



# Diagnosis of Venous Thromboembolism

## *An Educational Slide Set*

American Society of Hematology 2018 Guidelines  
for Management of Venous Thromboembolism

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# American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism

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CLINICAL GUIDELINES 

o American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism

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**Background** Modern diagnostic strategies for venous thromboembolism (VTE) incorporate pretest probability (PTP; prevalence) assessment. The ability of diagnostic tests to correctly identify or exclude VTE is influenced by VTE prevalence and test accuracy characteristics.

**Objective** These evidence-based guidelines are intended to support patients, clinicians, and health care professionals in VTE diagnosis. Diagnostic strategies were evaluated for pulmonary embolism (PE), deep vein thrombosis (DVT) of the lower and upper extremity, and recurrent VTE.

**Methods** The American Society of Hematology (ASH) formed a multidisciplinary panel including patient representatives. The McMaster University GRADE Centre completed systematic reviews up to 1 October 2017. The panel prioritized questions and outcomes and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess evidence and make recommendations. Test accuracy estimates and VTE population prevalence were used to model expected outcomes in diagnostic pathways. Where modeling was not feasible, management and accuracy studies were used to formulate recommendations.

**Results** Ten recommendations are presented, by PTP for patients with suspected PE and lower extremity DVT, and for recurrent VTE and upper extremity DVT.

**Conclusions** For patients at low (unlikely) VTE risk, using D-dimer as the initial test reduces the need for diagnostic imaging. For patients at high (likely) VTE risk, imaging is warranted. For PE diagnosis, ventilation-perfusion scanning and computed tomography pulmonary angiography are the most validated tests, whereas lower or upper extremity DVT diagnosis uses ultrasonography. Research is needed on new diagnostic modalities and to validate clinical decision rules for patients with suspected recurrent VTE.

**Summary of recommendations**

These guidelines are based on updated and original systematic reviews of evidence conducted by researchers and developed under the direction of the McMaster University GRADE Centre and the University of Kansas Medical Center, with international collaborators. The panel followed best practices for guideline development recommended by the Institute of Medicine (now National Academy of Medicine) and the Guidelines International Network (GIN).<sup>1,4</sup> The panel used the GRADE approach<sup>5,6</sup> to assess quality of evidence and formulate recommendations.

Accurate diagnosis of venous thromboembolism (VTE) is important due to the morbidity and mortality associated with missed diagnoses and the potential side effects, patient inconvenience and expense

Submitted 19 August 2018; accepted 2 October 2018. DOI: 10.1182/bloodadvances.2018024628. The full-text version of this article contains a data supplement. Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page [hematology.org/vte](http://hematology.org/vte). © 2018 by The American Society of Hematology

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## ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. Prevention and Treatment of VTE in Patients with Cancer
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. Pediatric VTE
9. VTE in the Context of Pregnancy
- 10. Diagnosis of VTE**

## How were these ASH guidelines developed?

### PANEL FORMATION

Each guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of COI

### CLINICAL QUESTIONS

10 to 20 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

#### Example: Clinical Question

“In a patient population with low clinical probability of PE, what is the optimal diagnostic strategy to evaluate for suspected first episode PE?”

### EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

### MAKING RECOMMENDATIONS

Recommendations **made** by guideline panel members based on evidence for all factors.

***ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.***

## How patients and clinicians should use these recommendations

	<b>STRONG Recommendation</b> ("The panel recommends...")	<b>CONDITIONAL Recommendation</b> ("The panel suggests...")
<b>For patients</b>	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
<b>For clinicians</b>	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use <b>shared decision making</b> .



## Objectives

By the end of this session, you should be able to

1. Describe a diagnostic strategy for suspected acute deep vein thrombosis (DVT) or pulmonary embolism (PE)
2. Describe a diagnostic strategy for suspected recurrent DVT or PE
3. Describe a diagnostic strategy for suspected upper extremity DVT

## What is this chapter about?

Establishing an **accurate diagnosis** of PE or DVT in the lower or upper extremities is critical.

Diagnostic strategies for VTE combine estimates of **pre-test probability** with **diagnostic testing**, although these tests are associated with error.

This chapter focuses on the **selection of optimal diagnostic testing** that is more likely to result in a diagnostic result, reduce the number of tests, and minimize exposure to radiation.

## Prevalence and PTP

- Venous thromboembolism (VTE) diagnosis is based on an assessment of the clinical probability of VTE in a population, prior to diagnostic testing (*pre-test probability; PTP*)
- Patients are classified into *low/intermediate/high probability* or *likely/unlikely* to have VTE
  - *Low PTP (unlikely)* = low prevalence of VTE
  - *(Intermediate)/High PTP (likely)* = high prevalence of VTE
- Prevalence of VTE within a population influences predictive value of diagnostic tests





## Pre-Test Probability for PE is determined using clinical prediction rules; for example:

Revised Geneva Score	
Component	Points
Pain on limb palpation	4
Previous DVT or PE	3
Unilateral lower limb pain	3
Tachycardia	0 / 3 / 5
Active cancer	2
Recent surgery or fracture	2
Hemoptysis	2
Age $\geq$ 65	1

**Score  $\geq$  11:** high PTP  
**Score 4 to 10:** intermediate PTP  
**Score 0 to 3:** low PTP

Wells Score for PE	
Component	Points
DVT signs / symptoms	3
No alternate diagnosis	3
Tachycardia	1.5
Immobilization/surgery	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Active cancer	1

