Guideline of VTE

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2014-05-10

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- Early mortality rates for PE range from <3% in clinically stable patients to 58% in patients with cardiogenic shock

- ICOPER Lancet 1999; 353:1386-12389

General approach to proven acute PE

- Anticoagulate unless contraindication
- If contraindication, place IVCF

- What is BP? Is there clear hemodynamic compromise?
  - if yes, are there contraindications to thrombolysis?
  - If not, give lytics (systemic or catheter based)

General approach to proven acute PE

- If no clear hemodynamic compromise but RV abnormal
  - Does patient look sick
  - How severe is the RV dysfunction?
  - What is patient's cardiopulmonary reserve
  - O2 requirement?
  - Extent of clot on CT?
  - BNP / Troponin?
  - HR trend? On more/less O2 than an hour ago?

- A 60 year-old man develops sudden dyspnea. He had an uncomplicated surgery for diverticulosis 3 weeks ago and has been ambulating much less than his baseline level since then.
- In the ED, the diagnosis of acute PE is made with extensive clot throughout both lungs. He requires oxygen (FiO_2 = 50%). An echo reveals RV dysfunction. His blood pressure is 80/50.
- An hour later, after 500ml of IV saline, the BP has improved to 88/60. His hematocrit is normal and no risk factors for bleeding

- Which of the following findings is the most acceptable indication for thrombolytic therapy?
  1. Hypoxemia
  2. Right ventricular dysfunction
  3. Hypotension
  4. Extensive amount of pulmonary emboli

Severity of pulmonary embolism

Hemodynamic

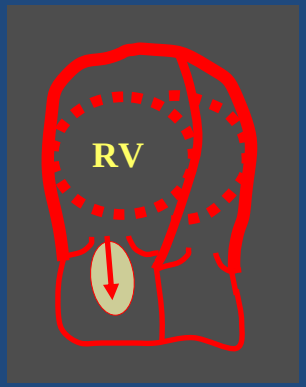
RV hypokinesis (Echo)

Clinical

submassive

Massive

Non-massive



ESC Task Force 2000

Pulmonary Embolism
Patient risk stratification AHA 2011 Guideline

Massive PE	Submassive PE	Minor/Nonmassive PE
High risk	Moderate risk	Low risk
Sustained hypotension (systolic PB < 90 mmHg for > 15 min) Inotropic support Pulselessness Persistent profound bradycardia (HR < 40 bpm with signs or symptoms of shock)	Normotensive (systolic BP > 90) RV dysfunction Myocardial necrosis Troponin T (> 0.4 ng/ml) Troponin I (0.1 ng/ml)	Systemically normotensive No RV dysfunction No myocardial necrosis

RV dysfunction
RV/LV ratio > 0.9 or RV systolic dysfunction on echo
RV/LV ratio > 0.9 on CT
Elevations of BNP (> 90 pg/mL)
Elevations of NT pro-BNP (> 500pg/mL)
ECG changes
new complete or incomplete RBBB
anteroseptal ST elevation or depression
anteroseptal T wave inversion

Circulation. 2011;123:1788-1830

ACCP 2012- thrombolytic therapy

- 5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulation therapy suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C)

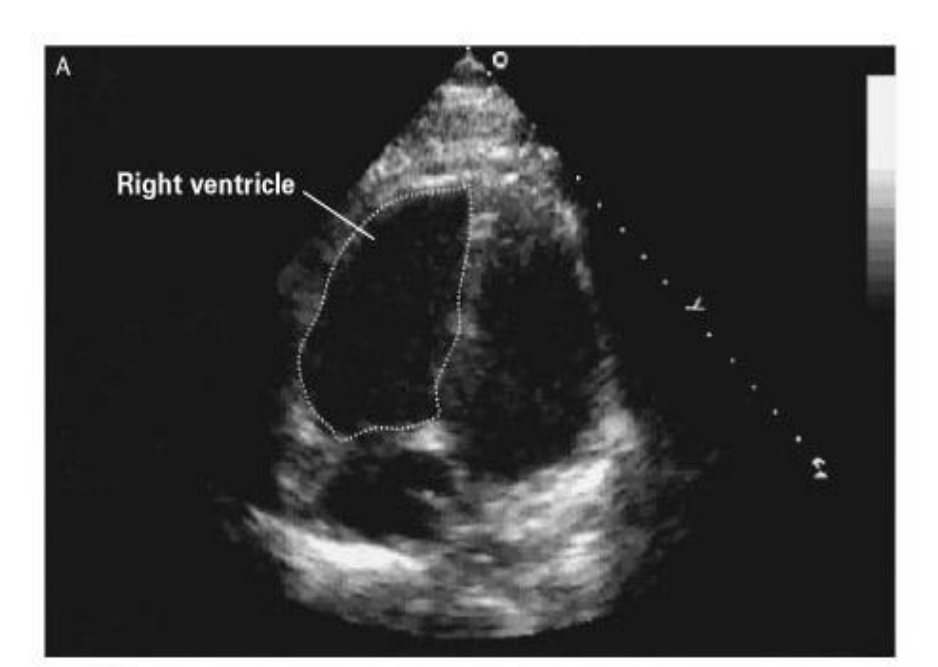
Kearon C. et al. Antithrombotic therapy for VTE. 9th ed: ACCP evidence-based Clinical practice guidelines. Chest 2012; 141: e419S

