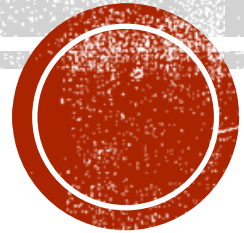
PULMONARY EMBOLISM:
HOW MUCH CLOT IS TOO MUCH CLOT

John Mariano



EPIDEMIOLOGY

- The annual incidence of pulmonary embolism in the population is 1 per 1000 people
- Increases sharply with age, from 1.4 per 1000 people aged 40-49 to 11.3 per 1000 aged 80 years or over.
- Recurrent venous thromboembolism occurs in 30% of people, making the attack rate (including incident and recurrent venous thromboembolism) higher, estimated as up to 30 per 1000 person years
- Risk factors with OR as shown

Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. BMJ. 2020 Aug 5;370:m2177. doi: 10.1136/bmj.m2177. PMID: 32759284.

Box 1: Transient risk factors for venous thrombosis[16]

Strong risk factor (odds ratio >10)
- Hip or leg fracture
- Hip or leg joint replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factor (odds ratio 2-9)
- Arthroscopic knee surgery
- Central venous lines
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factor (odds ratio <2)
- Bed rest >3 days
- Immobility due to sitting (eg, prolonged road or air travel)
- Increasing age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy (antepartum)
- Varicose veins

DIAGNOSIS

- How do we diagnose pulmonary embolism?
  - Two steps:
    - Clinical scoring systems:
      - Well's Criteria- Wells' Criteria for Pulmonary Embolism - MDCalc
      - PERC Rule- PERC Rule for Pulmonary Embolism - MDCalc
      - Revised Geneva Score- Geneva Score (Revised) for Pulmonary Embolism - MDCalc
    - Serologic/radiographic testing:
      - CTA- gold standard
      - V/Q scan- Limited by concurrent lung disease
      - D-dimer – an age old argument

Table 4. Results on CTA and CTA–CTV among Patients with a Confirmed Diagnosis of Pulmonary Embolism, According to the Composite Reference Standard.

Variable	Abnormal Findings on Composite Reference Standard	Normal Findings on Composite Reference Standard	Total
	number of patients		
Findings on CTA			
Abnormal findings	150	25	175
Normal findings	31	567	598
Indeterminate findings	11	40	51
Total	192	632	824
Findings on CTA–CTV			
Abnormal findings on either CTA or CTV	164	30	194
Normal findings on both CTA and CTV	19	524	543
Indeterminate findings*	9	78	87
Total	192	632	824

* Findings were normal on either CTA or CTV and the alternative CT method was not performed, or findings were of insufficient quality for conclusive interpretation.

Table 5. Positive and Negative Predictive Values of CTA, as Compared with Previous Clinical Assessment.*

Variable	High Clinical Probability		Intermediate Clinical Probability		Low Clinical Probability	
	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)
Positive predictive value of CTA	22/23	96 (78–99)	93/101	92 (84–96)	22/38	58 (40–73)
Positive predictive value of CTA or CTV	27/28	96 (81–99)	100/111	90 (82–94)	24/42	57 (40–72)
Negative predictive value of CTA	9/15	60 (32–83)	121/136	89 (82–93)	158/164†	96 (92–98)
Negative predictive value of both CTA and CTV	9/11	82 (48–97)	114/124	92 (85–96)	146/151†	97 (92–98)

* The clinical probability of pulmonary embolism was based on the Wells score: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. CI denotes confidence interval.

† To avoid bias for the calculation of the negative predictive value in patients deemed to have a low probability of pulmonary embolism on previous clinical assessment, only patients with a reference test diagnosis by ventilation–perfusion scanning or conventional pulmonary DSA were included.