**Score  $>$  6:** high PTP  
**Score  $\geq$  2 and  $\leq$  6:** intermediate PTP  
**Score  $<$  2:** low PTP

**Prevalence by PTP:**  
**High PTP:**  $\geq$  50%  
**Intermediate PTP:**  $\sim$ 20%  
**Low PTP:**  $\leq$  5%

## Clinical prediction rules (PTP) for DVT:

Wells Score for Leg DVT	
Component	Points
Active cancer	1
Localized tenderness	1
Entire leg swollen	1
Calf swelling > 3 cm	1
Pitting edema	1
Collateral superficial veins	1
Previous DVT	1
Bedridden/surgery	1
Paralysis	1
Alternate diagnosis	-2

**Score  $\geq 3$ :** high PTP ( $\geq 50\%$  prevalence)

**Score 1 to 2:** intermediate PTP ( $\sim 25\%$ )

**Score 0 or lower:** low PTP ( $\leq 10\%$ )

Constans Score for Upper Extremity DVT	
Component	Points
Venous material (central catheter, pacemaker)	1
Localized pain	1
Unilateral edema	1
Alternate diagnosis	-1

**Score 2 to 3:** likely PTP ( $\sim 40\%$  prevalence)

**Score  $\leq 1$ :** unlikely PTP ( $\sim 10\%$ )

## Test Accuracy

- No diagnostic test for VTE is perfectly accurate
  - True positive (TP), true negative (TN), false positive (FP), false negative (FN)
- **Diagnostic test accuracy** obtained from:
  - 1) studies evaluating diagnostic tests (CTPA, D-Dimer, etc.) compared to reference standard
  - 2) management studies

**Pre-test probability**  
(Prevalence of VTE in  
a group)



**Diagnostic test  
accuracy**



**Post-test  
probability  
of VTE**

## What these guidelines cover:

### Diagnosis of these sites of VTE:

- PE
- DVT of lower and upper extremities
- Recurrent PE and DVT

### Using these common diagnostic tests:

- Highly-sensitive D-dimer
- VQ scan
- Multidetector CTPA
- Compression +/- doppler US of proximal leg veins or whole leg US

All permutations of these tests were modeled for different **pre-test probabilities**, then compared with diagnostic studies to derive diagnostic algorithms.

## Case 1: Suspected Pulmonary Embolism

70 year old female

**Past Medical History:** Emphysema, diabetes, obesity (weight 160 kg)

**Medications:** Tiotropium, salbutamol, metformin

**Seen in the Emergency Department with:** chest pain, hemoptysis x 12 hr

- No DVT symptoms, no prior VTE. No recent surgery, immobilization, or active cancer.
- Recently had viral upper respiratory infection

Exam: heart rate 120, oxygen saturation 93% on room air, no leg swelling or edema

Chest X-Ray: hyperinflation consistent with emphysema.

You determine her clinical **pre-test probability** (by Wells Score) to be **intermediate** (2.5 points)

Your patient has intermediate pre-test probability for PE.

Which ONE of the following tests would you suggest to exclude a diagnosis of PE?

- A. CTPA
- B. High-sensitivity D-dimer
- C. Bilateral compression ultrasound of the legs
- D. Electrocardiogram
- E. Chest X-Ray

## Recommendation

The panel suggests using a strategy **starting with D-dimer** for excluding PE in a population with intermediate prevalence/PTP (approximately 20%), followed by VQ scan or CTPA in patients requiring additional testing (*conditional recommendation, high certainty on clinical outcomes, moderate certainty on diagnostic accuracy*)

The same diagnostic strategy (**starting with D-dimer**) is recommended for patients with low PTP

### Remarks:

- If D-dimer strategy is followed, a **highly-sensitive D-dimer assay** is required
- A negative D-dimer rules out PE, and no additional testing or anticoagulation is required

## D-dimer thresholds

- **D-dimer has limited utility in the following patient groups**, due to high frequency of positive results with standard thresholds
  - Hospitalized patients
  - Post-surgical
  - Pregnancy
- Use of **“age-adjusted” D-dimer** cutoff in outpatients older than 50 years is as safe as standard cutoff and increases diagnostic utility
  - **Age-adjusted cutoff = Age (years) x 10 µg/L** (using D-dimer assays with a cutoff of 500 µg/L)





Your 70 year old patient's D-dimer result is 845  $\mu\text{g/L}$  (NORMAL < 500  $\mu\text{g/L}$ , NORMAL age-adjusted D-Dimer < 700  $\mu\text{g/L}$ ).

What diagnostic test would you suggest next to exclude PE?

- A. Stop investigating (positive D-dimer is diagnostic for PE)
- B. Serial D-dimer test every 8 hours x 3
- C. CTPA
- D. VQ scan
- E. Chest X-Ray

## Recommendations

- The panel recommends against using a positive D-dimer alone to diagnose PE
- Patients who are likely to have a **non-diagnostic VQ scan** should undergo **CTPA**

