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Diagnosis of thrombosis and pulmonary embolism

Henri Bounameaux, MD

Director, Division of Angiology and Hemostasis
University Hospitals of Geneva

Professor of Medicine and Dean
Faculty of Medicine, University of Geneva
Geneva, Switzerland

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Disclosures for Henri Bounameaux, MD

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Speakers Bureau	No relevant conflicts of interest to declare
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Scientific Advisory Board	No relevant conflicts of interest to declare

Presentation includes discussion of the following off-label use of a drug or medical device: <N/A>

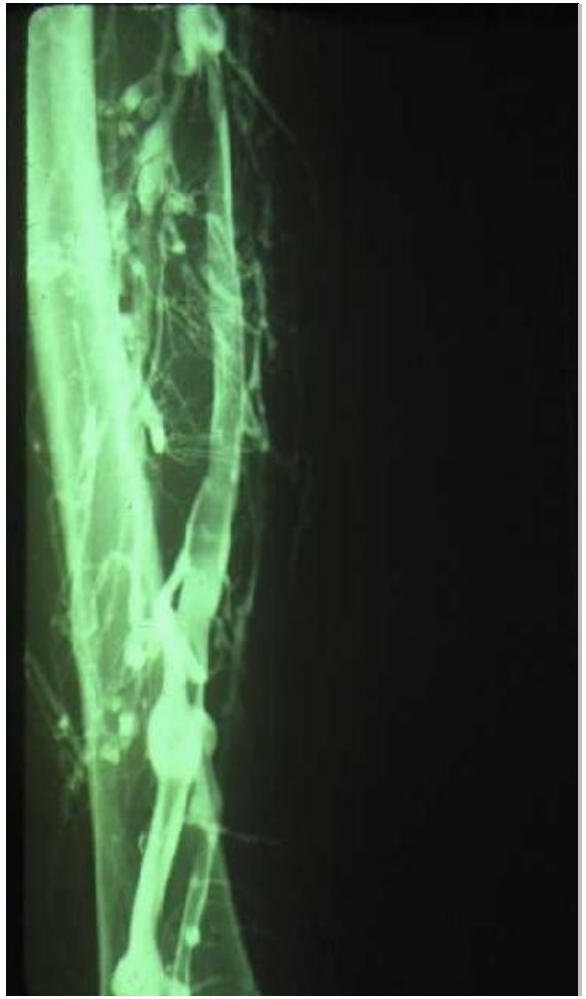
My talk today

- What is the 2015 diagnostic algorithm in suspected VTE?
- Are there graded recommendations on VTE diagnosis?
- Are there pitfalls and controversies?
- Is more less?

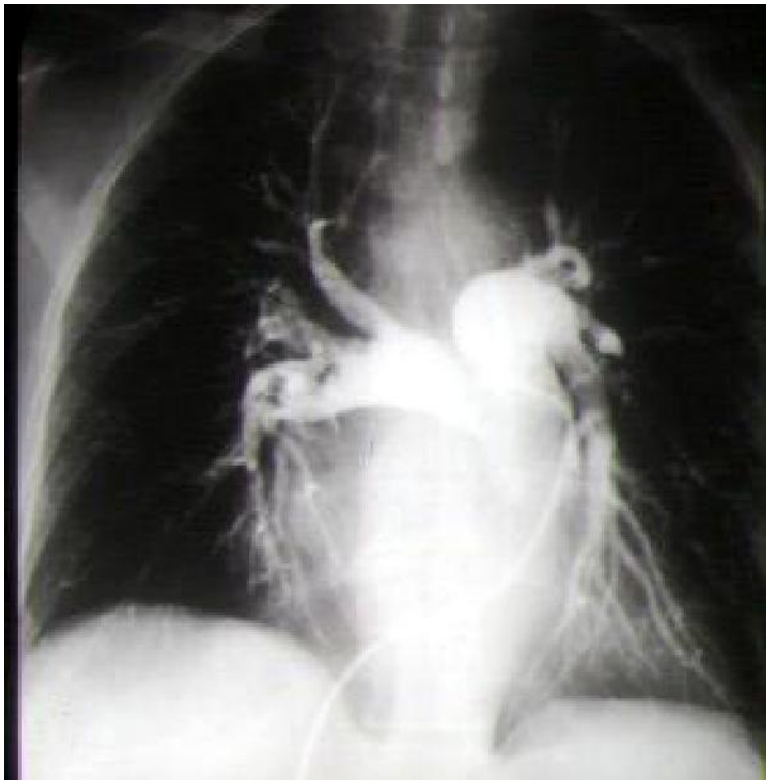
Goldhaber SZ and Bounameaux H. *Lancet* 2012;379:1835–46.
Bates SM et al. *Chest* 2012;141(2 Suppl.):e351S–e418S.

In the 70’s-80’s

- Invasive
- Costly
- Not devoid of risks



Phlebography



Pulmonary angiography

The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
- Venous compression ultrasonography
- Clinical probability
- Single-row CTPA
- Multi-row CTPA
- MRI ?

