients who were PERC negative patients. The study found that 0.5% (5 of 1070) of patients who were PERC negative were actually positive for PE after confirmation with D-Dimer test. An additional 15% of patients had a positive D-Dimer score, but additional imaging revealed the patient was negative for PE.

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. A systematic review of non-randomized studies was available.

**Strength of Recommendation:** Weak, GRADE 2

**References:**

**PICO 11:** In low risk PE but PERC negative or inapplicable, does negative D-Dimer rule out PE?

**Population, Patient or Problem:** Patients who have a low clinical probability of PE but one cannot apply PERC (e.g. 65 or older) or fails the PERC rule

**Intervention, Prognostic Factor, Exposure:** Does a negative quantitative D-Dimer

**Comparison:** Compared to non-use of D-Dimer testing in clinical decision making
**Outcome:** yield sufficiently low estimates of probability to cease further objective testing  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis  
**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.  
**Clinical Recommendation:** We recommend that a negative D-Dimer test is sufficient to exclude PE without the use of additional diagnostic testing in patients with low risk for PE. Current guidelines recommend that a negative D-Dimer measurement could be used to safely exclude PE in low risk patients.  

No studies could be identified on whether a negative D-Dimer result can exclude PE despite a positive PERC score in low risk patients. There is evidence to suggest however, that a negative D-Dimer result can exclude PE alone. The ESC 2014 guidelines recommend that in low risk patients (patients without shock or hypotension), a negative result of either a highly sensitive, or moderately sensitive D-Dimer test can be safely discharged.\(^1\) NICE and SIGN guidelines make the same recommendation.\(^2,3\) A similar recommendation was made by the American college of emergency physician’s clinical policies subcommittee.\(^4\) This recommendation was based on an RCT which found that patients at low risk for PE with a negative D-Dimer can be discharged without the need for additional testing.\(^5\)  
**Quality of Evidence:** High, GRADE A. We are very confident that the true effect lies close to that of the estimate of the effect.  
**Strength of Recommendation:** Strong, GRADE 1  

**References:**  

**PICO 12:** In patients with renal failure (insufficiency) is V/Q be preferred over CT to diagnose PE?

**Population, Patient or Problem:** In patients with renal failure

**Intervention, Prognostic Factor, Exposure:** V/Q scan

**Comparison:** CT with PE Protocol

**Outcome:** Sensitivity and specificity for PE diagnosis, maternal/foetal safety, impact on post-test renal function

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that while there is limited research on this patient population the European Society of Cardiology GL¹, NICE GL² and PIOPED II Investigators³ all recommend compression ultrasound if signs of DVT and/or V/Q scan for patients whose renal functional impairment makes CTPA too risky but they are clinically ‘likely’ to have PE. For chronic dialysis patients CTPA is the investigation of choice.

A retrospective study examined the characteristics of patients with impaired renal function who underwent CTPA and V/Q scanning, compared to those patients with renal failure who only received a V/Q.⁴ Recurrent PE, and mortality were similar between patients in both groups, while those patients that received only V/Q had significantly higher creatinine levels. The study noted no worsening of renal function in patients receiving CTPA. The study did not compare the sensitivity or specificity of PE diagnosis between CTPA and V/Q.

**Quality of Evidence:** Low, GRADE C. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Strength of Recommendation:** GRADE 2, Weak

**References:**


**PICO 13: In pregnant patients presenting to the ED with suspected PE can D-Dimer be used to rule out PE in low risk patients?**

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**Return to Initial Decision Making**  

**Population, Patient or Problem:** Pregnant patients with suspected low risk for PE  
**Intervention, Prognostic Factor, Exposure:** D-Dimer levels  
**Comparison:** D-Dimer levels in similar non-pregnant demographic population  
**Outcome:** Sensitivity for rule out PE  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis  

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that a negative D-Dimer in a low risk patient is as effective at ruling out PE in a pregnant patient as a non-pregnant patient.

Pregnancy is an independent risk factor for VTE with rates up to 10 fold higher than their non-pregnant cohort.1,2 At the same time during normal pregnancy, however, circulating D-Dimer levels progressing increase during the gestational period leading to significant numbers of false positives based on the standard 0.5 mg/L cuttoff.3

The ESC 2014 guidelines reports that D-Dimer levels increase throughout pregnancy. Currently, the usual values for D-Dimer cut-offs are applied when testing pregnant patients.1 There are currently no adjusted D-Dimer cut-offs for pregnant patients, to assist with decision making.3 The ESC 2014 guidelines recommends that in the case of a positive D-Dimer, lower-limb CUS should be conducted to confirm the diagnosis of DVT. No specific alternative test for PE was stated.

**Quality of Evidence:** Very Low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Strength of Recommendation:** Insufficient evidence to make any further recommendations reading how to interpret "normal" D-Dimer elevations in low PE risk pregnant patients.
References:

**PICO 14: In pregnant women with suspected PE, does V/Q minimize side effects to both mother and fetus, yet still have the accuracy to diagnose PE?**

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Return to Initial Decision Making

**Population, Patient or Problem:** In the pregnant population  
**Intervention, Prognostic Factor, Exposure:** V/Q scan  
**Comparison:** Compared to CT  
**Outcome:** Sensitivity and specificity for PE diagnosis, maternal/foetal safety  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that V/Q scanning is a viable and safe method of detecting PE in pregnant patients. The test does have a high risk of non-conclusive tests however, resulting in a need for further testing.