### Remarks:

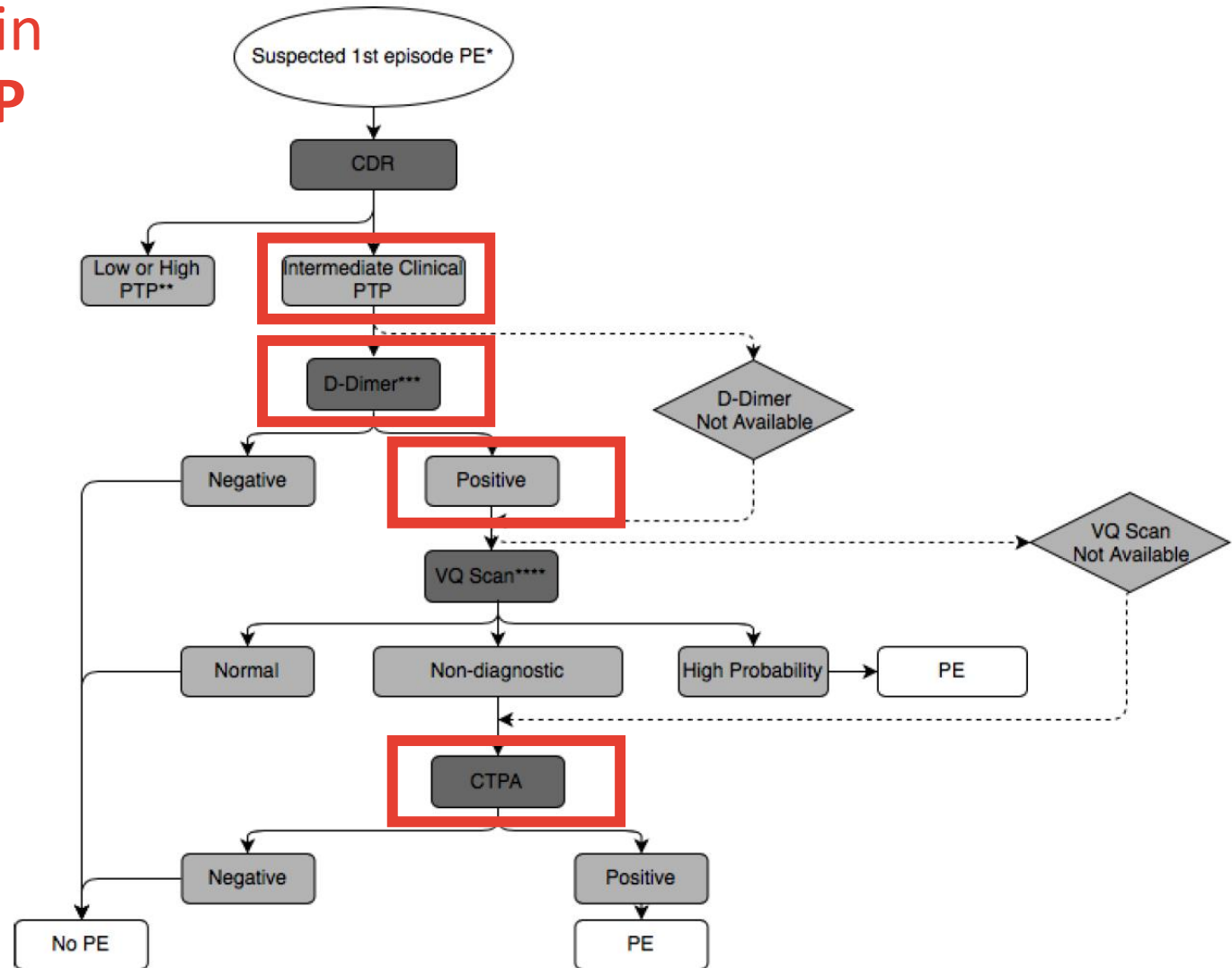
- VQ scan preferred over CTPA as subsequent test (*after D-Dimer*) to limit radiation exposure **in patients likely to have a diagnostic scan**, in centers with availability and expertise for interpretation
- **However, CTPA preferred when VQ scan is not feasible**

The likelihood of a diagnostic VQ result (normal or high probability) is less likely in older individuals, those with pre-existing lung disease, and those with an abnormal chest x-ray.

*Our patient is 70 years old with pre-existing lung disease and an abnormal chest x-ray, so CTPA preferred.*

## Flow chart for Diagnosis of PE in patients with **intermediate PTP**

CDR = Clinical Decision Rule (ie. Wells Score or Geneva Score)



## Imaging considerations for VQ scan and CTPA in suspected PE

Clinical Criteria or Concern	VQ Scan	CTPA
At risk for reaction to contrast media requiring premedication	+	-
Concern over radiation to female breast issue	+	-
Renal insufficiency	+	-
Suspected VTE recurrence or treatment failure with index PE diagnosed by VQ scan	+	-
Suspected VTE recurrence or treatment failure with index PE diagnosed by CTPA	+	+/-
Concern over radiation to fetus (especially in first trimester)	+/-	+/-
Minimizing risk of missed VTE at 3 months	+/-	+/-
Timely result required and both modalities accessible	-	+
Alternative or concomitant diagnoses actively sought (ex. cancer)	-	+
Abnormalities present on plain radiograph (hyperinflation, effusion)	-	+
Limited institutional access or expertise in Nuclear Medicine	-	+



***ASIDE:*** Imagine, instead, that your patient had initially been high PTP for PE (*orthopedic surgery 2 weeks ago, and signs of DVT on exam*) with Wells Score of 7.

In this case, what initial diagnostic test would you suggest?

- A. CTPA
- B. High-sensitivity D-dimer
- C. Bilateral compression ultrasound of the legs
- D. Electrocardiogram
- E. Chest X-Ray