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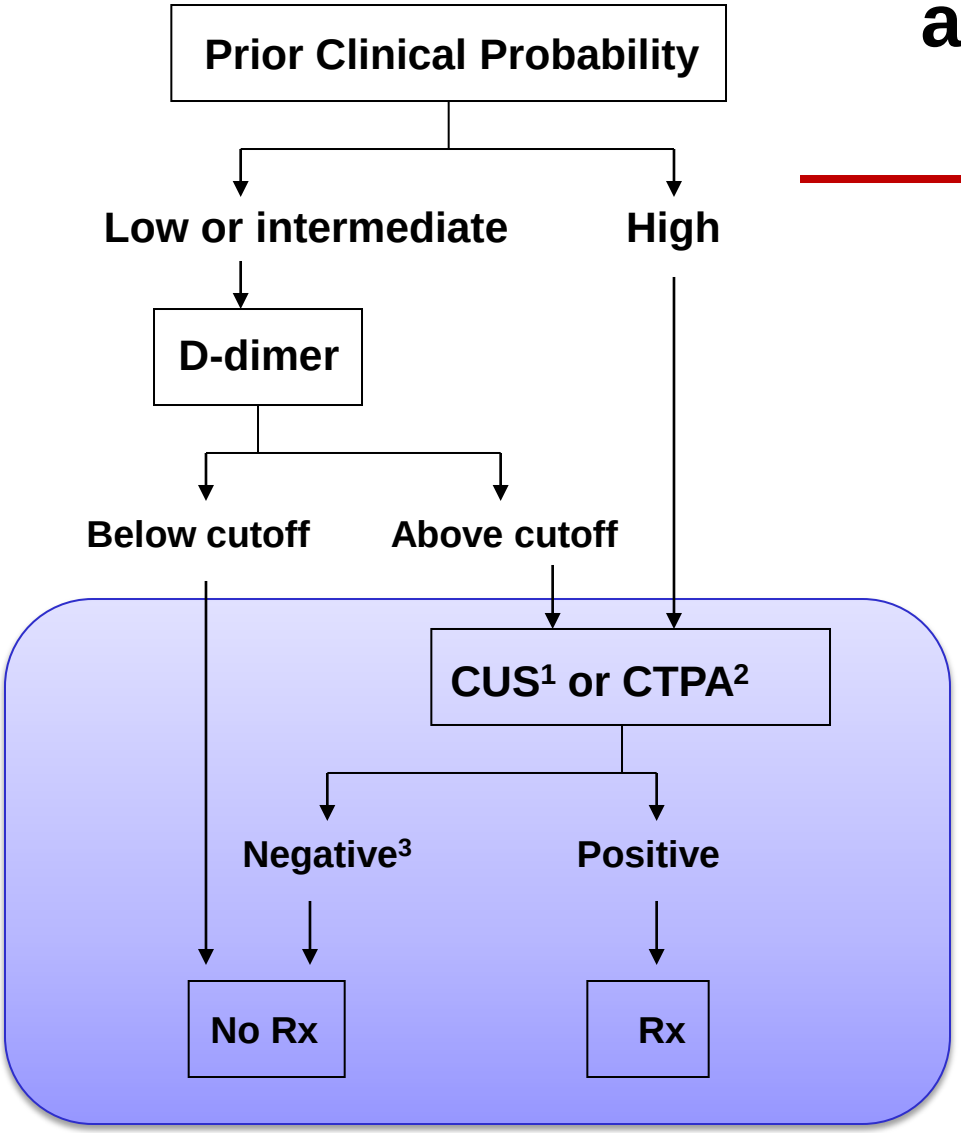
The 2014 diagnostic algorithm for suspected non high-risk VTE



[1]CUS (lower limb venous compression ultrasonography) in case of suspected DVT

[2]CTPA (multi-row) in case of suspected PE

[3]In case of negative CUS or MSCT and high prior clinical probability, consider additional imaging, e.g. venography (suspected DVT) or lung ventilation/perfusion scintigraphy or pulmonary angiography (suspected PE)

Rx stays for treatment

Righini M et al. *J Thromb Haemost* 2008;6:1059–71.
Goldhaber SZ and Bounameaux H. *Lancet* 2012;379:1835–46.

Clinical classification of PE

- **Massive (high-risk) PE** 5%

- **Non-massive (non-high risk) PE**
  - with RV dysfunction 30%
    (« submassive »)

  - without RV dysfunction 65%
    (« truly non massive »)

Suspected massive PE

- Massive PE
  - Schock or cardiorespiratory arrest
  - Timing: minutes …
  - Treatment: thrombolysis/embolectomy
- Diagnostic work-up less important than emergency treatment
  - Echocardiography useful (differential diagnosis, indirect arguments in direction of PE)
  - V/Q scan, CTPA for confirmation
  - No place for D-dimer or lengthy diagnostic sequences

The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)