The American thoracic society/Society of thoracic radiology clinical practice guidelines\(^1\) states that there are currently no high quality studies which have assessed the accuracy of V/Q scan to detect PE in pregnant patients. The American Thoracic Society/Society of thoracic radiology clinical practice guidelines recommends that pregnant patients with suspected PE and normal chest x-ray, lung scintigraphy should be the next imaging test used to detect PE rather than CT pulmonary angiography (CTPA). Non-randomized studies have found V/Q to be a safe test, with a reduced risk of radiation exposure compared to CT testing, and efficient in identifying PE.\(^{1,2,3,4,5}\) A major problem with V/Q, however, is the relatively high number of non-conclusive tests, resulting in the need for further tests.\(^6\) The efficacy of V/Q and CTPA were found to be similar, and that the choice of test should rely on concerns over radiation exposure.\(^{3,5,7}\)

The ESC guidelines state that the amount of radiation exposure to breast tissue is 10-70 mSv in CTPA while only 0.28 to 1.20 mSv in a perfusion lung scan.\(^8\)
A local study identified that PE can be ruled out in 82.4% of patients with a normal CXR.9

**Quality of Evidence:** Low, GRADE C. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Strength of Recommendation:** GRADE 2, Weak

**References:**


**PICO 15:** In pregnant women with suspected PE, are bilateral venous ultrasounds of the lower limb sufficient to diagnose PE?
**Population, Patient or Problem** Pregnant patients with suspected PE  
**Intervention, Prognostic Factor, Exposure:** Bilateral venous ultrasounds  
**Comparison:** Radioisotope imaging (V/Q or CT)  
**Outcome:** Sensitivity and specificity for PE diagnosis, maternal/fetal safety  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** There is insufficient evidence to support the indications for bilateral venous ultrasounds. If a woman presents with signs and symptoms of a PE and a DVT were identified on ultrasound VTE treatment would be required anyway, negating the need for subjecting the mother and fetus to any form of radiation, however, without clear signs of a DVT the likelihood of a positive ultrasound is low. This suggestion is based on expert opinion, as no evidence for the use of lower-limb CUS in pregnant patients to diagnosis PE is currently available.¹

The ESC 2014 does not specifically provide a recommendation on the use of ultrasounds for pregnant patients with PE.² The ESC guidelines recommend that for patients with suspected PE and DVT, a lower-limb CUS should be conducted to confirm the diagnosis.

The American thoracic society/Society of thoracic radiology clinical practice guidelines suggests that patients with suspected PE with no signs or symptoms of DVT should undergo studies of the pulmonary vasculature rather than lower-limb CUS.³ The guideline states that currently, there is no evidence for the use of bilateral lower-limb CUS for the diagnosis of PE. The authors suggest that for pregnant patients presenting with suspected PE and DVT, a bilateral lower-limb CUS should be conducted, followed by anticoagulation therapy if positive, and further testing if the results are negative.

**Quality of Evidence:** Very Low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Strength of Recommendation:** Insufficient evidence

**References:**
**PICO 16:** What is the sensitivity of a negative D-Dimer in Wells ‘unlikely’ or low and moderate pre-test probability patients?

**Population, Patient or Problem:** In adult ED patients at risk for PE (unlikely, low, and moderate PTP)

**Intervention, Prognostic Factor, Exposure:** A negative D-Dimer (weak test)

**Comparison:** PE selective diagnostic imaging (strong test)

**Outcome:** Sensitivity rule out a PE

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that a negative D-Dimer test is sufficient to clinically rule out unlikely or low-probability for PE patients applying Wells criteria or Geneva scores without further testing. Measuring D-Dimer in high probability patients should not be conducted due to the low negative predictive value.

The ESC 2014 and UK NICE guidelines recommend that in low probability patients, a negative result of either a highly sensitive, or moderately sensitive D-Dimer test can be safely discharged without further testing. A similar recommendation was made by the American college of emergency physician’s clinical policies subcommittee.

Randomized studies compared the efficacy of D-Dimer to exclude PE in patients assessed as low-probability (prevalence of PE 10-15%) vs. those patients assessed as either moderate or high probability (prevalence 30% or higher). They reported that it was safe to avoid additional diagnostic testing in low-probability patients with negative D-Dimer results.

**Quality of Evidence:** High, GRADE A. We are very confident that the true effect lies close to that of the estimate of the effect.

**Strength of Recommendation:** Strong, GRADE 1

**References:**


**PICO 17:** In ED patients receiving anticoagulation, with or without a previous VTE, what is the usefulness of the D-Dimer?

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**Return to Order Set Components - Lab Investigations**

**Population, Patient or Problem:** Undifferentiated ED patient on anticoagulation

**Intervention, Prognostic Factor, Exposure:** Diagnostic decision making supported by D-Dimer value

**Comparison:** Diagnostic decision making ignoring D-Dimer testing or value

**Outcome:** Sensitivity and specificity of PE diagnosis, patient safety, test performance

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** There is insufficient evidence and lack of consensus to make a recommendation regarding the usefulness of D-Dimer in patients receiving anticoagulation.

**Quality of Evidence:** Very Low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Strength of Recommendation:** Insufficient evidence

**PICO 18:** Is it safe to exclude PE in older patients with an age adjusted D-Dimer cutoff?
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Return to Order Set Components - Lab Investigations

Population, Patient or Problem: In older patients with unlikely probability of PE and a D-Dimer above the standard cutoff

Intervention, Prognostic Factor, Exposure: Age adjusted value under which no further investigations (V/Q, CT, U/S) are needed

Comparison: Non age adjusted values with increased testing

Outcome: Sensitivity and specificity to rule in or rule out a PE

Design: Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

Search Strategy: Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

Clinical Recommendation: We suggest that older patients who are unlikely/low risk to have PE and have a negative D-Dimer using the age adjusted cutoff values can forgo further testing.1 Current evidence suggests that the age-adjusted D-Dimer cut-offs have excellent sensitivity and improved specificity over conventional D-Dimer cut-offs, suggesting that following standard procedures of conducting additional testing after positive D-Dimer testing to confirm PE diagnosis should be implemented.