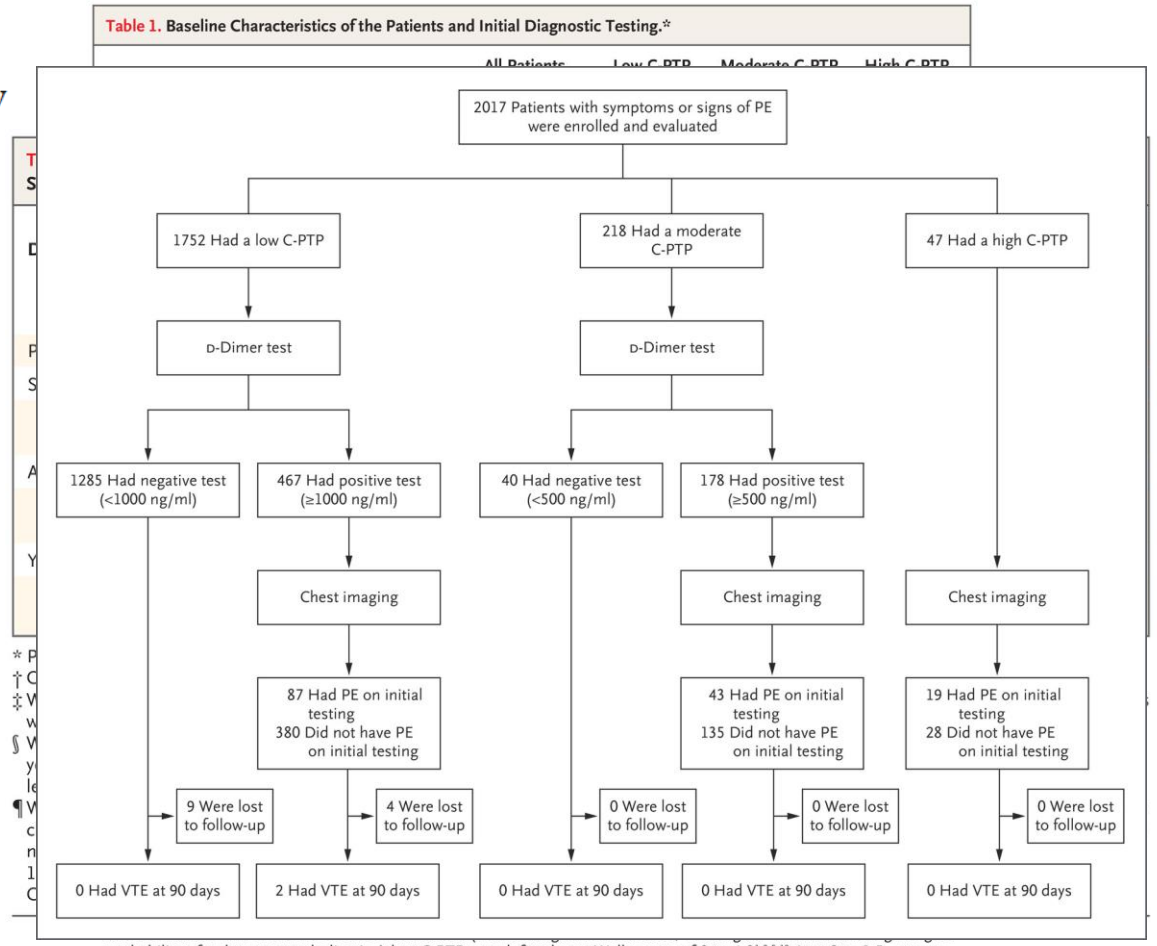
A NOTE ON D-DIMER…

ORIGINAL ARTICLE

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability

Clive Kearon, M.B., Ph.D., Kerstin de Wit, M.B., Sameer Parpia, Ph.D., Sam Schulman, M.D., Ph.D., Marc Afilalo, M.D., Andrew Hirsch, M.D., Frederick A. Spencer, M.D., Sangita Sharma, M.D., Frédérick D'Aragon, M.D., Jean-François Deshaies, M.D., Gregoire Le Gal, M.D., Ph.D., Alejandro Lazo-Langner, M.D., et al., for the PEGeD Study Investigators*

- Prospective study of 2017 Canadian patients primarily ED or outpatient
- Demographics
  - Incidence of PE 7.4% in study
  - Low average age with slight female predominance
- Results
  - Only 1 "missed VTE" and imaging performed 35% of patients as compared to 50% in other algorithms



probability of pulmonary embolism). A low C-PTP was defined as a Wells score of 0 to 4.0[1,2,5,12] (not 0 to 1.5, as was originally proposed for a low C-PTP; a score of 0 to 4.0 also corresponds to pulmonary embolism being "unlikely"),[13] a moderate C-PTP was defined as a Wells score of 4.5 to 6.0, and a high C-PTP was defined as a Wells score of 6.5 or higher. CT denotes computed tomography, DVT deep-vein thrombosis, NA not applicable, and VTE venous thromboembolism.