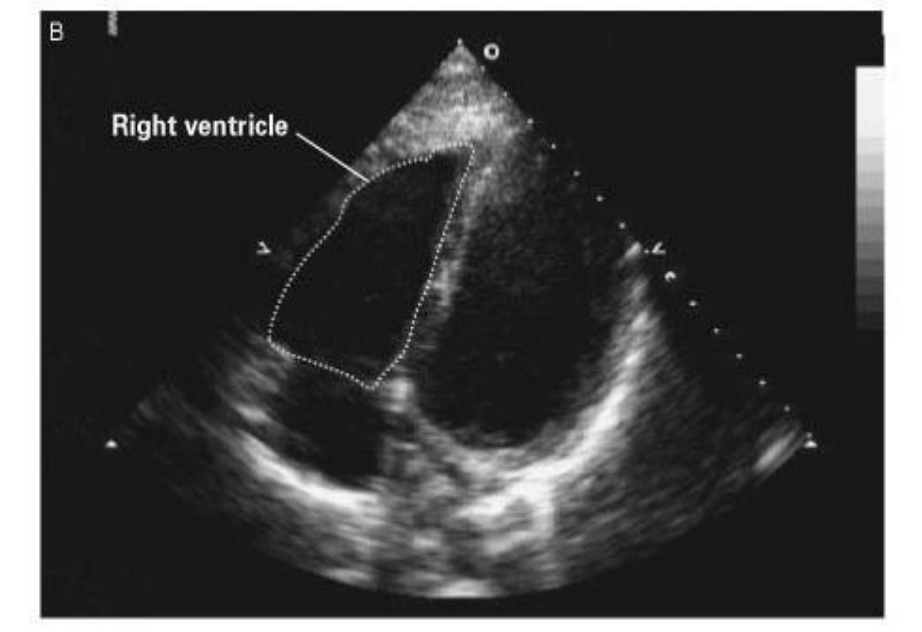
ICOPER

- RV hypokinesis on baseline echo associated with ~40% higher 3 month mortality rate

- Lancet 1999

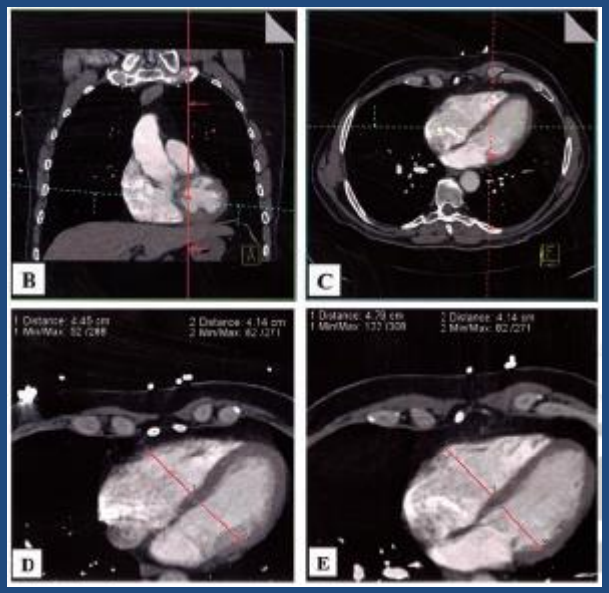
Echocardiographic Detection of RV Dysfunction / Enlargement in PE

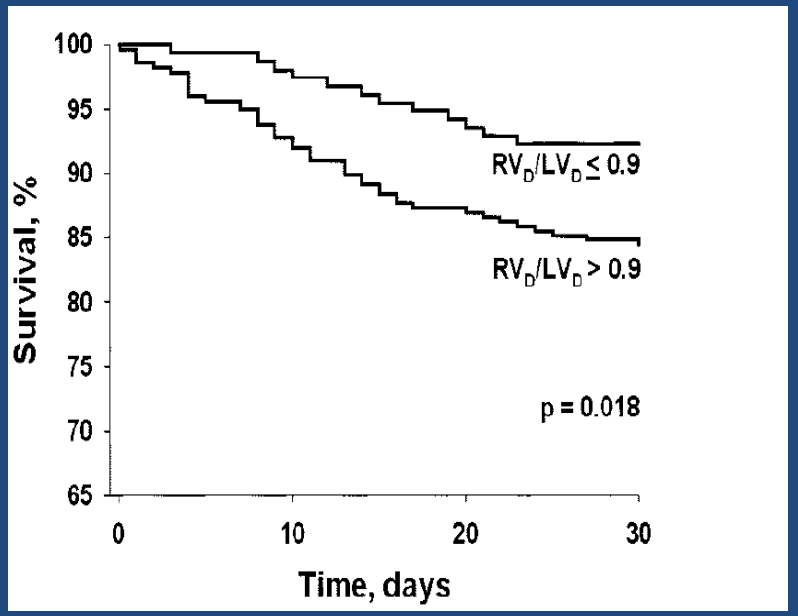




NEJM 2002;347:1161

CT for risk stratification in PE





RVD/LVD 0.9

For in-hospital/30-day death

OR 3.36 – 4.02

Schoepf Circulation 2004
Quiroz Circulation 2004

Treatment triage

Start i.v. Heparin,

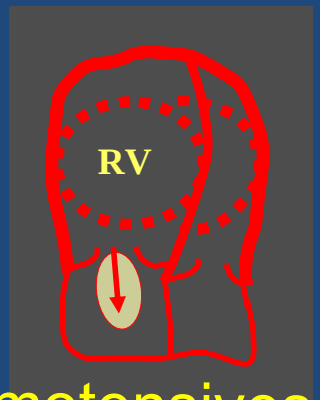
Take your time to decide - do not hurry,