A prospective trial, the ADJUST-PE study examined the diagnostic yield of an age adjusted d-dimer cutoff 2. Patients with a low/intermediate probability for PE were tested with D-Dimer. In patients younger than 50 yrs, PE was excluded using a D-Dimer value of lower than 500 µg/L. In patients whom were 50 yrs old or older, a D-Dimer test was considered negative if the results of their D-Dimer test was lower than the patient’s age multiplied by 10 (age x 10 µg/L). The study found that using the age adjusted D-Dimer cut-off increased the diagnostic yield of D-Dimer testing. The proportion of patients 75 yrs and older and whom a diagnosis of PE could be safely ruled out with a single D-Dimer test increased from 43 of 673 patients (6.4% [95%CI, 4.8%-8.5%]) to 200 of 673 patients (29.7% [95%CI, 26.4%-33.3%]), without any additional false-negative findings. A retrospective multicentre European study found that applying the age-adjusted cutoff values to 1331 unlikely risk PE suspected patients the exclusion rate increased from 36 to 42% without an increase in the miss rate.3 A Belgian validation study also replicated similar findings with the greatest benefit observed in patients over 75 years of age where the number needed to test (NTT) halved from 8.1 to 3.6.4

A systematic review was identified which compared conventional D-Dimer cut-off (500 µg/L) vs. an age-related cut-off (age x 10 µg/L) in patients with suspected PE or DVT. Thirteen cohort studies were identified. The review found that specificity of the conventional D-Dimer cut-off decreased as the patients got older: 51-60 yrs 57.6% (95% CI: 51.4% to 63.6%), 61-70 yrs 24.5% (95% CI: 20.0% to 29.7%), and 71-80 yrs 14.7% (95% CI: 11.3% to 18.6%). In comparison, specificity increased using the age adjusted cut-offs in patients 51-60 yrs 62.3% (95% CI: 56.2% to 68%), 61-70 yrs 49.5% (95% CI: 43.2% to 55.8%), 71-80 yrs 44.2% (95% CI: 38.0% to 50.5%). Sensitivity of the age related cut-off remained high (greater than 97%) in all age groups. The review concluded that age related cut-offs increases the clinical utility of D-Dimer testing in low probability patients.
aged 50 yrs and older.\textsuperscript{5}

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Strength of Recommendation:** Weak, GRADE 2

**References:**

**PICO 19:** In emergency patients requiring imaging is CT-A more sensitive and/or specific than V/Q scan for the diagnosis of PE?

**Population, Patient or Problem:** Emergency patients who require advanced imaging for the evaluation of PE

**Intervention, Prognostic Factor, Exposure:** CT-A

**Comparison:** Nuclear scintigraphy (V/Q scan)

**Outcome:** Sensitivity and specificity, mortality, efficiency, availability, ED LOS

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that CTA and V/Q have similar abilities to rule out PE, though there is some evidence to suggest that more patients with clinically insignificant PE were diagnosed using CTA requiring additional clinical judgement in deciding when and who to treat. In
patients where exposure to radiation should be minimized (e.g. pregnant patients) Q scan +/- V/Q scanning maybe preferable.

The ESC 2014 guidelines state that V/Q maybe preferable in low probability patients with a normal chest x-ray, young, female, pregnant, patients with history of contrast medium-induced anaphylaxis and strong allergic history, severe renal failure, patients with myeloma and paraproteinaemia as a way to reduce exposure to radiation.¹

A multi-centre RCT compared CTA vs V/Q scanning.² The study found that more patients were diagnosed with PE in the CTA group, compared to patients receiving V/Q. Among patients in whom PE was initially excluded, 2 of 561 patients in the CTA group, and 6 of 611 in the V/Q group were found to have developed venous thromboembolism at follow-up, including one patient who underwent V/Q scanning who passed away as a result of PE. A prospective multi-center study found similar sensitivity between CTA and scintigraphy, though CTA had a higher specificity than lung scintigraphy.³

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Strength of Recommendation:** Weak, GRADE 2

**References:**

**PICO 20:** In patients with intermediate or high pre-test probability of PE, does a negative CT-A reliably exclude VTE?
Comparison: Additional testing
Outcome: Sensitivity and specificity to exclude the risk of missed VTE at 30 days, morbidity and mortality and specificity, mortality, efficiency, availability, ED LOS
Design: Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

Search Strategy: Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

Clinical Recommendation: We suggest that a normal CT angiogram safely excludes PE in most likely/intermediate or high risk patients.

The ESC 2014 guidelines recommends that CT angiography may safely exclude PE in patients with high clinical probability or PE-likely. The NICE guidelines offer the same recommendation with the caveat that any signs or concerns suggestive of DVT warrant CUS before ruling out VTE and looking for alternative causes of the patient’s presentation. The PIOPED II authors take a more cautious approach and for high risk negative CTPA recommend a venous CUS or MR venography and if still concerned either serial CUS, pulmonary subtraction angiography, or pulmonary scintography. These recommendations were based on their study results which suggested the negative predictive value of a normal CT angiogram was 60% and CT angiogram/CT venogram combined was 82%.

Quality of Evidence: Very low, GRADE D. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Strength of Recommendation: Weak, GRADE 2

References:

**PICO 21:** In the undifferentiated ED patient with a high pre-test probability for PE, is a...
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**Revision Date: January 2017**

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**negative V/Q sufficient to rule out PE?**

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**Return to Order Set Components - Diagnostic Imaging**

**Population, Patient or Problem:** ED patient deemed high risk for PE and V/Q scan negative

**Intervention, Prognostic Factor, Exposure:** Discharge and follow up

**Comparison:** CT-A prior to discharge

**Outcome:** Sensitivity and specificity, 30-day morbidity and mortality, cost

**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that in high probability patients with a normal chest x-ray and normal V/Q scan is generally sufficient to rule out PE.

The ESC 2014 guidelines recommends that a “normal perfusion lung scintigram excludes PE”.¹ Recommendations were made from the results of the Pulmonary Embolism Diagnosis (PIOPED) II trial.² The investigators found that in patients with a normal or near normal chest x-ray only 9% had non diagnostic V/Q scans, requiring further investigations. Anderson et al suggested that high probability patients with undiagnostic V/Q, a CTA should be considered to rule out PE, however, that CTPA was not inferior to V/Q scanning in ruling out pulmonary embolism.³ They posited, like several other authors that CTPA may in fact over diagnose clinically insignificant PEs leaving us in the dilemma to treat or not treat.