† Other D-dimer assays included HemosIL HS in 14 patients (the usual threshold level of 230 ng per milliliter D-dimer units was used in patients with a moderate C-PTP, and a level of 460 ng per milliliter D-dimer units was used in patients with a low C-PTP) and Roche Cardiac Reader in 7 patients. The assay type was not recorded for 4 patients.

‡ Patients could undergo both CT pulmonary angiography and ventilation–perfusion scanning.

ACUTE MANAGEMENT- RISK STRATIFICATION

- Risk Stratification:
  - **Massive:** hemodynamic instability, defined as systolic blood pressure below 90 mm Hg for 15 minutes or more, only 5% of cases; short term mortality exceeds 15%
  - **Submassive:** signs of R heart strain
    - NT-pro BNP elevation
    - Echo/CTA R heart strain
    - Troponin elevation
  - **Low risk:** none of the above
- Clinical scoring systems:
  - PESI, sPESI
  - Hestia Criteria for admission

Table 2 | Comparison of pulmonary embolism risk prediction scores

Variable	Points
Pulmonary Embolism Severity Index (PESI)*[87]	
Age, per year	Age, in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse rate ≥110/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified Pulmonary Embolism Severity Index (sPESI)†[88]	
Age >80 years	1
History of cancer	1
History of chronic lung disease	1
Pulse rate ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxygen saturation <90%	1
Hestia criteria‡[89]	
Is the patient hemodynamically unstable?	–
Is thrombolysis or embolectomy necessary?	–
Active bleeding or high risk of bleeding?	–
>24 h of oxygen supply to maintain oxygen saturation >90%?	–
Is pulmonary embolism diagnosed during anticoagulant treatment?	–
Severe pain needing intravenous pain medication for >24 h?	–
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?	–
Does the patient have a creatinine clearance of <30 mL/min?	–
Does the patient have severe liver impairment?	–
Is the patient pregnant?	–
Does the patient have a documented history of heparin induced thrombocytopenia?	–

*66-85 class I; 86-105 class II; 106-125 class III; >125 class IV; class V. Class I and II defined as low risk.
†0 low risk; ≥1 high risk.
‡Yes to any question, admission required.

TO LYSE OR NOT TO LYSE

- Previous risk stratification based in RCT called PEITHO Trial looked at fibrinolysis in "intermediate risk" PE
  - Intermediate defined as:
    - Echo (or CTA) evidence of R heart strain
    - AND Troponin elevation
  - Tenactaplase vs. Placebo

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., et al., for the PEITHO Investigators*

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

* Plus–minus values are means ±SD. Odds ratios and P values are provided for efficacy outcomes that were prespecified in the trial protocol.

* Between-group differences in the characteristics listed here were not significant except for low-molecular-weight heparin or fondaparinux given before randomization (P=0.02).

TO ADMIT OR NOT TO ADMIT…

(JK THEY'LL DEF BE ADMITTED NO MATTER WHAT)