Carefully assess bleeding risk

Monitor HR, BP, PaO2, acidosis, diuresis

TnT – if negative repeat after 6 h

BNP – if still in doubt repeat after 6 h



in normotensives

ICU

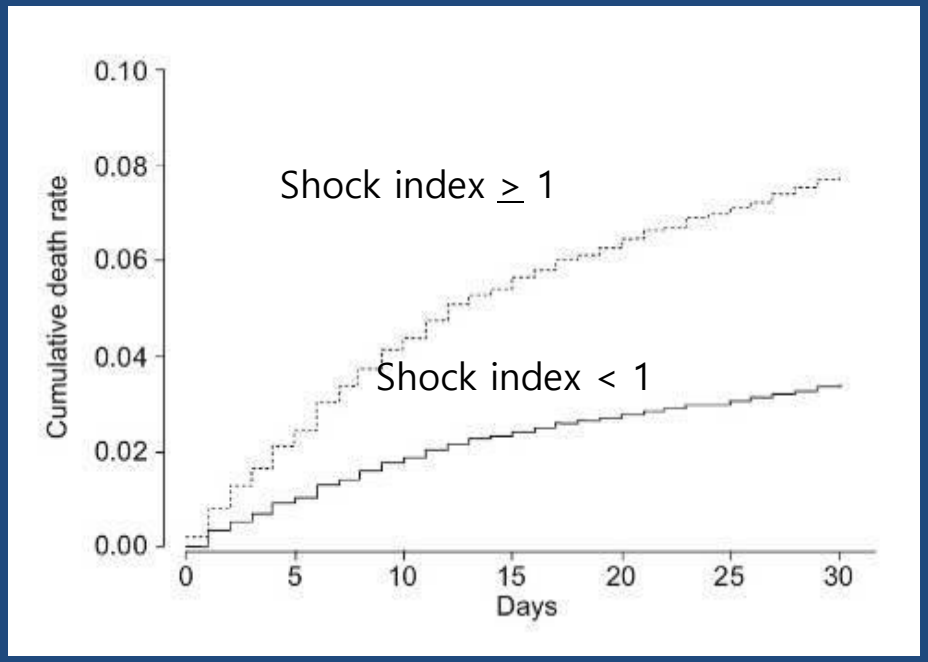
heparin

thrombolysis

Shock index as a predictor of short-term mortality

Shock index: heart rate/blood pressure

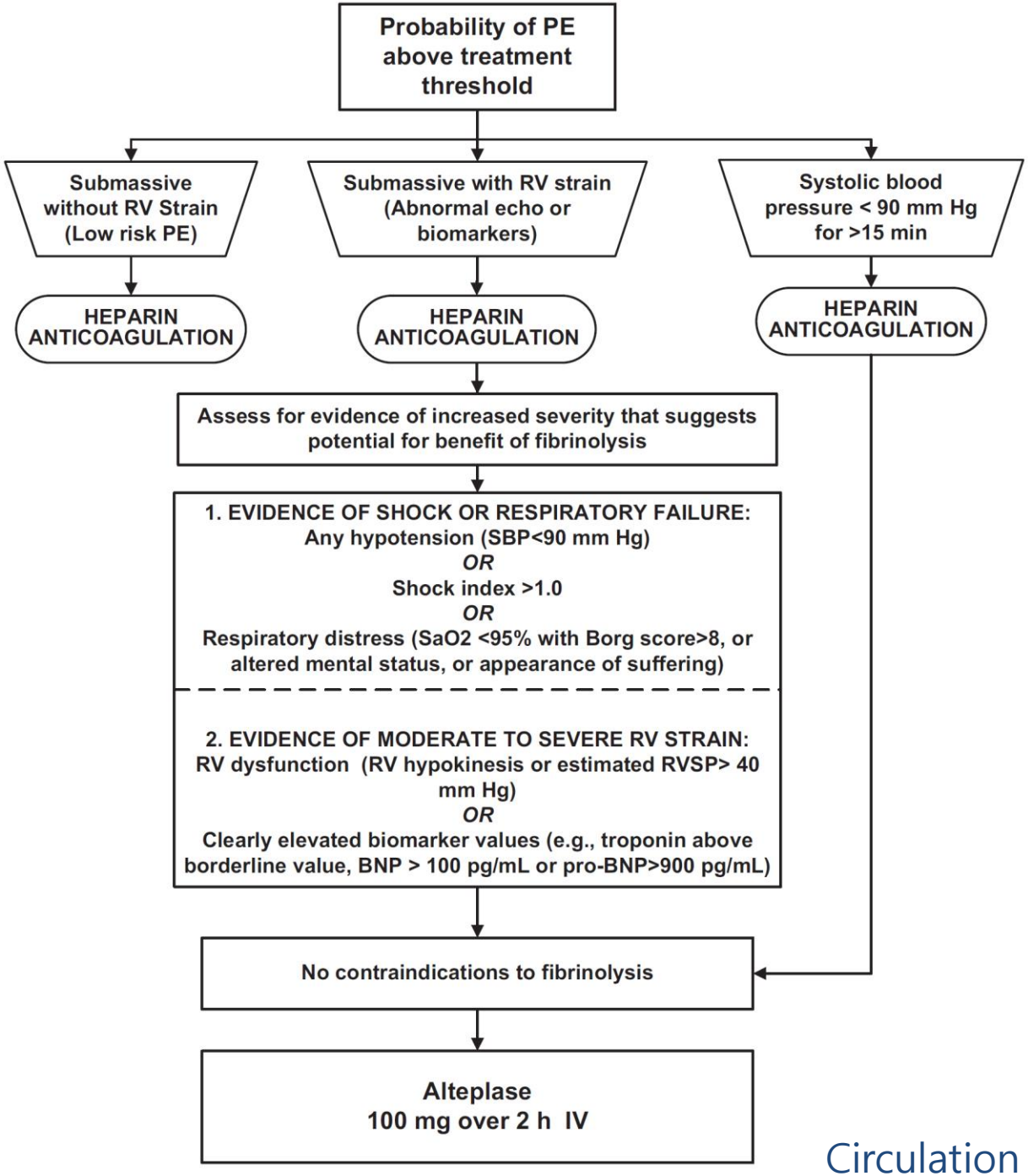
Shock index as a predictor of short-term mortality