- **D-dimer**
- Venous compression ultrasonography
- Clinical probability
- Single-row CTPA
- Multi-row CTPA
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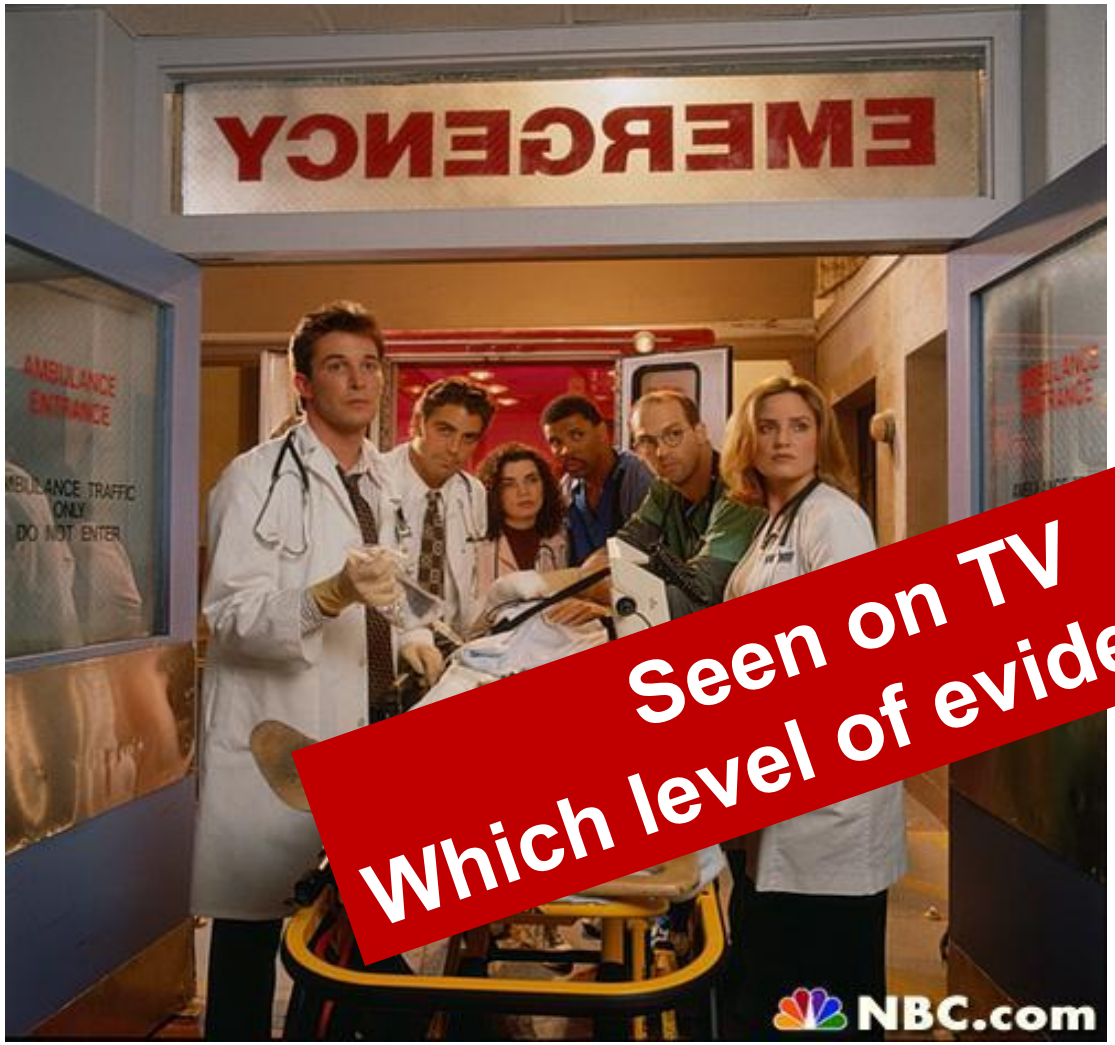
D-dimer for PE: what evidence?



ER: Dr. Green says:

« Electrolytes, CBC, blood gases **and D-dimer!** »

Seen on TV
Which level of evidence ??

D-dimer in Suspected DVT

Type of D-dimer	Deep vein thrombosis		Pulmonary embolism	
(number of studies)	Sn, %	Sp, %	Sn, %	Sp, %
Microplate ELISA				
Asserachrome (24)	**94** (83-98)	47 (29-65)	96 (80-99)	44 (21-69)
Membrane ELISA				
Instantia (13)	**86** (59-96)	65 (43-81)	89 (54-98)	62 (33-84)
Nycocard (23)	**88** (68-96)	50 (31-68)	91 (64-98)	47 (23-72)
Latex quantitative				
Tinaquant (12)	**92** (75-98)	53 (32-73)	94 (71-99)	50 (23-76)
STA-lia test (25)	**94** (83-98)	46 (28-64)	96 (80-99)	43 (20-68)
ELFA				
VIDAS (40)	**96** (93-98)	44 (36-52)	97 (91-99)	41 (26-57)
Whole-blood assay				
SimpliRed (40)	**82** (59-93)	72 (56-84)	86 (43-97)	70 (44-87)

Di Nisio et al, *J Thromb Haemost* 2007;5:296–304.

D-dimer in Suspected PE

Type of D-dimer	Deep vein thrombosis		Pulmonary embolism	
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Microplate ELISA				
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RIETE data
(N>17,000)

90.6 (87.0-94.1)