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Strength of Recommendation:** Weak, GRADE 2

**References:**


**PICO 22:** *In ED patients with a suspected central PE what are the indications for TEE compared to other diagnostic imaging modalities?*

**Population, Patient or Problem:** In patients with a suspected central PE  
**Intervention, Prognostic Factor, Exposure:** TEE  
**Comparison:** CT-A  
**Outcome:** Sensitivity and specificity, safety (not transported to DI, no contrast, able to sit up, etc.)  
**Design:** Prospective or Cohort studies (using Reference standard +/- ROC curves)/meta-analysis

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We suggest that patients TEE only be used to diagnose PE in hemodynamically unstable patients with unexplained dyspnea, syncope, or right heart failure.

The ESC guidelines\(^1\) recommends that if a test for a cardiac biomarker is positive, than either a TEE should be done to assess RV function, or RV size should be reassessed by CT. A narrative review recommended that TEE not be performed as the routine diagnostic test for those suspected with PE, because most patients with PE have normal echocardiograms.\(^2\) The review suggests that TEE is a useful diagnostic tool for hemodynamically unstable patients with unexplained dyspnea, syncope, or right heart failure. A prospective study found TEE in patients with suspected PE to have low sensitivity (between 29-52%; specificity 96 – 87%) and to not be effective in diagnosing PE. In comparison, the sensitivity of TEE in patients with right ventricular pressure overload was 80.5% with a specificity of 97.2%.\(^3\)

**Quality of Evidence:** Low, GRADE C. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Strength of Recommendation:** Weak, GRADE 2

**References:**
**PICO 23:** In ED patients with a diagnosis of PE, are the new anticoagulants as effective and as safe as warfarin?

*Population, Patient or Problem:* In ED patients with a diagnosis of PE  
*Intervention, Prognostic Factor, Exposure:* Direct oral anticoagulants (rivaroxaban, dabigatran)  
*Comparison:* Warfarin  
*Outcome:* Efficacy (recurrent PE, development of pulmonary hypertension), safety (bleeding risk)  
*Design:* Randomized Controlled Trials (RCTs)/meta-analysis of RCTs

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that new oral anticoagulants are a safe alternative to warfarin but not recommended in patients with severe renal impairment. While the evidence suggests that new oral anticoagulants are as similarly effective as warfarin in the treatment of recurrent VTE, current evidence suggests that patients receiving new oral anticoagulants are at a reduced risk of clinically relevant bleeding.¹

A systematic review was identified which compared direct oral anticoagulants (DOACs:, dabigatran, rivaroxaban, apixaban, edoxaban) vs. standard treatment in the treatment of venous thromboembolism.² The review included 10 studies of which six studies examined acute treatment of DOAC vs. warfarin in patients with either PE, DVT, or VTE. Overall, DOAC were similarly effective as standard therapy (heparin + warfarin) for treating VTE recurrence (RR: 0.91; 95% CI: 0.79-1.06) in patients with PE, DVT or VTE. Subgroup analysis of studies assessing patients with PE only (11,589 patients) found DOAC to be comparable in treating recurrent VTE as standard treatment (RR: 0.88; 95% CI: 0.70-1.11). Treatment with DOAC was found to reduce bleeding risk (RR=0.72; 95% CI: 0.57-0.941). Significant heterogeneity was found (I²=87%).

**Quality of Evidence:** High, GRADE A. We are very confident that the true effect lies close to that of the estimate of the effect.

**Strength of Recommendation:** Strong, GRADE 1

**References:**
2. Gomez-Outes A, Suarez-Gea ML, Lecumberri R, Terleira-Fernandez AI, Vargas-Castrillon E.

**PICO 24: What are the indications for thrombolysis in both hemodynamically unstable and stable patients with acute PE?**

*Population, Patient or Problem:* Hemodynamically stable and unstable ED patients with acute PE  
*Intervention, Prognostic Factor, Exposure:* Thrombolysis plus anticoagulation  
*Comparison:* Standard anticoagulation treatment  
*Outcome:* Short and long term morbidity (especially secondary pulmonary hypertension, and decreased exercise tolerance) and mortality with massive and submassive PEs  
*Design:* Randomized Controlled Trials (RCTs)/meta-analysis of RCTs  

**Search Strategy:** Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

**Clinical Recommendation:** We recommend that thrombolytics should only be provided to hemodynamically unstable patients with a high risk for mortality, or hemodynamically stable patients with right ventricular dysfunction and without risk factors for bleeding. This approach is not recommended for patients over age 75. Thrombolysis appears to increase the risk of major bleeding in patients.

The ESC 2014 guidelines states that while the clear majority (greater than 90%) of patients benefit from thrombolysis, the greatest benefit is seen when thrombolysis treatment is started within 48 hours after symptom offset.¹

A systematic review was identified which compared Thrombolysis to Heparin for the treatment of PE.² Eleven studies were identified. The study found that thrombolytics only provided a significant reduction in recurrent PE or death (9.4% vs. 19.0%; OR: 0.45; 95% CI: 0.22-0.92) in trials which included patients with hemodynamically unstable PE. The review suggested that only high risk hemodynamically unstable patients with a high risk of mortality benefit from treatment with thrombolytics.

A recent meta-analysis identified 16 trials³ found that thrombolytics reduced mortality (OR: 0.53; 95% CI: 0.32-0.88) but increased major bleeding (OR: 2.73; 95% CI: 1.91-3.91) in hemodynamically unstable PE patients with right ventricular dysfunction. Patients who had intermediate risk for PE had lower mortality (OR: 0.48; 95% CI: 0.25-0.92) and increased major bleeding (OR: 3.19; 95% CI: 2.07-4.92).
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Quality of Evidence: High, GRADE A. We are very confident that the true effect lies close to that of the estimate of the effect.