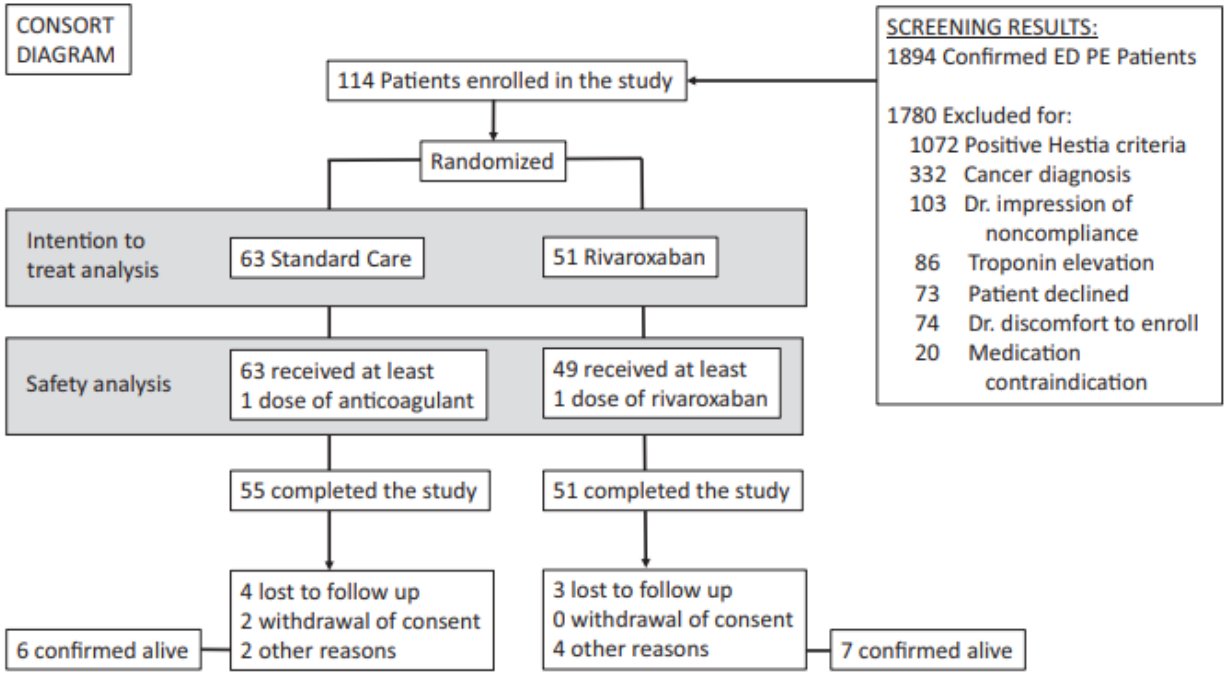
Emergency Department Discharge of Pulmonary Embolus Patients

W. Frank Peacock, MD, Craig I. Coleman, PharmD, Deborah B. Diercks, MD, Samuel Francis, MD, Christopher Kabrhel, MD, Catherine Keay, MD, Jeffrey A. Kline, MD, Jacob Manteuffel, MD, Peter Wildgoose, PhD, Jim Xiang, PhD, and Adam J. Singer, MD

- 114 ED patients:
  - 51 Rivaroxaban and 63 standard of care
  - Standard of care received a variety but 50% rivaroxaban, 25 % apixaban, and 16% warfarin
  - No difference in safety outcomes
  - Significant cost savings in reduced hospital stay

- In defense of the difficult position of ED/outpatient providers, other studies have shown 4 fold increase in 30d mortality if positive troponins present in low-risk PE so question long from answered

Table 1
Adapted HESTIA Criteria (Any Present Exclude Early Discharge Option)



Pregnant
Known history of heparin-induced thrombocytopenia

GI = gastrointestinal; HTN = hypertension; PE = pulmonary embolism.

CHOICE OF THERAPY

Box 2: Phases of pulmonary embolism treatment[104]

Initial (0-7 days)
- Apixaban 10 mg BID for 7 days
- Rivaroxaban 15 mg BID for 21 days
- LMWH/fondaparinux for minimum 5 days* and INR ≥2 for 2 days

Long term (1 week to 3 months)
- Apixaban 5 mg BID
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily
- Warfarin for INR 2-3

Extended (3 months to indefinite)
- Apixaban 5 mg BID or 2.5 mg BID‡
- Acetylsalicylic acid 81-100 mg daily, if anticoagulation not possible
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily or 10 mg daily‡
- Warfarin for INR 2-3

BID=twice daily; INR=international normalized ratio; LMWH=low molecular weight heparin
*LMWH is needed for 5-10 days before starting dabigatran or edoxaban
†30 mg daily if creatinine clearance is 30-50 mL/min or weight <60 kg
‡Dose reduction may be considered after 6 months of therapy