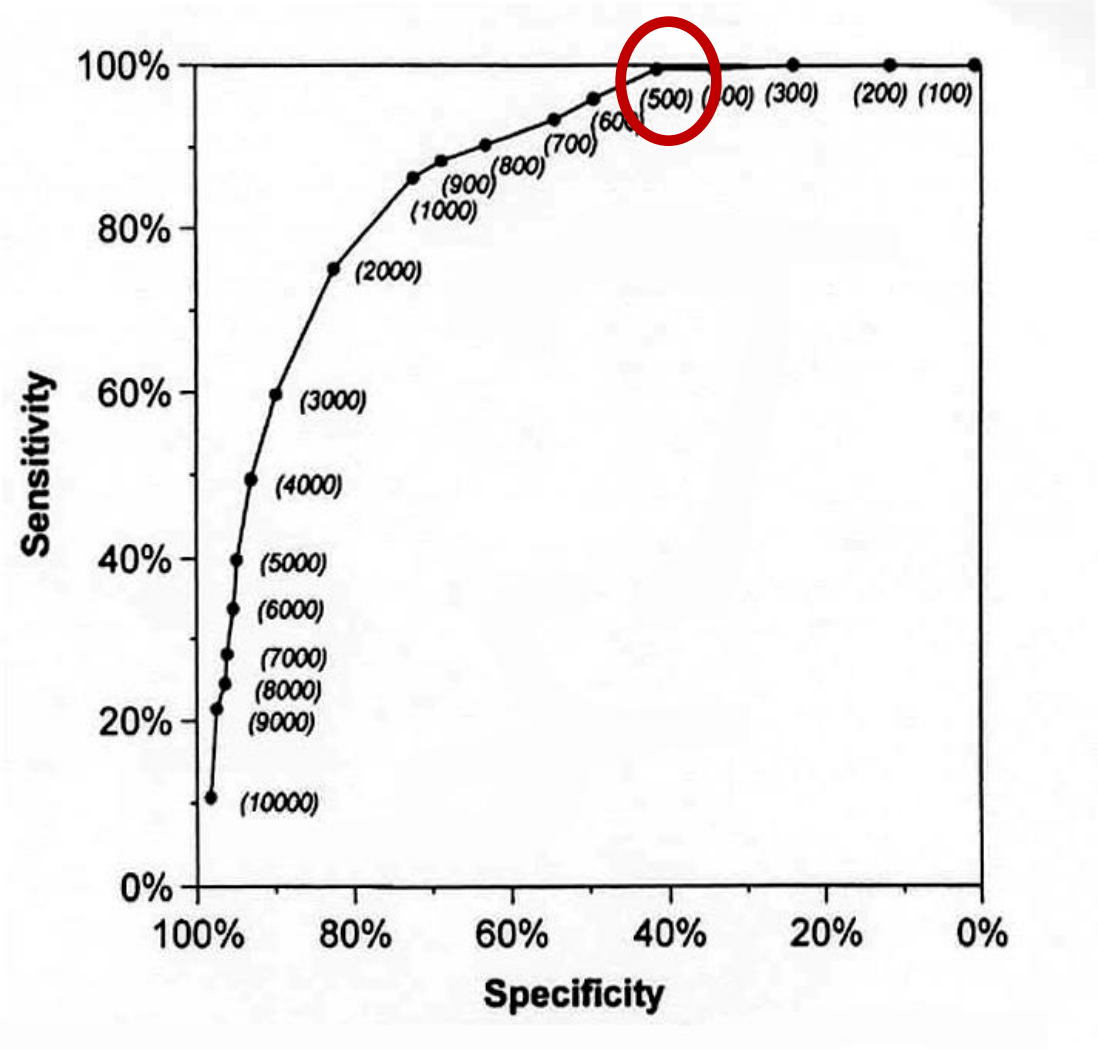
97.3 (96.7-97.8)

97.6 (97.0-98.2)

Soto MJ et al. *J Thromb Haemost* 2011;9:407–10.

Di Nisio et al, *J Thromb Haemost* 2007;5:296–304.

Receiver Operating Characteristic (ROC) Curve to Define the Diagnostic Cut-off in Suspected PE



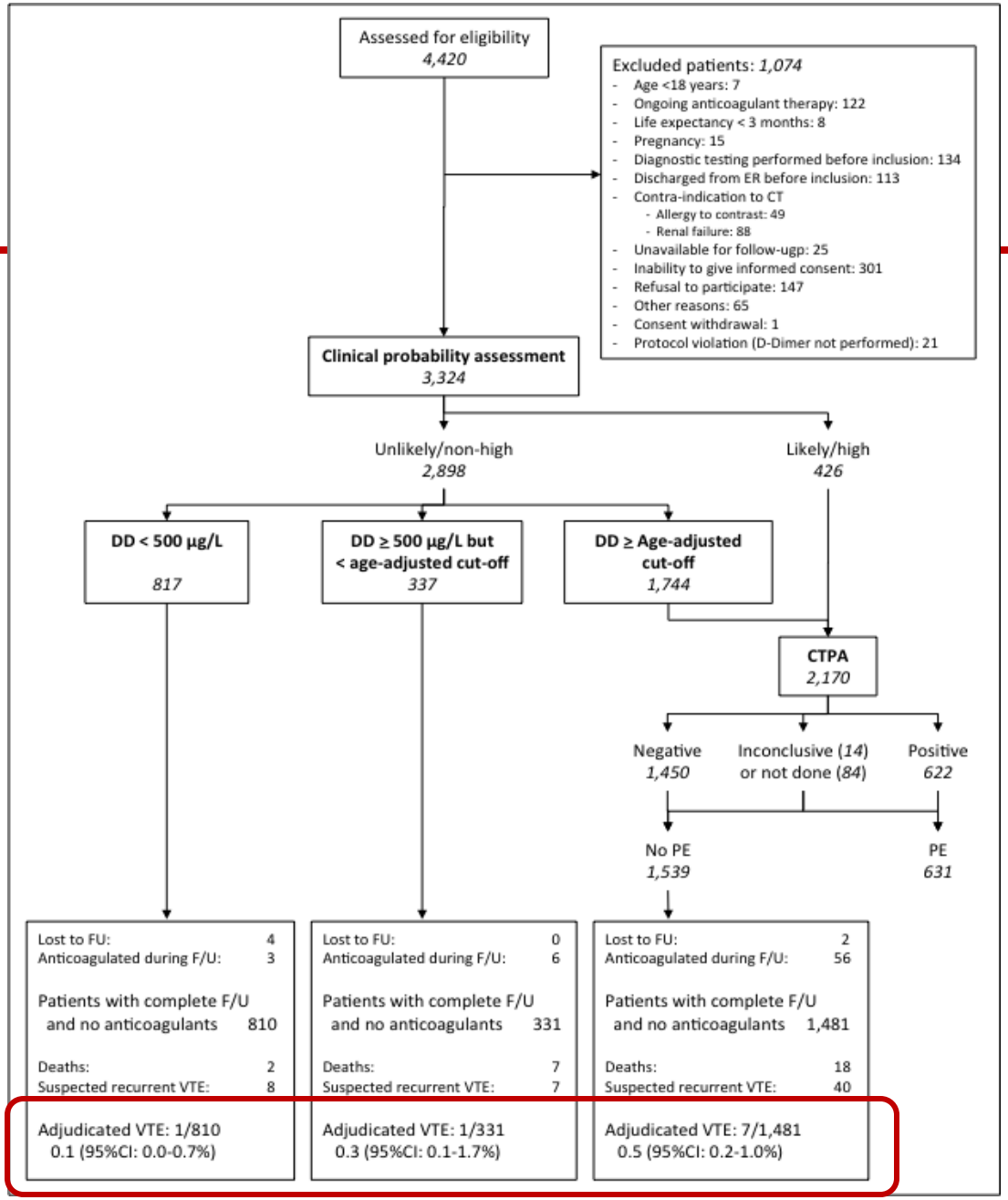
Perrier A et al. *Am J Respir Crit Care Med* 1997;156:492–6.