The RIETE registry

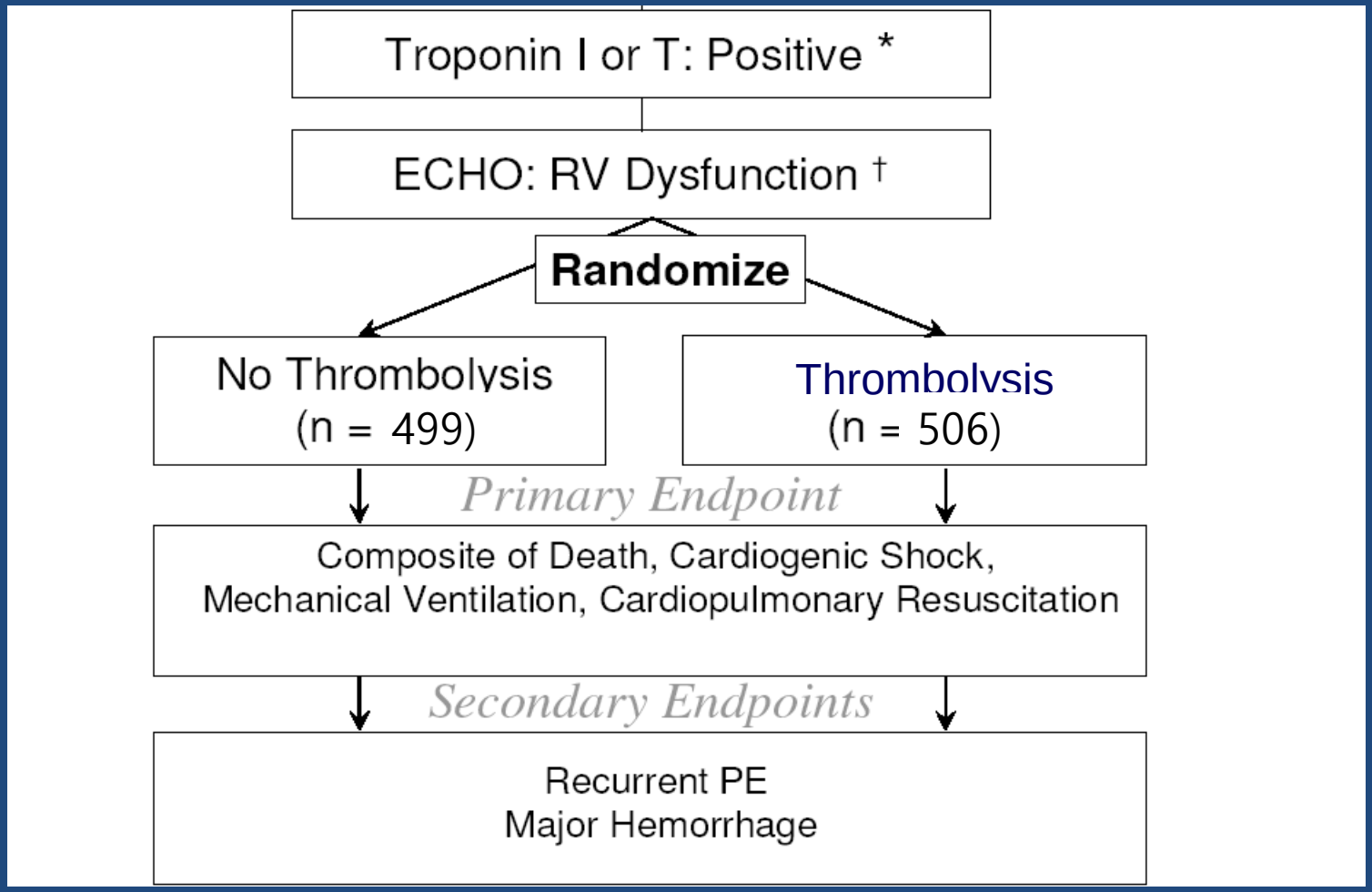
sensitivity for 30-day mortality: 0.31
specificity for 30-day mortality: 0.86

R Otero et al., Eur Respir J, 2007



Circulation 2011; 123:1788

“PEITHO”
Acute PE without hypotension



Konstantinides, G. Meyer et al. N Engl J Med 2014;370:1402-11.

PEITHO – inclusion criteria

ECHO: RV Dysfunction

At least 1 of the following:

1) RV dilation (RVED>30 mm, or RVED/ LVED > 0.9)
(apical or subcostal 4-CH view, parasternal short-axis view)

2) Hypokinesis of RV free wall
(any view)

3) Tricuspid systolic velocity > 2.6 m/s
(apical 4-CH view, parasternal short-axis view)

Konstantinides, G. Meyer et al. N Engl J Med 2014;370:1402-11.

Table 3. Efficacy Outcomes.*

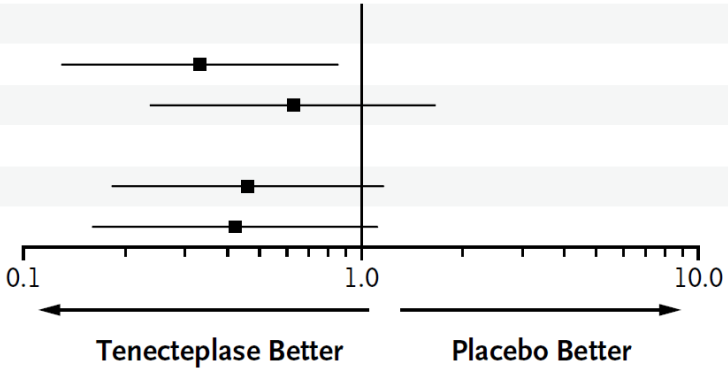
Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Thrombolytic treatment other than study 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

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		

A Death or Hemodynamic Decompensation

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.36
≤75 yr	6/344 (1.7)	17/335 (5.1)	0.33 (0.13–0.85)	
>75 yr	7/162 (4.3)	11/164 (6.7)	0.63 (0.24–1.66)	
Sex				0.90
Male	7/242 (2.9)	14/231 (6.1)	0.46 (0.18–1.16)	
Female	6/264 (2.3)	14/268 (5.2)	0.42 (0.16–1.12)	