Table 3 | Cl

Drug
Dabigatran
Apixaban
Edoxaban
Rivaroxaban

*Rivaroxaban

Table 4 | Phas

Trial characteri
Sample size
Single agent (ie,
Duration of treat
Primary outcom
Major bleeding
Major or CRNM
Dosing schedule

BID=twice a day; C
antagonist; VTE=v

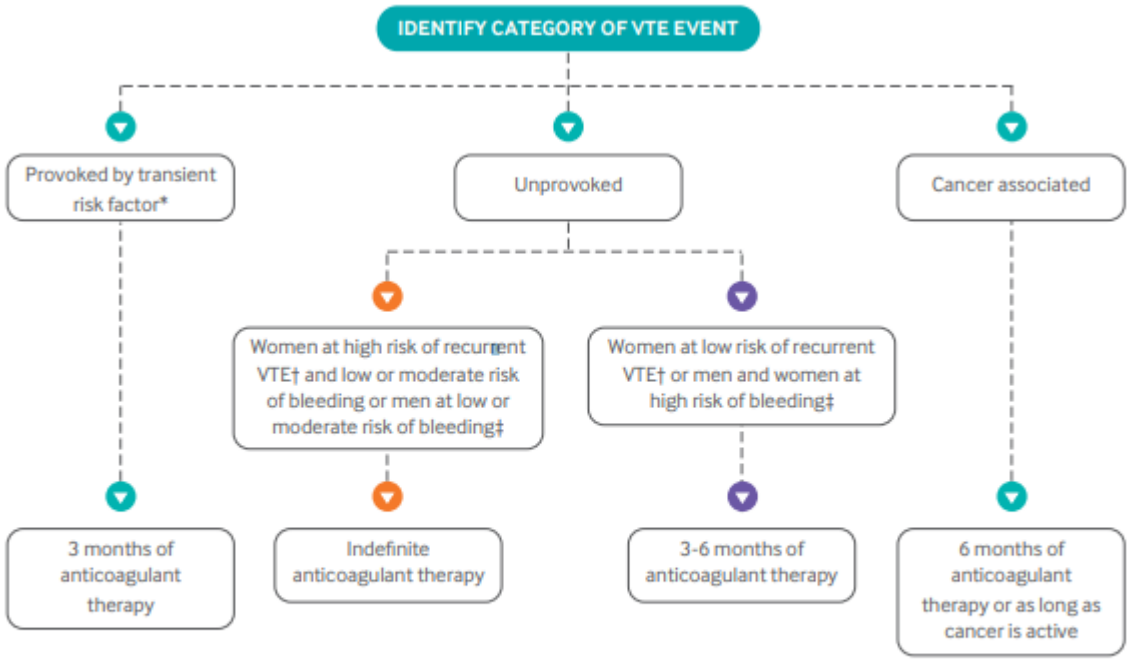


Fig 4 | Approach to duration of treatment of venous thromboembolism (VTE). *If transient risk factor is non-surgical (eg, immobilization, pregnancy, or estrogen therapy), extended treatment can be considered given the safety profile of direct oral anticoagulants. †According to "Men continue and HERDOO2" risk prediction score: low=women with 0-1 points; high risk=all men and women with ≥2 points. ‡Bleeding risk according to HAS-BLED score: low risk 0-2 points or high risk ≥3 points. Adapted from Tritschler T, et al. *JAMA* 2018[147]

Protein binding (%)
35
85
55
90

	Rivaroxaban[7 107]
	8281
	Yes
	3, 6 or 12
to 1.13)	HR 0.89 (0.66 to 1.19)
to 1.21)	HR 0.54 (0.37 to 0.79)
to 0.94)	HR 0.93 (0.81 to 1.06)
	BID then OD

ctionated heparin; VKA=vitamin K

MISC TIDBITS

- Thrombophilia testing not recommended as it would not change management
- In the event of unprovoked PE could however consider testing for antiphospholipid syndrome as the preferred therapy is warfarin and management would change
- Subsegmental PE without associated DVT may not need anticoagulation and can have a risk/benefit discussion with patients