Controversy: DD and Age (Individuals Suspected of PE*)

Age	Sensitivity %	Specificity %	DD <500, % pts.	NNT
<40	100 (86-100)	67 (60-74)	58	2
40-49	100 (86-100)	67 (59-75)	56	2
50-59	100 (83-100)	56 (47-65)	49	2
60-69	99 (93-100)	40 (3-49)	26	4
70-79	99 (93-100)	26 (19-34)	17	6
80+	100 (98-100)	9 (44-51)	5	20

*n=1034 patients

Righini et al. *Am J Med* 2000;109:357–61.



ADJUST-PE Study

Cut-off (above age of 50) =

Age x 10

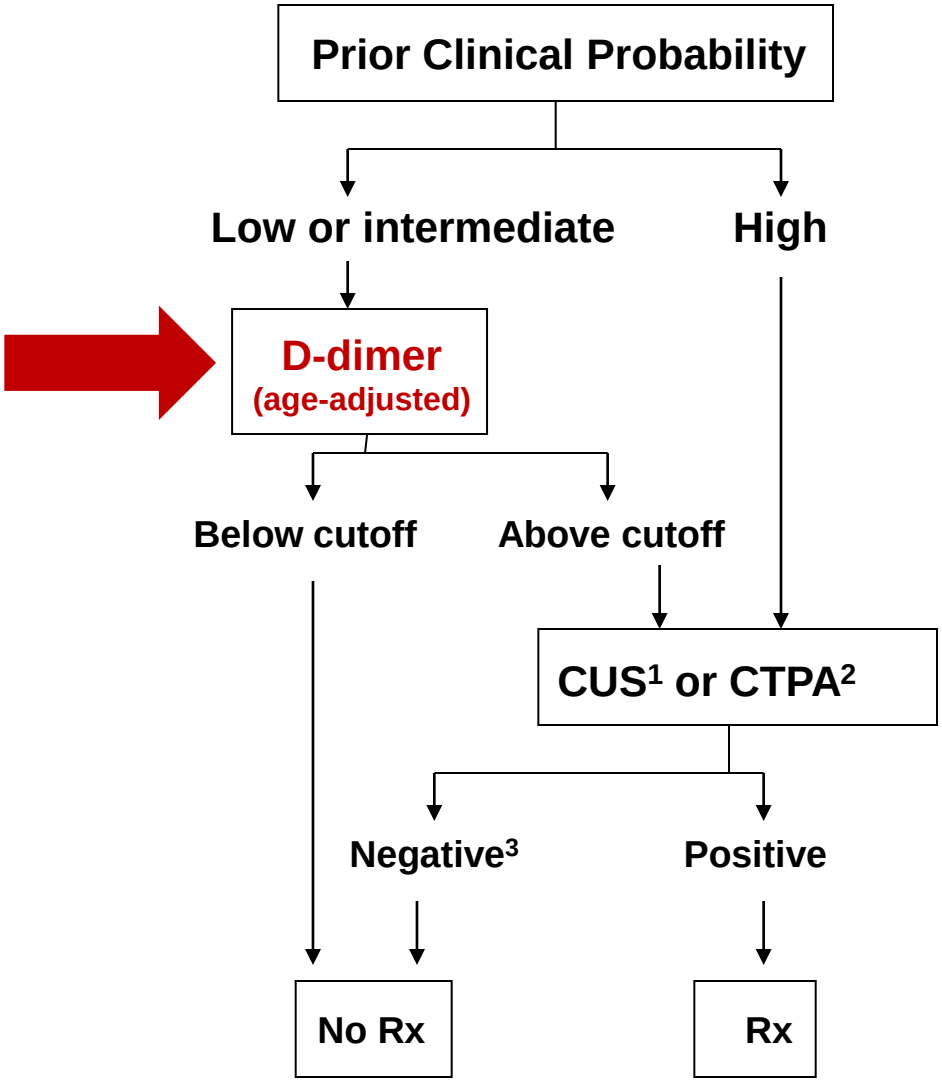
Number Needed to Test (NNT)
to rule out one event

Conventional	Age-adjusted
16	**3.4**

in patients aged 75+

Righini M et al. *JAMA* 2014;311:1117–24.

The 2014 revised VTE diagnostic algorithm



Among the 766 patients 75 years or older, of whom 673 had a non-high clinical probability, using the age-adjusted cutoff instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer 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.

The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
- **Venous compression ultrasonography**
- Clinical probability
- Single-row CTPA
- **Multi-row CTPA**
- MRI ?