B Major Extracranial Bleeding

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.09
≤75 yr	14/344 (4.1)	5/335 (1.5)	2.80 (1.00–7.86)	
>75 yr	18/162 (11.1)	1/164 (0.6)	20.38 (2.69–154.53)	
Sex				0.13
Male	11/242 (4.5)	4/231 (1.7)	2.70 (0.85–8.61)	
Female	21/264 (8.0)	2/268 (0.7)	11.49 (2.67–49.53)	

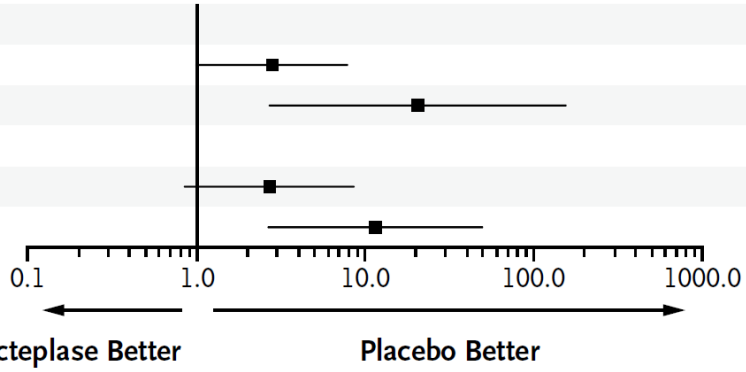


Figure 1. Efficacy and Safety Outcomes in Prespecified Subgroups.

Absolute Indications for IVC Filters

- DVT or PE with contraindication to anticoagulation therapy
- DVT or PE in patient with a complication of anticoagulation therapy
- Failure of anticoagulation therapy
- Chronic thromboembolic pulmonary hypertension

PREPIC 1

- 400 patients with proximal DVT considered to be at high risk for PE were randomized to receive either an IVC filter or no IVC filter
- Patients were randomized receive enoxaparin or unfractionated heparin bridging to warfarin therapy, which was continued for at least three months

NEJM 1998; 338:409-415

IVC Filters Reduce Recurrent PE

TABLE 2. PRINCIPAL END POINTS WITHIN THE FIRST 12 DAYS AFTER RANDOMIZATION TO THE FILTER OR NO-FILTER GROUP.

END POINT	FILTER	NO FILTER	ODDS RATIO (95% CI)*	P VALUE
	number (percent)			
Pulmonary embolism				
Symptomatic†	2	5		
Asymptomatic	0	4		
All‡	2 (1.1)	9 (4.8)	0.22 (0.05–0.90)	0.03
Major bleeding	9 (4.5)	6 (3.0)	1.49 (0.53–4.20)	0.44
Death	5 (2.5)	5 (2.5)	0.99 (0.29–3.42)	0.99

*CI denotes confidence interval.

†The category includes certain or highly probable fatal pulmonary embolism.

‡Information about the primary end point was missing for 28 patients. Percentages were based on the 372 patients who were evaluated.