Strength of Recommendation: Strong, GRADE 1

References:

PICO 25: In ED patients diagnosed with PE are PESI and sPESI the best tools to identify those patients requiring/benefiting from hospital admission?

Population, Patient or Problem: ED patients diagnosed with PE
Intervention, Prognostic Factor, Exposure: PESI / sPESI
Comparison: Gestalt / local practice patterns
Outcome: Morbidity, mortality, quality of life, return to normal activity, cost
Design: Randomized Controlled Trials (RCTs)/meta-analysis of RCTs

Search Strategy: Cochrane library, Medline, and Pubmed for systematic reviews and clinical trials. Guidelines were checked.

Clinical Recommendation: We recommend that the PESI and sPESI are reliable validated tools for identifying patients with a low or high risk of mortality. Patients with a high risk for mortality will likely benefit from admission. Interestingly, while there have been several studies on the ability for PESI and sPESI to identify low risk patients suitable for discharge, no studies have been completed on identifying high risk patients suitable for admission.

The ESC 2014 guidelines state that the PESI and sPESI are the most extensively validated prediction scores and can be used to identify patients who are suitable for discharge. The PESI and sPESI have a strong ability to accurately predict patients at low and high risk for 30 and 90 day mortality.
A meta-analysis was conducted which examined the efficacy of different clinical prediction rules for identifying the risk of mortality in PE patients. The review identified 40 studies which examined rules including PESI, sPESI, ESC tools, and GRACE. Overall, the review found that the prediction rules had high sensitivity, but low specificity. In addition, patients identified as high-risk patients by the PESI, sPESI, or ESC tools had 4-fold increased odds of dying compared to low-risk patients. The review suggested that the PESI, sPESI, and ESC tools are the most reliable tools for identifying low-risk patients, due to their higher sensitivities, and that they have been validated in various studies.

**Quality of Evidence:** Moderate, GRADE B. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Strength of Recommendation:** Strong, GRADE 1

**References:**
Appendix B - PICO-D Methodology and GRADE Terminology

Key components of high quality and trustworthy clinical guidance include: i) recommendations that are clearly stated and based on scientific evidence of benefits, harms and where possible, costs, and ii) a guideline rating system that is used to communicate quality and reliability of both the evidence and the strength of its recommendations. In the development of these guidelines, clinical questions were formulated based on the PICO-D format as supported by Sackett\(^1\) and Guyatt\(^2\) in their User's Guide to the Medical Literature to define the clinical question. The GRADE terminology, where possible, is used to address the questions regarding Quality of Evidence and Strength of Recommendations. The components of PICO-D format and the GRADE methodology are described below.

**PICO-D**

**P - Population, Patient, or Problem:** This element defines the group of patients or characteristics of the patients.

**I - Intervention, Prognostic Factor, Exposure:** This element defines the main intervention being considered.

**C - Comparison:** This element defines the main alternative to compare with the intervention, such as comparison of two drugs or tests, or a medication to no medication or placebo.

**O - Outcome:** This defines what you are trying to accomplish, measure, improve or affect.

**D - Design:** The type of question (related to diagnosis, harm/etiology, prognosis, or therapy) will define which study design is best suited to provide evidence to answer the clinical question.

Definitions of Study Types\(^2,3\)

1. **Meta-analysis:** a statistical technique that summarizes the results of several studies in a single weighted estimate, in which more weight is given to results of studies with more events and sometimes to studies of higher quality.

2. **Systematic Review:** attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question using explicit, systematic methods selected with a view to minimizing bias. This provides more reliable findings from which to draw conclusions.\(^4,5\) The key characteristics of a systematic review are: i) clearly stated objectives with pre-defined eligibility criteria for studies; ii) an explicit and reproducible methodology; iii) a systematic search that attempts to identify all studies meeting the eligibility criteria; iv) an assessment of validity for the included studies, (e.g. through the assessment of risk of bias; and v) a systematic synthesis and presentation, of the characteristics and findings of the included studies.\(^6\)

3. **Randomized Controlled Trial (RCTs):** a trial in which participants are randomly assigned to two or more groups: at least one (the experimental group) receiving an intervention that is being tested and another (the comparison or control group) receiving an alternative treatment or placebo. This design allows assessment of the relative effects of interventions.

4. **Controlled Clinical Trial (CCTs):** a trial in which participants are assigned to two or more
different treatment groups in a non-randomized or quasi-randomized method. Examples of quasi-randomized allocation are birthdate and medical record numbers. Studies in which the randomization process is not explicitly stated as randomized are considered CCTs. CCTs are more likely to suffer from bias than RCTs.

5. **Observational Studies:**
   a. **Cohort Study**: an observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, to examine people who were exposed or not exposed (or exposed at different levels) to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective (or historical) cohort study identifies subjects from past records and follows them from the time of those records to the present.
   b. **Case control study**: a study design that examines a group of people who have experienced an event (usually an adverse event) and a group of people who have not experienced the same event, and looks at how exposure to suspect (usually noxious) agents differed between the two groups. This type of study design is most useful for trying to ascertain the cause of rare events, such as rare cancers.
   c. **Case Series**: analysis of series of people with the disease (there is no comparison group in case series).