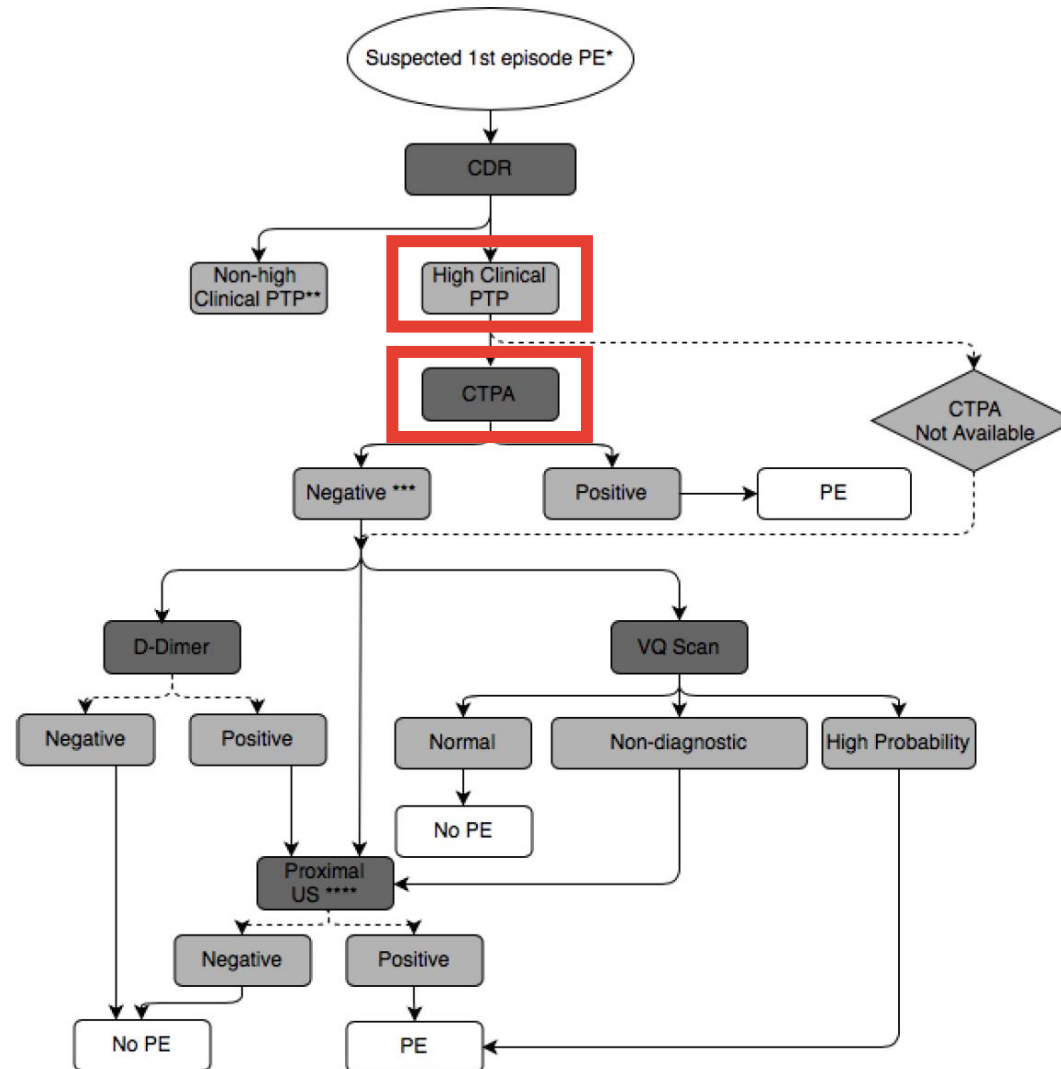
## Recommendation

The panel suggests using a strategy **starting with CTPA** for assessing patients suspected of having PE in a population with **high PTP ( $\geq 50\%$ )** (*conditional recommendation, very low certainty for clinical outcomes, moderate certainty for diagnostic accuracy*)

### Remarks:

- If CTPA is not feasible (contrast dye allergy, renal impairment, unavailability), VQ scan may be acceptable if non-diagnostic scans are followed by additional testing
- When clinical suspicion for PE remains high after negative initial CTPA, **additional testing** with VQ scan or proximal ultrasound of lower extremities may be considered

## Flow chart for Diagnosis of PE in patients with high PTP





## Case 1: Continued

- Your patient is found to have acute bilateral segmental pulmonary emboli on CTPA.
- She is started on a direct oral anticoagulant and treated for 3 months. At the end of treatment she feels back to her prior baseline.
- 3 years later, she returns with chest pain, dyspnea, and signs of right leg DVT. She has been having hemoptysis and is tachycardic. **You feel that she is “*high (likely)*” PTP for recurrent PE (Wells score of 7)**





You are concerned about the possibility of recurrent PE. You feel that your patient has highly/likely PTP.

What test would you suggest to exclude recurrent PE?

- A. CTPA
- B. High-sensitivity D-dimer
- C. Bilateral compression ultrasound of the legs
- D. Electrocardiogram
- E. Chest X-Ray

## Recommendation

- Patients with a **positive D-dimer, or those who have a likely PTP** should undergo **CTPA** (*conditional recommendation, low certainty for clinical outcomes, moderate certainty on diagnostic accuracy*)
- The panel suggests using a strategy **starting with D-dimer** for excluding recurrent PE in a population with **unlikely PTP**.

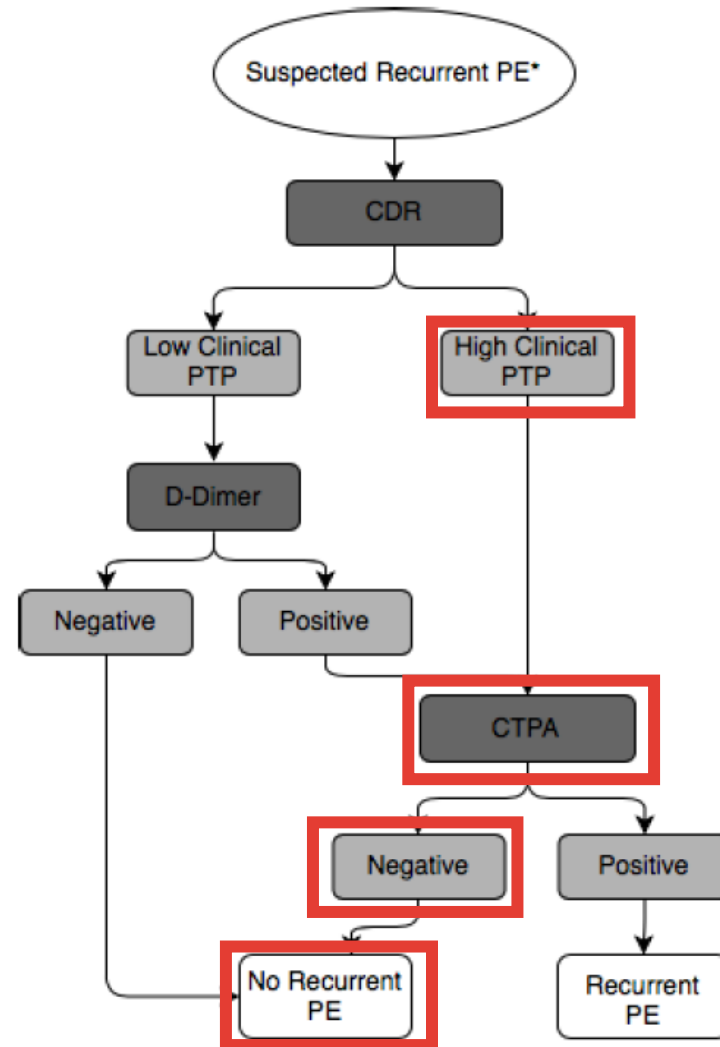
In studies examining this diagnostic strategy for recurrent PE, **the Wells and Geneva Scores** were used as clinical prediction rules.  
Note: they have not been specifically validated in patients with suspected recurrent PE