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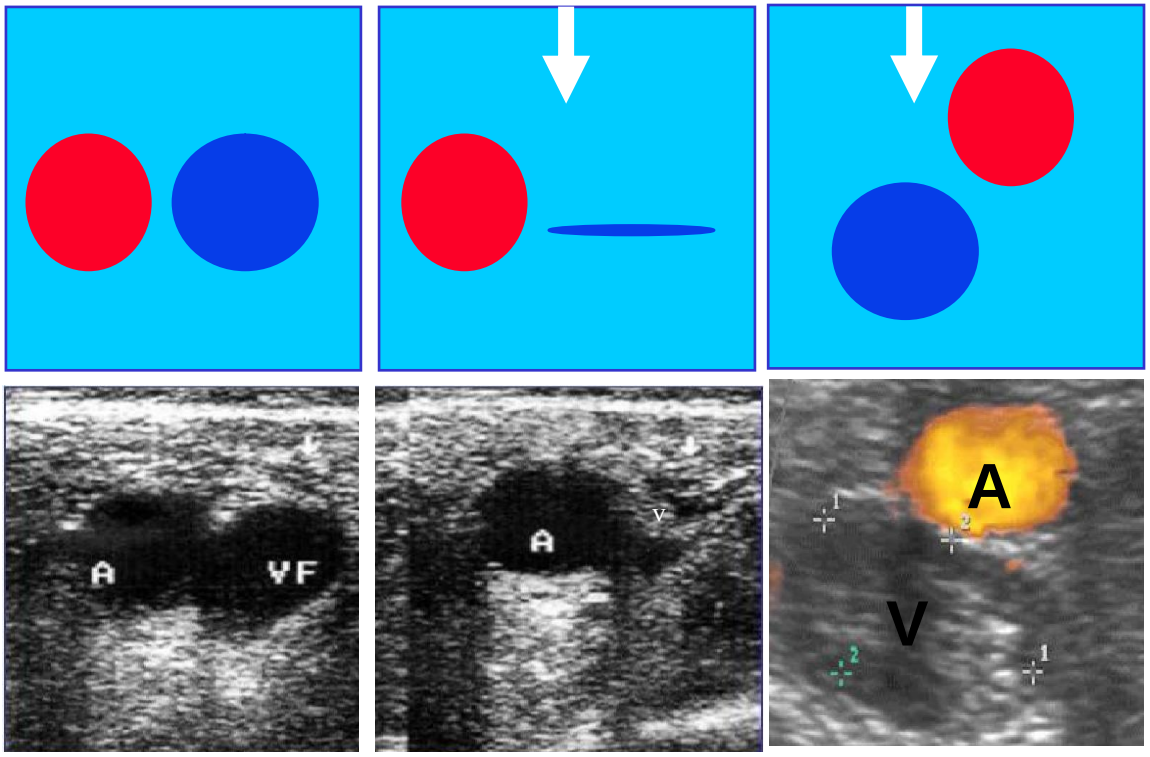
Compression ultrasonography (CUS)



Goldhaber SZ and Bounameaux H. *Lancet* 2012;379:1835–46.

Controversy: Proximal or complete CUS?

1. Proximal CUS only*
2. Complete (proximal and distal) CUS

* Often in combination or not with repeat exam (after 7 days) (so-called serial CUS), ideally in combination with other tests (DD, clinical probability) in order to increase the yield and cost-effectiveness

Righini M. *J Thromb Haemost* 2007;5(Suppl 1):55–9.
Palareti G and Schellong S. *J Thromb Haemost* 2012;10:11–9.

ACCP guidelines: 9th edition

- In patients with a **low pretest clinical probability**, we recommend initial testing with D-dimer or ultrasound (US) of the proximal veins over no testing (1B), venography (1B) or whole-leg US (2B).
- In patients with **moderate pretest clinical probability**, we recommend initial testing with a highly sensitive D-dimer test, proximal or whole-leg US rather than no testing (1B) or venography (1B).
- In patients with a **high pretest clinical probability**, we recommend proximal or whole-leg US over no testing (1B) or venography (1B).

Bates SM et al. *Chest* 2012;141(2 Suppl.):e351S–e418S.

Is more less ? (I)

- Using whole-leg CUS rather than just proximal CUS is associated with a substantial increase of patients who require anticoagulant treatment
- With no obvious benefit in 3-month outcome
- With an increased risk of adverse bleeding events

Controversy: why using these algorithms?

Table 3. **Patient Outcomes at 3 Months after Exclusion of Pulmonary Embolism***

Diagnostic Work-up	Patients Receiving Appropriate Management (n = 418)	Patients Receiving Inappropriate Management (n = 506)	*P* Value
Total thromboembolic events, n (%)	5 (1.2)	39 (7.7)	<0.001
Nonfatal thromboembolic event, n	2	10	0.045
Unexplained sudden death, n	3	29	<0.001

Roy PM et al. *Ann Intern Med* 2006;144:157–164.

The Diagnostic Tools

- Pulmonary angiography
- Phlebography
- Ventilation/Perfusion lung scan
- Echocardiography: reserved for hemodynamically unstable patients (not focus of the present talk)
- D-dimer
- Venous compression ultrasonography
- **Clinical probability (implicit or explicit)**
- Single-row CTPA
- Multi-row helical CTPA
- MRI ?

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PIOPED II: Results in relation to clinical probability assessment (explicit, after Wells)

23% of positive CTs

Clinical probability	Prevalence of PE, n/n (%)*	
	CT positive	CT negative
Low	22/38 (58%)	8/164 (4%)
Intermediate	93/101 (92%)	15/136 (11%)
High	22/23 (96%)	6/15 (40%)

2% of negative CTs

Stein PD et al. *N Engl J Med* 2006;354:2317–27.

**as compared with a composite reference standard.*

Revised Geneva CPR for suspected PE

- Age > 65 years + 1
- Previous DVT/PE + 3
- Surgery/fracture (4 w) + 2
- Active cancer + 2
- Pulse rate
  - 75–94 /min + 3
  - ≥ 95 /min + 5
- Pain by palpation of leg and edema + 4

- Symptoms
  - Unilateral leg pain + 3
  - Haemoptysia + 2
- Maximum score + 25

Probability of PE	Score	Prevalence of PE
Low	0–3	8%
Intermediate	4–10	29%
High	≥ 11	74%

Le Gal G et al. *Ann Intern Med* 2006;144:165–71.