**GRADE Methodology**
Whenever possible answers are identified from recent high quality guidelines or high quality systematic reviews and recommendations provided are based on GRADE definitions. Where guidelines or systematic reviews are not available to answer certain questions rapid reviews are undertaken and/or a consensus approach used to try to answer clinically relevant questions. **Only where the evidence is supportive and the benefits clearly outweigh the harm is a “we recommend” strength of recommendation applied.**

<table>
<thead>
<tr>
<th>GRADE Quality of Evidence</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>High (GRADE A)</td>
<td>We have high confidence that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate (GRADE B)</td>
<td>We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Low (GRADE C)</td>
<td>Our confidence in the effect estimate is low: The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very low (GRADE D)</td>
<td>We have very low confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>
Table 2. GRADE Strength of Recommendations

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<tr>
<th>Strength</th>
<th>Description</th>
<th>Wording of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Strong recommendation, with desirable effects clearly outweighing undesirable effects/burdens (or vice versa).</td>
<td>We recommend in favor of / We recommend against…</td>
</tr>
<tr>
<td>GRADE 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak</td>
<td>Weak recommendation, with desirable effects closely balanced with undesirable effects.</td>
<td>We suggest in favor of / We suggest against…</td>
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<tr>
<td>GRADE 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient</td>
<td></td>
<td>There is insufficient evidence or the confidence in the effect estimates is so low that the panel is unable to make a recommendation regarding…</td>
</tr>
<tr>
<td>evidence or no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>consensus</td>
<td></td>
<td></td>
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</table>

References:
Appendix C - Patient Education and Discharge Material

Pulmonary Embolism: After Your Visit

How to Give a Heparin Shot: After Your Visit
https://myhealth.alberta.ca/health/AfterCareInformation/pages/conditions.aspx?HwId=zp4251

Taking Blood Thinners Other Than Warfarin: After Your Visit
https://myhealth.alberta.ca/health/AfterCareInformation/pages/conditions.aspx?HwId=abo9742

Taking Warfarin Safely: After Your Visit
https://myhealth.alberta.ca/health/AfterCareInformation/pages/conditions.aspx?HwId=abk1586
Appendix D - Scoring Tools / Risk Scores

Wells’ Criteria for Pulmonary Embolism
https://www.mdcalc.com/wells-criteria-pulmonary-embolism

Revised Geneva Score
http://www.mdcalc.com/geneva-subcutaneously-revised-for-pulmonary-embolism/

PERC Rule for Pulmonary Embolism
http://www.mdcalc.com/perc-rule-for-pulmonary-embolism/

Adapted from: 2014 European Society of Cardiology (ESC) guidelines on the diagnosis and management of pulmonary embolism.

Table 1. Two-level Modified PE Wells’ Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate greater than or equal to 100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery or immobilization within the past four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Probability</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE unlikely</td>
<td>4 points or less</td>
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<tr>
<td>PE likely</td>
<td>more than 4 points</td>
</tr>
</tbody>
</table>

The percentage of patients in the PE unlikely category is approximately 10% and in the PE likely category it is greater than 30%.

Revision Date: January 2017

Version 1.3
Table 2. PERC Rule for Pulmonary Embolism\textsuperscript{8}

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age greater than or equal to 50</td>
<td>yes/no</td>
</tr>
<tr>
<td>Heart rate greater than or equal to 100</td>
<td>yes/no</td>
</tr>
<tr>
<td>O2 sat on room air less than 95%</td>
<td>yes/no</td>
</tr>
<tr>
<td>Prior history of venous thromboembolism</td>
<td>yes/no</td>
</tr>
<tr>
<td>Trauma or surgery within 4 weeks</td>
<td>yes/no</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>yes/no</td>
</tr>
<tr>
<td>Exogenous estrogen</td>
<td>yes/no</td>
</tr>
<tr>
<td>Unilateral leg swelling</td>
<td>yes/no</td>
</tr>
</tbody>
</table>

Generally rules out PE if no criteria are present and low pre-test probability.

If any criteria are positive, the PERC rule is not satisfied and cannot be used to rule out PE.

For patients who were PERC negative and pre-test probability was less than 15% the false negative rate at 45 days was 1.0% with a sensitivity of 97.4% and specificity of 21.9%.
Algorithm: Pulmonary Embolism Clinical Risk Estimation

Figure 1. Pulmonary Embolism Clinical Risk Estimation

Assessing patients for 'Signs and Symptoms' of: dyspnea, tachypnea, tachycardia, chest pain, hemoptysis, signs of DVT, etc AND

'Risk factors' such as: cancer, recent surgery or immobilization, exogenous hormones, extended flight or thrombophilia

allows the clinician to determine an initial clinical impression of PE likelihood.

Patients deemed low risk or unlikely

Go to Figure 2

Patients deemed moderate to high risk or likely

Go to Figure 3
Algorithm: Pulmonary Embolism Unlikely based on two-level Modified Wells score and/or PERC Rule

Figure 2. Pulmonary embolism Unlikely or low risk

- Patient considered clinically to be low risk for PE
- Apply Modified Wells score
  - Wells score 4 points or less (PE Unlikely)
    - YES: Is a CTPA suitable and available immediately?
      - YES: CTPA (or a V/Q scan)
        -Was the CTPA (or V/Q scan) positive?
          - YES: Diagnose as PE and treat
          - NO: Is DVT suspected?
            - YES: Consider proximal leg vein ultrasound scan
              - Refer to DVT guidelines
            - NO: Advise the patient it is not likely they have a PE. Discuss with them the signs and symptoms of PE, when to seek follow up, and consideration alternative diagnosis
      - NO: Order D-Dimer
        - Was D-Dimer positive?
          - YES: Advise the patient it is not likely they have a PE. Discuss with them the signs and symptoms of PE, when to seek follow up, and consideration alternative diagnosis
          - NO: Apply PERC Rule
            - WAS one or more criteria present?
              - YES: PERC rule positive
              - NO: PERC rule negative

Adapted from: National Institute for Health and Care Excellence (NICE) Guidelines and 2014 European Society of Cardiology (ESC) Guidelines and Kline studies
Algorithm: Pulmonary Embolism Likely based on two-level Modified Wells score

Figure 3. PE Likely or moderate to high risk

1. **PERC rule positive OR not applied**
2. **Apply Modified 2-level Wells PE Score**
3. **Patient with Modified Wells score of more than 4 points (PE Likely)**
4. **Is a CTPA suitable and available immediately?**
   - **YES**
     - **Order CTPA (or V/Q scan)**
     - **Was the CTPA (or V/Q scan) positive?**
       - **YES**
         - **Diagnose PE and treat**
       - **NO**
         - **Is DVT suspected?**
           - **YES**
             - **Consider a proximal leg vein ultrasound scan**
           - **NO**
             - **Advise the patient it is not likely they have a PE. Discuss with them the signs and symptoms of PE, when to seek follow up, and consideration alternative diagnosis**

Table 3. Simplified PESI\textsuperscript{12,13}

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age greater than 80</td>
<td>1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1</td>
</tr>
<tr>
<td>History of chronic cardiopulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate greater than or equal to 110</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP less than 100 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>O2 sat less than 90%</td>
<td>1</td>
</tr>
</tbody>
</table>

IF score is 0 this equals a 30-day mortality risk of 1.0%.