If prior imaging is available, ***comparison of previous and current imaging*** warranted to determine if findings are new and represent recurrent PE

## Flow chart for Diagnosis of recurrent PE

### Case 1: Continued

- Your patient's PTP is high/likely, so you arrange for CTPA
- The CTPA does not demonstrate PE, and recurrent PE is ruled out





## Case 1: Summary

In patients with low or intermediate PTP for PE, a high-sensitivity D-dimer, if negative, can safely exclude PE with no additional testing

CTPA is preferred over VQ scan in individuals who are likely to have a non-diagnostic VQ result, including patients who are elderly or who have pre-existing lung disease

Patients with suspected recurrent PE should be stratified into likely or unlikely PTP to determine subsequent testing, although clinical prediction rules have not been extensively validated for recurrent PE

## Case 2: Suspected Deep Vein Thrombosis

45 year old male

**Past Medical History:** Hypertension, lung cancer

**Medications:** Ramipril, amlodipine, chemotherapy (cisplatin/gemcitabine)

**Seen in the Emergency Department with:** left calf pain and swelling x 48 hr

- No recent surgery or immobilization
- Receiving chemotherapy
- No chest pain, dyspnea
- No varicose veins

Exam: heart rate 80, oxygen saturation 97% on room air.

- Left calf circumference 5 cm greater than right calf
- Localized tenderness along venous system
- Pitting edema in left leg

You determine his **clinical pre-test probability to be high** (by Wells Score = 4)

Your patient with high PTP undergoes a left leg proximal compression ultrasound. The ultrasound does not demonstrate evidence of DVT.

Which diagnostic test would you suggest next?

- A. Stop investigations as his ultrasound is negative
- B. Serial proximal compression ultrasound within one week
- C. High-sensitivity D-dimer
- D. Venography
- E. CTPA

## Recommendation

- The panel suggests using a strategy **starting with proximal lower extremity or whole leg ultrasound** for assessing patients suspected of having DVT in a population with high prevalence/PTP ( $\geq 50\%$ ).
- *This should be followed by serial ultrasound if the initial ultrasound is negative and no alternative diagnosis is identified* (conditional recommendation, very low certainty on clinical outcomes, high certainty on diagnostic accuracy)

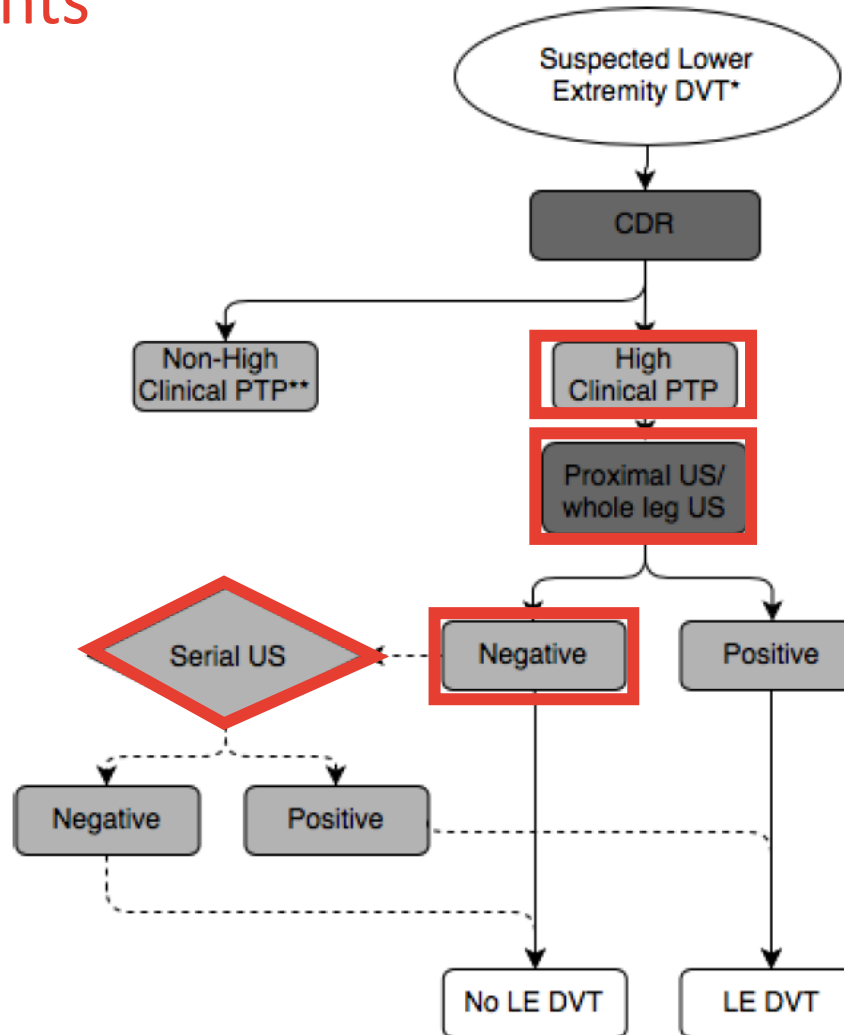
### Remarks:

- If a two-level clinical decision rule (ie. likely vs. unlikely) is utilized, this recommendation corresponds to the “likely DVT” category

## Flow chart for Diagnosis of DVT in patients with **high PTP**

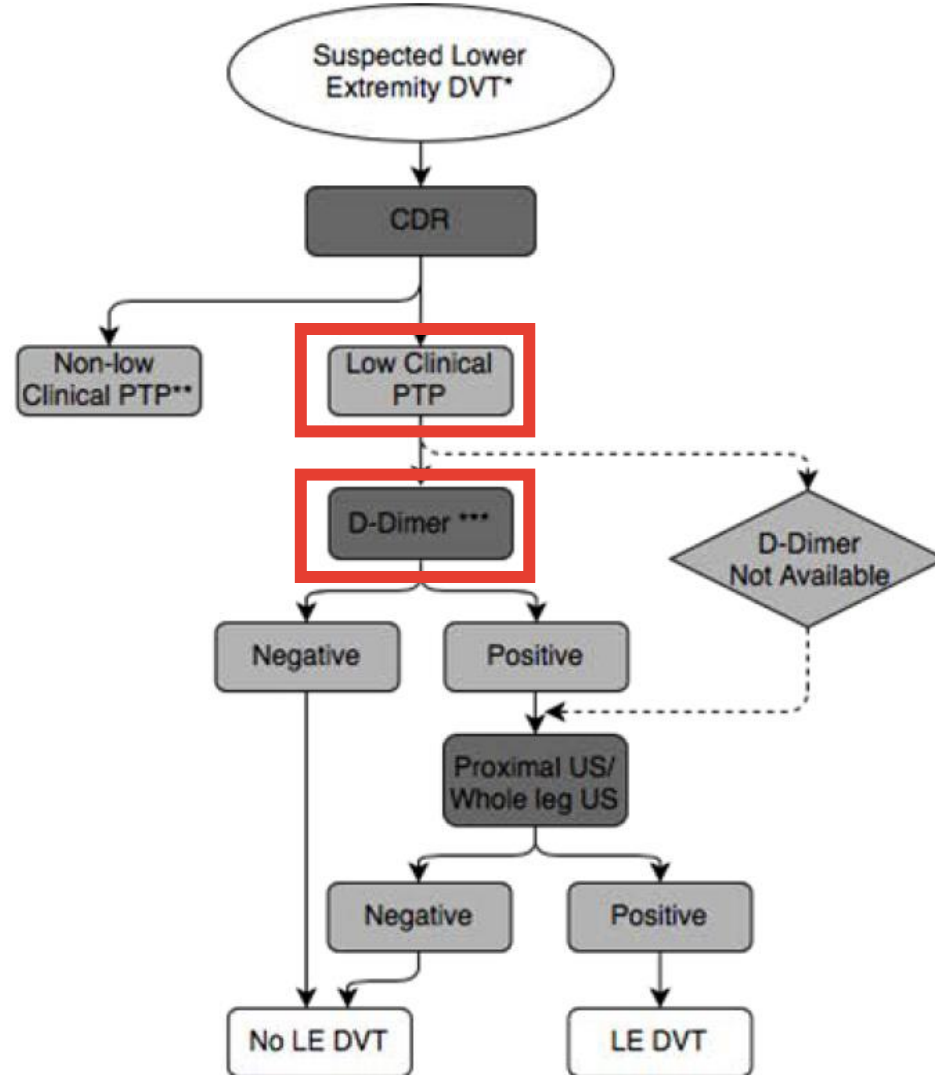
For patients at high PTP, a single proximal or whole leg US is not sufficient to rule out DVT.

Subsequent testing with serial US is required.





By contrast, in patients with **low PTP for DVT**, D-dimer recommended as first diagnostic test to exclude DVT.





## Case 2: Continued

- Your patient, whose PTP was high, has a serial proximal ultrasound in 7 days. This ultrasound demonstrates occlusive DVT within the left popliteal and superficial femoral veins.
- Your patient is started on anticoagulation with LMWH and you arrange for follow up in the thrombosis clinic

## Case 2: Four months later

- Four months later he remains compliant on full-dose anticoagulation with LMWH
- Unfortunately his lung cancer is progressing despite chemotherapy, with worsening metastatic disease
- He presents to hospital with swelling and tightness in his left (ipsilateral) calf. There is localized pain and unilateral edema. ***You feel his PTP for recurrent DVT is likely (Wells Score of 4)***



Your patient who sustained DVT 4 months ago presents with recurrent leg symptoms and likely PTP.

What diagnostic test would you suggest at this point?