ACCP guidelines: 9th edition

To treat or not to treat while awaiting test results

- In patients with a **high clinical suspicion** of DVT/PE, we suggest treatment with parenteral anticoagulants over no treatment (2C).
- In patients with an **intermediate clinical suspicion** of DVT/PE, we suggest treatment with parenteral anticoagulants over no treatment if the results of the diagnostic tests are expected to be delayed for more than 4 hours (2C).
- In patients with a **low clinical suspicion** of DVT/PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours (2C).

Kearon C et al. *Chest* 2012;141(2 Suppl.):e419S–e494S.

Multi-row Detector CTPA in Suspected PE:
Outcome Studies

Aim: To assess safety of a negative mrCT for ruling out PE

- Without lower limb venous ultrasonography
- In patients with a non-high clinical probability (Geneva score) or a dichotomized Wells' score below 4 points (« unlikely »)

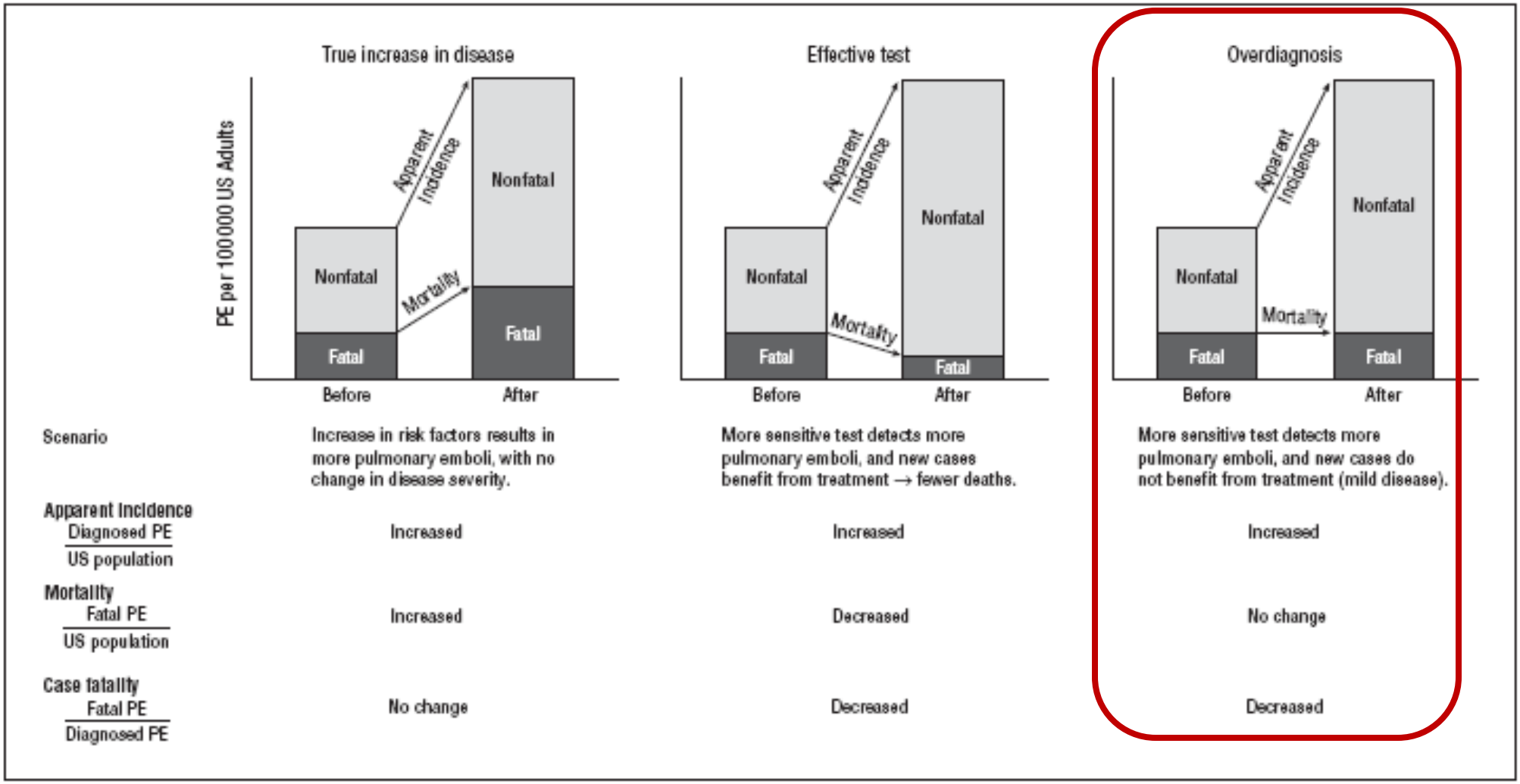
3-month venous thromboembolic risk in patients not given anticoagulant therapy based on a negative mrCT AND a negative CUS:

Swiss-Belgian-French Consortium	1.7% (0.7 to 3.9)
CHRISTOPHER Study	1.3% (0.7 to 2.2)

Both studies suggest that mrCTpPA may safely rule out PE without lower limb venous compression ultrasonography, which was subsequently confirmed in a RCT*

Perrier A et al. *N Engl J Med* 2005;352:1760–8
CHRISTOPHER Study Investigators. *JAMA* 2006;295:172–9
*Righini M et al. *Lancet* 2008;371:1343–52

Controversy: Do we overdiagnose PE?



Scenario	Increase in risk factors results in more pulmonary emboli, with no change in disease severity.	More sensitive test detects more pulmonary emboli, and new cases benefit from treatment → fewer deaths.	More sensitive test detects more pulmonary emboli, and new cases do not benefit from treatment (mild disease).
Apparent Incidence: Diagnosed PE / US population	Increased	Increased	Increased
Mortality: Fatal PE / US population	Increased	Decreased	No change
Case fatality: Fatal PE / Diagnosed PE	No change	Decreased	Decreased

Figure 1. Expected change in mortality and case fatality in various scenarios of rising apparent incidence. PE indicates pulmonary embolism.