TAKEAWAYS

- Clinical criteria are key to diagnosis and management of PE
- Addition of cardiac markers and echocardiogram are likely somewhat helpful for risk stratification but have unclear significance in driving therapy in intermediate risk or submassive PEs
- Most PE management can occur outpatient with guidance of clinical criteria assessments

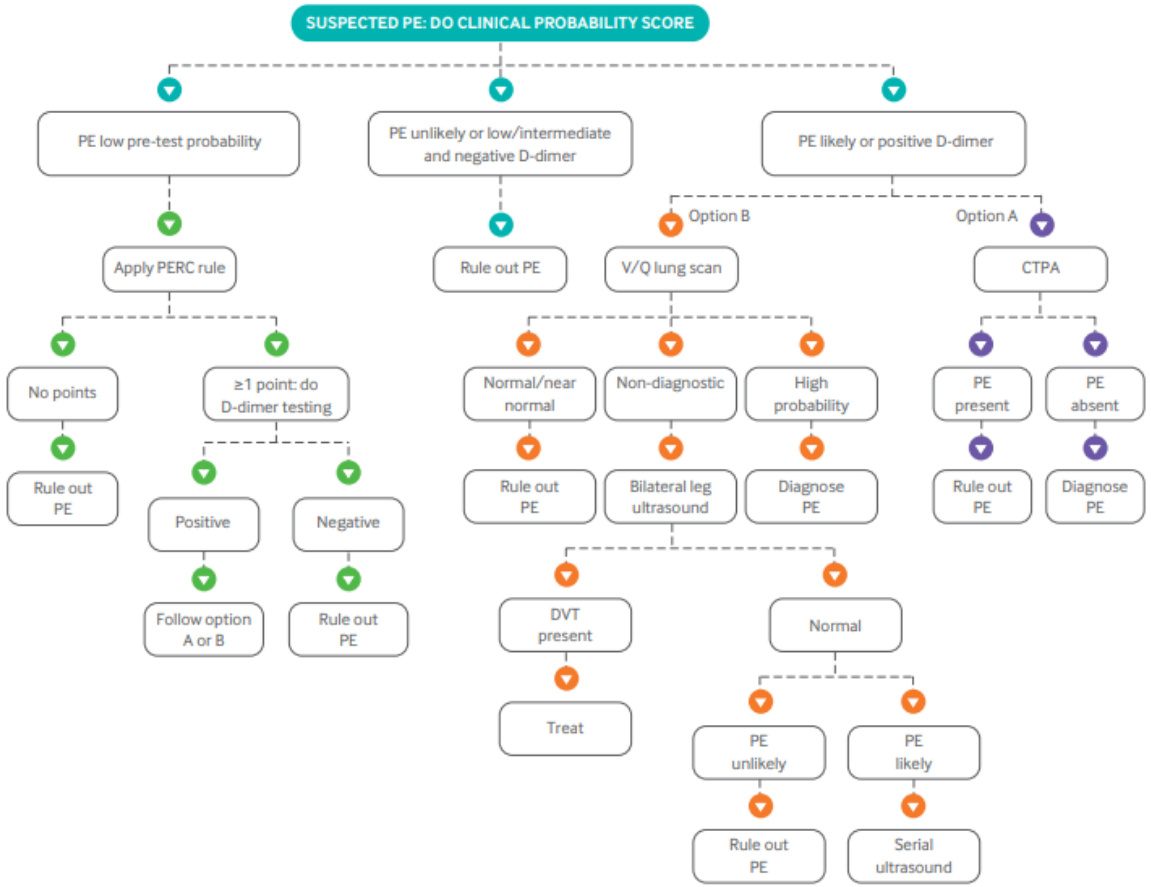


Fig 2 | Diagnostic work-up of patients with suspected pulmonary embolism (PE). CTPA=computed tomography pulmonary angiography; PERC=pulmonary embolism rule-out criteria; V/Q=ventilation-perfusion. Adapted from Wells PS, et al. *Ann Intern Med* 2018[44]

REFERENCES

- Acknowledged within slide with most important reference from recent review:
  - Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. BMJ. 2020 Aug 5;370:m2177. doi: 10.1136/bmj.m2177. PMID: 32759284