- A. CT scan of the abdomen
- B. High-sensitivity D-dimer
- C. Venography
- D. Left leg compression ultrasound

*In patients with a prior history of DVT, what is the optimal diagnostic strategy to evaluate for suspected recurrent DVT?*

## Recommendation

- **Patients with positive D-dimer or those who have likely PTP:** should undergo proximal lower extremity ultrasound (*conditional recommendation, low certainty*)
- **In a population with unlikely PTP:** the panel suggests using a strategy starting with D-dimer for excluding recurrent DVT

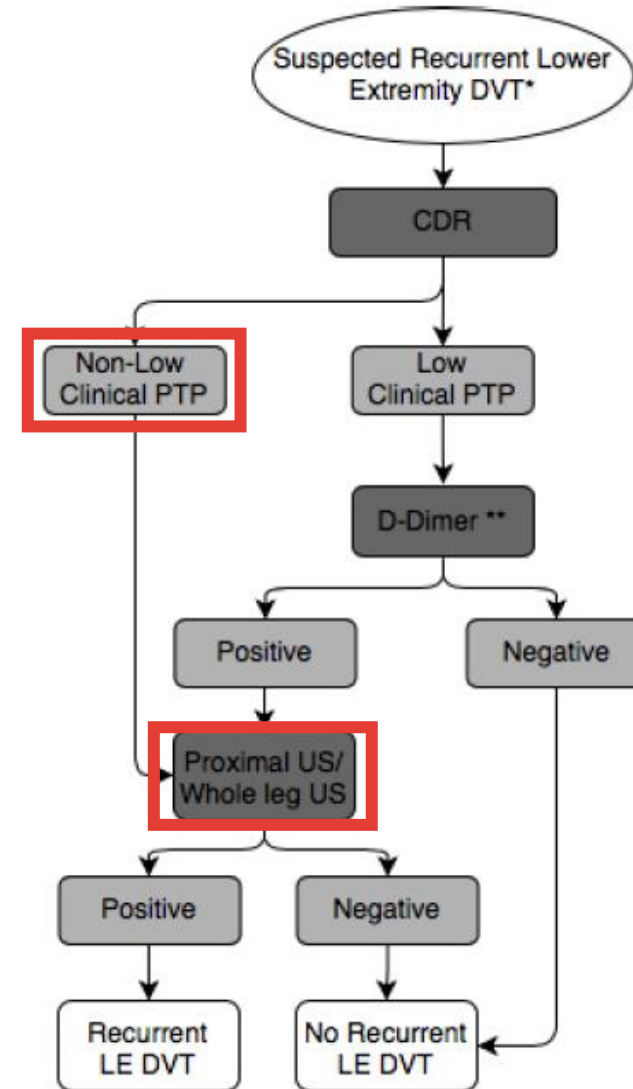
If prior imaging is available, **comparison of the previous and current imaging** is warranted to determine if the findings are new and represent recurrent PE

Ultrasound findings of recurrent DVT may include involvement of new venous segment or increase in non-compressibility of >4mm.



## Flow chart for Diagnosis of recurrent DVT

In studies assessing this diagnostic strategy for suspected recurrent DVT, a **modified Wells score** was used to assess clinical probability



## Case 2: Conclusion

- As your patient has likely PTP, he undergoes a compression US which reveals a non-occlusive left leg popliteal vein thrombosis, which is improved compared with his previous DVT
- He is advised that he does not have recurrent DVT, and he remains on LMWH anticoagulant therapy

## Case 2: Summary

In patients with high PTP and negative initial compression ultrasound, serial imaging is indicated to exclude DVT

In patients with low PTP, D-dimer is the first recommended diagnostic test to exclude DVT

When assessing for recurrence of DVT, comparison of prior and current imaging is warranted to determine if radiographic findings are old or represent recurrence





## Case 3: Suspected Upper Extremity DVT

45 year old male

**Past Medical History:** Hypertension, lung cancer

**Medications:** Ramipril, chemotherapy (cisplatin/gemcitabine)

### **Seen in the Emergency Department with:**

- Right arm pain, edema, and swelling x 48 hours
- Has pain around site of peripherally-inserted central catheter (PICC) which is being used for administration of chemotherapy
- No chest pain or shortness of breath

## What is his PTP for upper extremity DVT (UEDVT)?

Constans Clinical Decision Score	
Item	Count
Venous material (central catheter, pacemaker)	1
Localized pain	1
Unilateral edema	1
Other diagnosis at least as plausible	-1

Score 2 to 3: UEDVT likely

Score  $\leq$  1: UEDVT unlikely

His PTP is “likely”  
(score is 3)



Your patient has likely PTP for UEDVT.

Which diagnostic test would you recommend at this point?

- A. High-sensitivity D-dimer
- B. Venography of upper extremities
- C. Duplex ultrasound of upper extremities
- D. Contrast CT of upper extremities
- E. Transthoracic echocardiogram

Either A or C  
would be  
appropriate

*In patients with a **likely** clinical PTP of UEDVT, what is the optimal diagnostic strategy?*

## Recommendation

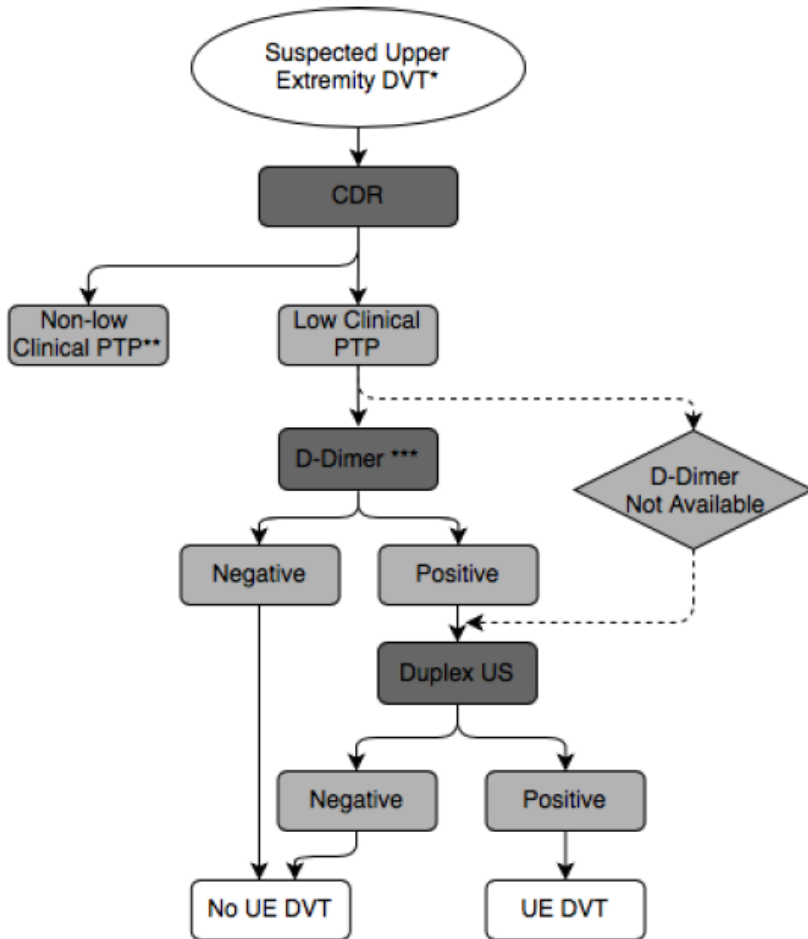
The panel suggests a strategy of *either*:

- D-dimer followed by duplex ultrasound/serial duplex ultrasound, or
- Duplex ultrasound/serial duplex ultrasound alone (*conditional recommendation, very low certainty on clinical outcomes, low-moderate certainty on diagnostic accuracy*)

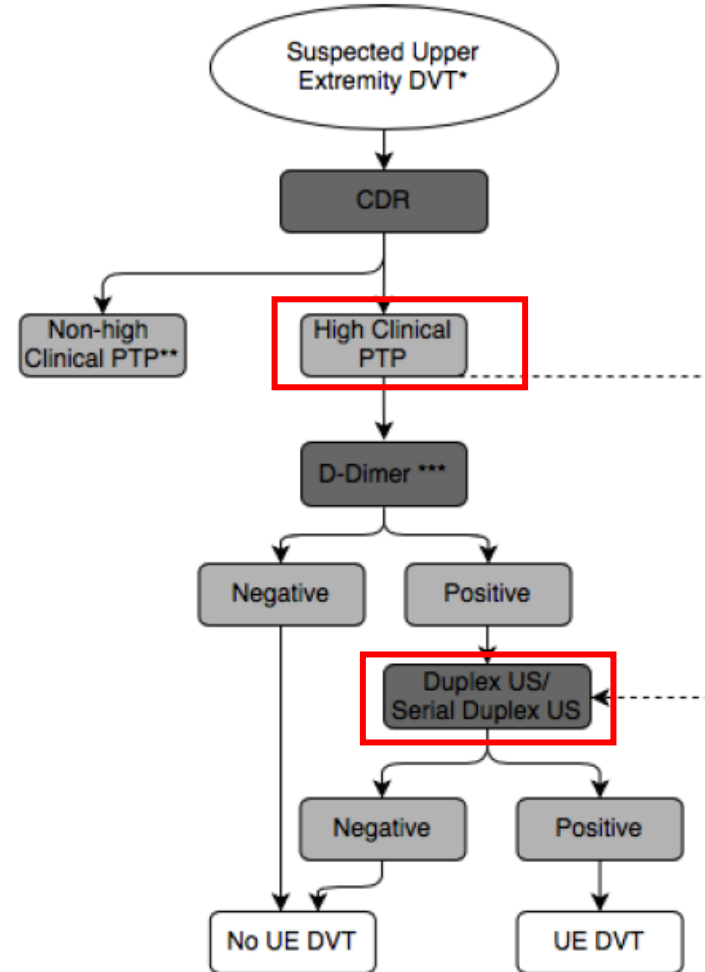
## Remarks:

- For a population with **high (likely) PTP**, none of the evaluated diagnostic pathways met initial threshold set by panel, and **duplex US as sole diagnostic tool was inadequate**
- Diagnostic threshold for excluding UEDVT was met when additional tests were added, including either **serial duplex US** or **D-dimer** (as long as positive result followed by US)

## Unlikely Clinical PTP



## Likely Clinical PTP



## Case 3: Conclusion

- Your patient, whose PTP for UEDVT was “likely,” undergoes a duplex ultrasound of his right upper extremity
- The ultrasound reveals an occlusive thrombus within the axillary and subclavian veins, and he is started on appropriate anticoagulant therapy for his PICC-associated UEDVT



## Case 3: Summary

In patients with suspected UEDVT, an assessment of PTP (for example, Constans score) should be performed before initial diagnostic tests are selected.

In patients with likely PTP, D-dimer (followed by ultrasound if positive) or ultrasound are the recommended initial diagnostic test

In patients with unlikely PTP, D-dimer is the first recommended diagnostic test to exclude UEDVT



## Future Priorities for Research

- Clinical prediction rules for recurrent DVT and PE
- Diagnostic findings in recurrent DVT and PE
- Further validation of diagnostic strategies for UEDVT
- Evaluation of newer diagnostic modalities: MRI, VQ SPECT, SPECT CT



## In Summary: Back to our Objectives

1. Describe a diagnostic strategy for suspected acute deep vein thrombosis (DVT) or pulmonary embolism (PE)
  - Establish clinical PTP, then select initial diagnostic test (D-dimer or CTPA versus VQ scan) to exclude VTE
2. Describe a diagnostic strategy for suspected recurrent DVT or PE
  - Establish clinical PTP, then select initial diagnostic test (D-dimer or ultrasound) to exclude recurrent VTE
3. Describe a diagnostic strategy for suspected upper extremity DVT
  - For patients with likely PTP, initial test can be D-dimer or doppler ultrasound of the upper extremity



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See more about the **ASH VTE guidelines** at <http://www.hematology.org/VTEguidelines>