Decousus H et al. N Engl J Med 1998;338:409-416

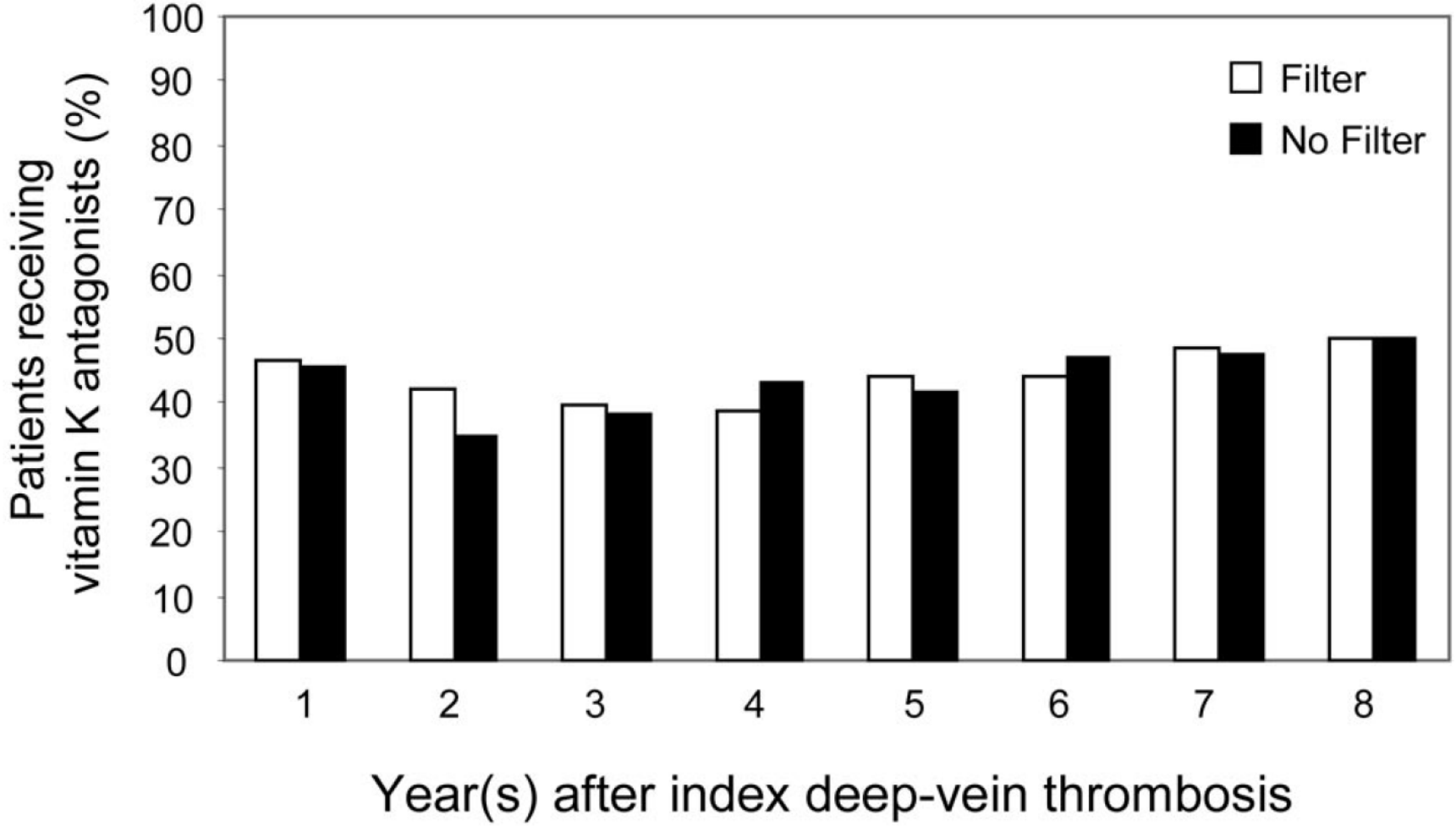
PREPIC 1

- Results
  - Day 12
    - Incidence of PE significantly lower in the filter group than in the no-filter group (1.1% vs 4.8%,; OR 0.22; P = 0.03)
    - Incidence of PE lower in the enoxaparin group than in the UFH group (1.6% vs 4.2%, OR 0.38,; P = 0.14)
  - 2 year
    - Recurrent DVT occur of 20.8% patients in filter group and 11.6% of patients with control group (OR 1.87; P 0.02)
    - No significant differences in mortality or other outcomes
- Conclusions
  - Permanent IVC filters decreased the incidence of PE
  - Coutnterbalanced by increased incidence of DVT
  - **No overall moratlity benefit**

PREPIC II

- Methods: 8-year follow-up (in addition to original 2-year follow-up) to assess the long-term effect of IVC filters
- Patient population
  - Outcome data available on 396 patients (99%)
- Results: confirmed 2-year observations
    - Reduced incidence of PE (6.2% vs 15.1%
    - Inreased risk of DVT (35.7% vs 27.5%)
    - No effect on survival

Circulation 2005; 112: 416-422


Patients receiving vitamin K antagonists (%)
100
90
80
70
60
50
40
30
20
10
0
Filter
No Filter
1
2
3
4
5
6
7
8
Year(s) after index deep-vein thrombosis

Complications

- Review of 1765 IVC filters placed over a 26-year period showed an incidence of acute/major complications of only 0.3% of procedures
- Other study showed 29% of patients with IVC filters have complications
- Complications include
  - 7% improper anatomic
  - 0.1%-5% imgration
  - 2%; anticoagulation of filter
  - 1%-6% caval stenosis
  - 2%-4% filter occlusion
  - 1% air embolism
  - 0.1%-2% penetration of caval wall
  - 13%: lower extremity edema
  - 27% sequelae of venous stasis

Radiology 2000; 216:54-66
Surg Gynecol Obstet. 1993; 177:463-467
J Vasc Surg 2000; 32:490-497

2. A patient is hospitalized for acute GI bleeding, with hematocrit decreasing from 35 to 24 by day 2 of admission. On day 3, dyspnea and chest pain develop and acute PE is diagnosed. At this time, the precise source of the bleeding remains unclear, but melena is still present

- Which of the following should we do?

1. Initiate low dose anticoagulation
2. Place IVC filter
3. Perform serial USG
4. Refer to catheter-directed thrombus removal

- IVC filter placement is recommended when anticoagulation is contraindicated (as well as in the setting of recurrent PE on therapeutic anticoagulation).

- The ACCP 2012 statement offers that "If a patient has an acute PE and a short-term contraindication to anticoagulation, provided there is no proximal DVT on US, it is reasonable not to insert an IVC filter immediately; serial USG can be performed to ensure that the patient remains free of proximal DVT while anticoagulation is withheld." However no formal recommendation is made in these guidelines

Kearon C. et al. Antithrombotic therapy for VTE. 9th ed: ACCP evidence-based Clinical practice guidelines. Chest 2012; 141: e419S

- 2.13.2. In patients with acute proximal DVT and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade IB)
- 2.13.3. In patients with acute proximal DVT and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulation therapy if their risk of bleeding resolves (Grade 2B)
- Remarks: We do not consider that a permanent IVC filter of itself, is an indication for extended anticoagulation

Kearon C. et al. Antithrombotic therapy for VTE. 9th ed: ACCP evidence-based Clinical practice guidelines. Chest 2012; 141: e419S

3. An obese 40 year-old woman who is 30 weeks pregnant and has no other medical history develops pain and swelling in her right calf, followed by sudden, progressive dyspnea with pleuritic chest pain. After 3 days, she presents to the ED where her heart rate is 120/min and her right calf is swollen and tender. You have a high clinical suspicion for acute PE, which you confirm by calculating a Wells scores of 7.5.

Which of the following should be next?

1. Order a D-dimer test and if negative do no further testing
2. Initiate empiric anticoagulation
3. Obtain results from a V/Q scan to rule in or out PE
4. Obtain results from computed tomographic angiography to rule in or out PE

폐색전증 진단을 위한 진료실에서의 예비검사

High clinical likelihood of PE

PE likely > 4

임상적 특징	점 수
심재정맥혈전증의 임상적 증상 및 징후	3.0
폐색전증을 우선적 진단으로 고려하는 경우	3.0
심박수가 분당 100회를 초과	1.5
지난 4주 동안에 수술이나 3일 이상 거동이 안된 경우	1.5
심재정맥혈전증이나 폐색전증의 과거력	1.5
객혈	1.0
활동중인 암 (6개월 이내에 치료를 받았거나 보존적 치료)	1.0

Wells PS et al. Thromb Haemost 2000;83:416

Harrison's Internal Medicine 17th ed.