IF score is greater than or equal to 1 this equals a 30-day mortality risk of 10.9%.

Simplified PESI predicts 30-day outcome of patients with PE, with fewer criteria than the original PESI.

References:
Appendix E - Direct Oral Anticoagulant Guideline

Important Note: The information contained in this appendix comes from a provincial guideline and does not show the guideline in its entirety. The content below is not guaranteed to be up to date and it is recommended that the full guideline be accessed.

To access the full AHS guideline go to:  https://extranet.ahsnet.ca/teams/policydocuments/1/clp-prov-direct-oral-anticoagulant-agents-guideline-hcs-115-01.pdf

Please see relevant VTE treatment information below from the: Direct Oral Anticoagulants Document effective April 23, 2015. Information referenced below was added in August 2015.

Recommendations for the use of dabigatran, rivaroxaban, and apixaban:

- These agents do not require routine anticoagulation monitoring of PT INR or PTT.
- Specific reversal agents are not currently available to control active bleeding.
- All three drugs require some degree of renal clearance, least for apixaban and greatest for dabigatran.

**DOACS and Venous thromboembolism:**

All of the new DOAC’s found to be non-inferior to vitamin K antagonists (VKA’s) based on rates of recurrence of VTE and bleeding risk. They have been studied for DVT and PE and Health Canada has approved all three agents for VTE treatment.

1. **DOAC dosing:** rivaroxaban and apixaban have initial higher BID dosing for VTE while dabigatran used an initial 5-10 days of low molecular weight heparin (LMWH) or unfractionated heparin (UFH).

2. **Massive VTE:** For patients with massive DVT or PE, not included in prior DOAC studies, it would be prudent to use standard therapies with LMWH/UFH if considering for thrombolysis or thrombectomy. LMWH is suggested for the first 3 months for proximal ileofemoral DVT or submassive PE and patients with active cancer as there is evidence for specific benefit with LMWH for these groups.

3. **Thrombophilia and Cancer:** Because few patients with active cancer or thrombophilia were included in clinical trials with DOACs these higher risk patients should be reviewed with Oncology or Hematology before considering DOACs for their initial management.
4. **Longer term therapy/Secondary prevention:** Studies looking at continuing DOACs for an additional 6-12 months, after the initial 6 month treatment period, have shown significant benefit in preventing VTE recurrence; however, there was a significantly higher bleeding risk with dabigatran and rivaroxaban compared to placebo but equivalent to placebo when apixaban was used.

5. **Medication interactions:** While there are not many drug interactions with the DOACs there are specific situations they should be avoided if certain drugs need to be continued including: rifampin, phenytoin, carbamazepine, clarithromycin, fluconazole and other azoles and protease inhibitors.

**Monitoring:**

- Anticoagulation monitoring is not routinely required.
- Patients who require high risk bleeding procedures, a normal INR/PTT will not exclude significant residual effect of DOAC.
- For dabigatran, a PPT value greater than 2 times normal is associated with increased risk of bleeding and a normal thrombin time can be used to exclude any significant residual anticoagulant effect.
- For Xa inhibitors (rivaroxaban and apixaban), a heparin calibrated anti-Xa level less than 0.1 will exclude any significant residual effect of rivaroxaban anticoagulant.

**Dosing:**

Rivaroxaban and Apixaban are currently the only DOACs covered under Alberta Government funded insurance plans and does require a ‘special request’ form to be completed before the plan will agree to cover the cost.

**Table 1. Recommended dosages:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE</strong></td>
<td>LMWH x 7 days then dabigatran 150 mg PO BID</td>
<td>15 mg PO BID x 3 weeks then</td>
<td>10 mg PO BID x 7 days then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg po daily</td>
<td>5 mg PO bid</td>
</tr>
</tbody>
</table>
**Management of Bleeding on these Agents:**

### A. Dabigatran

#### Table 2. Patients on Dabigatran (Pradaxa) with Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Minor Bleeding</th>
<th>Moderate Bleeding</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>• CBC, INR/PTT;</td>
<td>• CBC, INR/PTT;</td>
<td>• CBC, INR/PTT;</td>
</tr>
<tr>
<td></td>
<td>• Creatinine;</td>
<td>• Creatinine;</td>
<td>• Creatinine;</td>
</tr>
<tr>
<td></td>
<td>• Fibrinogen;</td>
<td>• Fibrinogen;</td>
<td>• Fibrinogen;</td>
</tr>
<tr>
<td></td>
<td>• Type and Screen;</td>
<td>• Type and Screen;</td>
<td>• Type and Screen;</td>
</tr>
<tr>
<td></td>
<td>• Thrombin Time</td>
<td>• Thrombin Time</td>
<td>• Thrombin Time</td>
</tr>
</tbody>
</table>

| **Supportive Therapy** | Local therapy | Local therapy/site control; | Transfusion; |
|                       |               | Surgery/Intervention;       | Surgery/Intervention; |
|                       |               | Consider platelet transfusion if antiplatelet agents are in use |

| **Drug Dosing** | Hold Dabigatran; | Hold Dabigatran; | Hold Dabigatran; |
|                | Hold antiplatelet agents | Hold antiplatelet agents | Hold antiplatelet agents |

| **Reversal/Removal** | None | Consider charcoal less than 2-4 hours post-dose; | Consider dialysis; |
|                     |      | Consider dialysis; | Consider dialysis; |

| **Procoagulant Agents** | None | Tranexamic acid (10mg/kg IV or 25 mg/kg PO)b | Consider FEIBA 25 - 50 unit/kg for major bleeding, 50-100 unit/kg for ICH or PCC 25 - 50 unit/kg |
|                        |      | Tranexamic acid (10 mg/kg IV)b | |