Wiener RS et al. *Arch Intern Med* 2011;171:831–9.

Pitfall: Evidence for increased risk of anticoagulation treatment

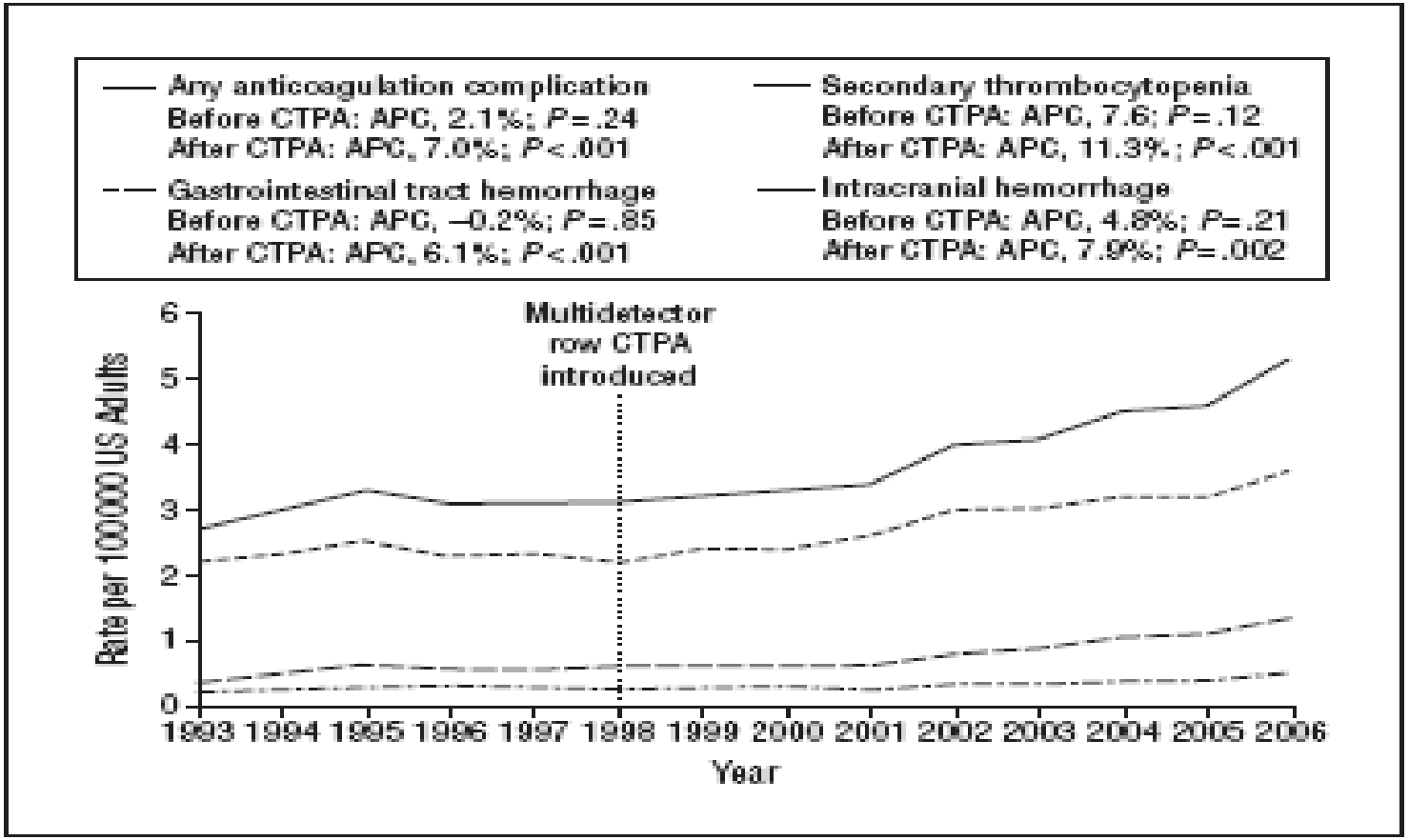


Figure 3. Rates of potential complications of anticoagulation treatment among US adults hospitalized with a pulmonary embolism, 1993-2006. APC indicates annual percentage change; and CTPA, computed tomographic pulmonary angiography.

Wiener RS et al. *Arch Intern Med* 2011;171:831–9.

Is more less ? (II)

- Using CTPA as diagnostic test for suspected PE is associated with a substantial increase in patients who require anticoagulant treatment
- With no change in disease mortality
- With an increased incidence of bleeding events
- With increased radiation

The true question

Is not which patients do have a clot ?

but

Which patients with VTE do need anticoagulant treatment?

- Patients with subsegmental PE (NCT01455818)
- Patients with isolated distal DVT (NCT00421538)

?

Of note, these studies have recruitment and funding problems. *These issues should encourage a move towards a model where funds are pooled into a central and impartial agency that decides what trials to administer.*

(Prasad V et al. *Arch Intern Med* 2012;172:955–8).

Take home messages

- Diagnosis of DVT and PE has changed considerably over the past two decades (it has become non-invasive, sequential, and easy)

- It includes initial clinical assessment, D-dimer measurement (except for high-probability patients) and CUS (suspected DVT) or CTPA (suspected PE)

- Recent “advances” (*whole-leg* CUS instead of *proximal* CUS for suspected DVT, new generations of scanners with increased sensitivity to minor, potentially clinically non-relevant PE) may lead to overdiagnosis and hence overtreatment with its inherent risks

Thank you for your attention

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