- 5.2.1 In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)

- 5.2.2. In patient with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if result of diagnostic tests are expected to be delayed for more than 4 h

- 5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)

Kearon C. et al. Antithrombotic therapy for VTE. 9th ed: ACCP evidence-based Clinical practice guidelines. Chest 2012; 141: e419S

Early Anticoagulation Is Associated With Reduced Mortality for Acute Pulmonary Embolism

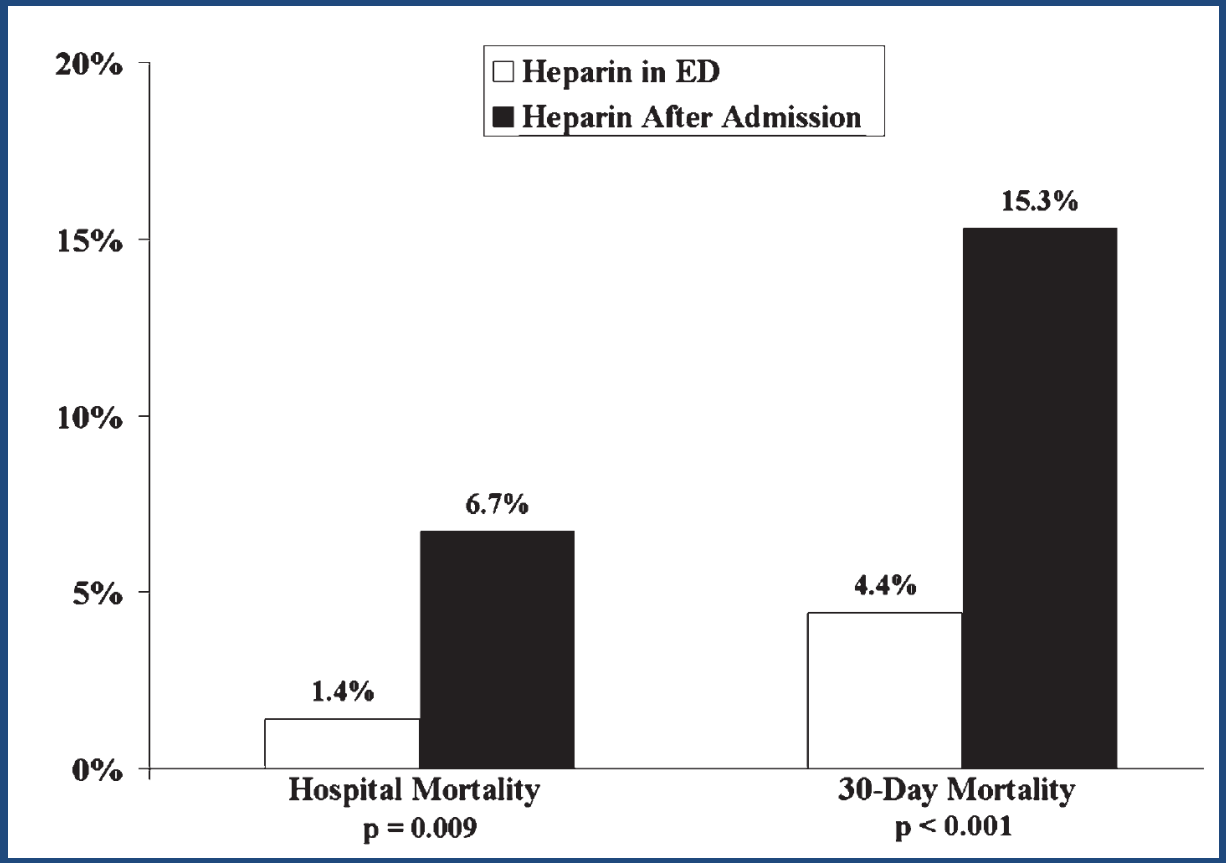
Methods:

400 consecutive patients in the ED diagnosed with acute PE by CTA and treated in the hospital with IV UFH from 2002 to 2005.

Patients received heparin either in the ED or after admission. Time from ED arrival to therapeutic aPPT was calculated. Outcomes included in-hospital and 30-day mortality, hospital and ICU lengths of stay, hemorrhagic events on heparin, and recurrent VTE within 90 days.