Note: 

- Major upper GI bleeding is a relative contraindication for activated charcoal
- Upper urinary tract bleeding is a relative contraindication for Tranexamic acid, which can cause “clot colic”;

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B. Rivaroxaban/Apixaban

Table 3. Patients on Rivaroxaban (Xarelto) or Apixaban (Eliquis) with Bleeding

<table>
<thead>
<tr>
<th>Minor Bleeding</th>
<th>Moderate Bleeding</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>• CBC, INR/PTT</td>
<td>• CBC, INR/PTT;</td>
</tr>
<tr>
<td></td>
<td>• Fibrinogen;</td>
<td>• Fibrinogen;</td>
</tr>
<tr>
<td></td>
<td>• T &amp;S;</td>
<td>• T &amp;S;</td>
</tr>
<tr>
<td></td>
<td>• Anti Xa level</td>
<td>• Anti Xa level</td>
</tr>
<tr>
<td><strong>Supportive Therapy</strong></td>
<td>• Local therapy</td>
<td>• Local Therapy;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Transfusion;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery/Intervention;</td>
</tr>
<tr>
<td><strong>Drug Dosing</strong></td>
<td>• Hold Rivaroxaban/Apixaban;</td>
<td>• Hold Rivaroxaban/Apixaban;</td>
</tr>
<tr>
<td></td>
<td>• Hold antiplatelet agents</td>
<td>• Hold antiplatelet agents</td>
</tr>
<tr>
<td><strong>Reversal</strong></td>
<td>• None</td>
<td>• Consider charcoal(^a) (no evidence for effectiveness);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not dialyzable</td>
</tr>
<tr>
<td><strong>Procoagulant agents</strong></td>
<td>• None</td>
<td>• Consider charcoal(^a) (no evidence for effectiveness);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not dialyzable</td>
</tr>
<tr>
<td></td>
<td>• Tranexamic acid (10 mg/kg IV or 25 mg/kg PO)(^b)</td>
<td>• Consider PCC 25-50 unit/kg or fixed dosage of PCC 2000 units or rFVIIa 40 - 90 mcg/kg;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tranexamic acid (10 mg/kg IV)(^b)</td>
</tr>
</tbody>
</table>

Note: 
\(^a\)Major upper GI bleeding is a relative contraindication for activated charcoal
\(^b\)Upper urinary tract bleeding is a relative contraindication for Tranexamic acid, which can cause “clot colic”;

If an emergent/urgent procedure is required:

1. For patients needing emergent surgery, reversal cannot be achieved prior to proceeding nor is there time for coagulation testing.
2. Draw blood for: CBC, INR, PTT, fibrinogen, thrombin time, anti-Xa activity, type and screen, Creatinine, then proceed and transfuse as necessary along with other products as time permits.
3. Time permitting, measure the level of effect of the oral anticoagulant agent and wait until the effect is minimal or below detection prior to proceeding.
4. Dabigatran’s effect will be influenced more by renal dysfunction than that of rivaroxaban or apixaban.

Reference:
Appendix F - Apixaban/Dabigatran/Rivaroxaban – Alberta Blue Cross
Special Authorization Request Form

Please click here to access the Blue Cross form: https://www.ab.bluecross.ca/dbl/pdfs/60019.pdf
Appendix G - Clinical Working Group Membership

We would like to acknowledge the contributions of the Provincial Clinical Knowledge Working Group members as follows. Your participation and time spent is appreciated.

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Role</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge Lead</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael Bullard</td>
<td>Physician</td>
<td>Knowledge Lead</td>
<td>Provincial</td>
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<tr>
<td><strong>Topic Lead</strong></td>
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<tr>
<td>Pat San Agustin</td>
<td>Physician</td>
<td>Topic Lead</td>
<td>Provincial</td>
</tr>
<tr>
<td><strong>Working Group Members</strong></td>
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<tr>
<td>Chris Hall</td>
<td>Physician</td>
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<td>Calgary Zone</td>
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<tr>
<td>Lyle Thomas</td>
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<tr>
<td>Ni Lam</td>
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<td>Andrew McRae</td>
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<td>Eddy Lang</td>
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<td>Jennifer Pritchard</td>
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<td>Sara Nosworthy</td>
<td>Registered Nurse</td>
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<td>Calgary Zone</td>
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<td>Shelly Lynn Franklin</td>
<td>Registered Nurse</td>
<td>Working Group Member</td>
<td>North Zone</td>
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<tr>
<td>Thora Skeldon</td>
<td>Registered Nurse</td>
<td>Working Group Member</td>
<td>Central Zone</td>
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<tr>
<td><strong>Multidisciplinary</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bruce Ritchie</td>
<td>Physician</td>
<td>Content Expert</td>
<td>Edmonton Zone</td>
</tr>
<tr>
<td>Elizabeth Mackay</td>
<td>Physician</td>
<td>Content Expert</td>
<td>Calgary Zone</td>
</tr>
</tbody>
</table>
Thank you to the following clinicians who participated in the colleague review process. Your time spent reviewing the knowledge topics and providing valuable feedback is appreciated. Ian Wishart, Donald Nixon, Lori Jordens, Essam Elbeshti, Scott Ross, Jennifer Lowerison, Adrienne Haponiuk, Cam MacGougan, Aref Yeung

For questions or feedback related to this knowledge topic please contact Clinical Knowledge Topics by emailing ClinicalKnowledgeTopics@albertahealthservices.ca