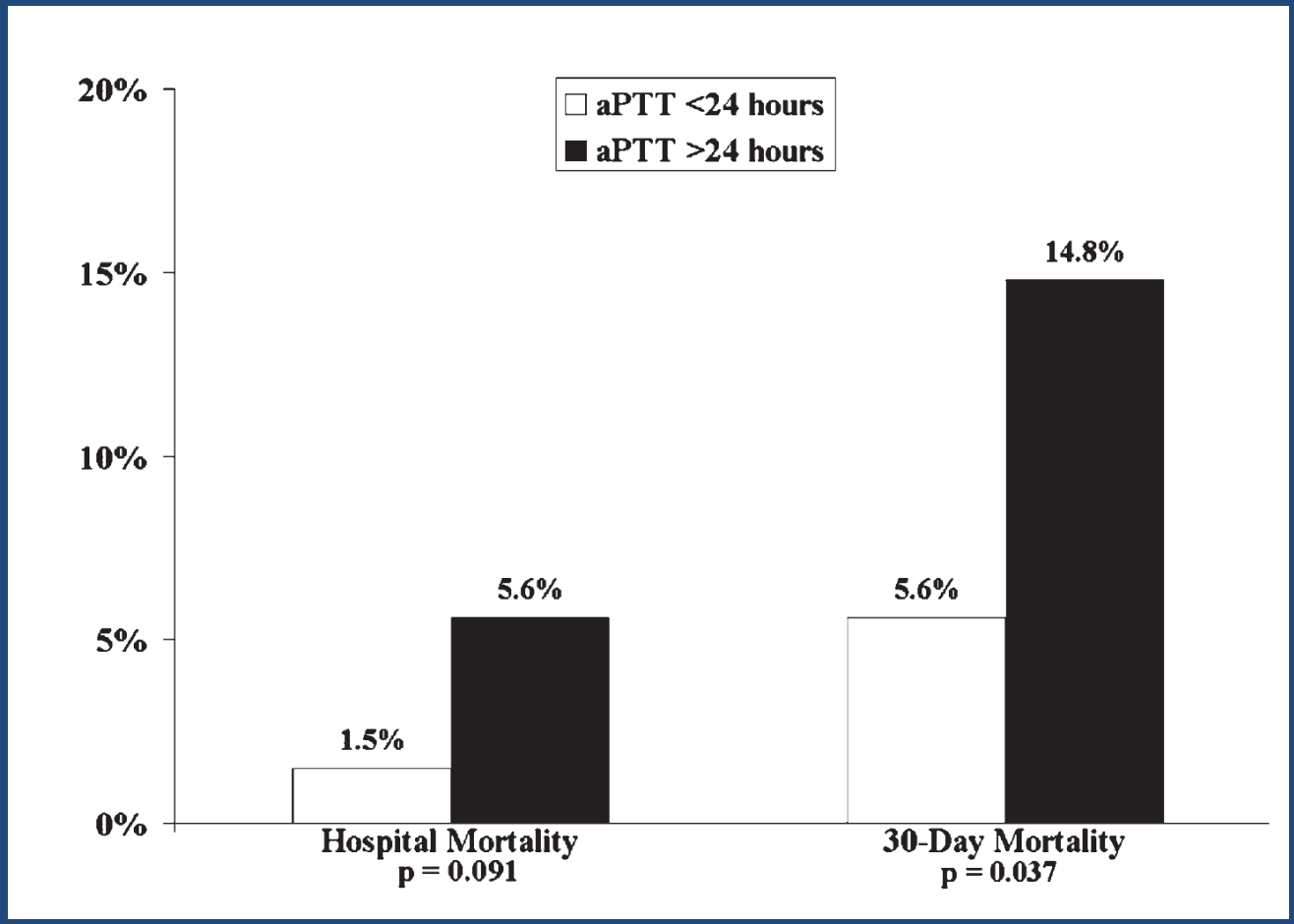
Chest 2010; 137: 1382-1390

Early Anticoagulation is Associated with Reduced mortality for acute PE



- Hospital and 30-day mortality rates for patients who received heparin in the ED compared with those who received heparin after admission.

Chest 2010; 137: 1382-1390



Hospital and 30-day mortality rates for patients who achieved a therapeutic aPTT prior to 24h from ED arrival compared with those who achieved a therapeutic aPTT after 24 hours.

Chest 2010; 137: 1382-1390

4. A 65 year-old man with a previous diagnosis of lymphoma undergoes a chest CT scan with intravenous contrast as a routine follow-up to look for disease progression. He denies all symptoms except a 5 kg weight loss over 2 months. The CT reveals increasing adenopathy and bilateral segmental acute PE.

Which of the following should you do next?

A. Initial anticoagulation.
B. Repeat the CT scan in two weeks.
C. Repeat the CT scan in four weeks.
D. Follow for symptoms of pulmonary embolism.

4. Rationale: Asymptomatic PE occurs in 1% to 4% of patients who undergo CTA, with the majority being patients with proven malignancy.

"Incidental" subsegmental PE that appears acute(e.g., discovered by CTA performed in a patient in whom PE was not clinically suspected), should be taken seriously.

The ACCP guidelines state that patients with asymptomatic PE should be treated the same as symptomatic PE, meaning that anticoagulation should be started as soon as the diagnosis is made.

Chest 2012; 141: e419S
J Clin Oncol 2006; 24:4928-32
Radiology 2006; 240: 246-55

Unsuspected PE in Cancer Patients: Clinical Correlates and Relevance

- PE was clinically unsuspected in approximately half of positive CTA scans in outpatient oncologic patients(51.1%, 202/395)
- This is consistent with prior clinical and autopsy studies.
- Unfortunately, there are no randomized treatment data.
- However, these authors and ACCP consensus statement both suggest that these patients should be treated the same as symptomatic patients with acute PE

J Clin Oncol 2006; 24:4928-32

5. A 64year-old business executive develops acute deep venous thrombosis (DVT) in the right leg after a flight from Chicago to Incheon. An ultrasound reveals clot filling the venous trifurcation below the knee including the base of a long popliteal vein segment, but most of the popliteal vein is free of clot. In the emergency department, his right calf is very swollen, tender, and is so painful he cannot stand.

Which of the following should be done next?

A. Serial ultrasound studies.
B. Initial anticoagulation.
C. Catheter-directed thrombolysis
D. IVC filter insertion.

- The patient`s DVT involves the popliteal vein(i.e., it is a proximal DVT), which confers an increased risk of PE. Therefore, the patient should be anticoagulated.
- Serial US studies are not appropriate for proximal DVT, due to the increased risk for PE. However, if a clot has not reached the popliteal vein (i.e., it is a distal DVT) and there are no severe symptoms or risk factors for extension, then serial imaging of the deep veins for 2 weeks is reasonable because the primary concern with such DVT is whether or not it is going to extend proximally (2C).

Calf DVT

2.3.1 In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation(Grade 2C).

2.3.2 In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension, we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

Kearon C. et al. Antithrombotic therapy for VTE. 9th ed: ACCP evidence-based Clinical practice guidelines. Chest 2012; 141: e419S

Should we treat superficial-vein thrombosis in the leg?

- 3002 SVT patients, randomized, D-B trial:
- SC fondaparinux, at 2.5mg qd, or placebo for 45 days.
- Primary efficacy outcome=composite of death from any cause or symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of SVT at day 47.

- Primary efficacy outcome occurred in 13 of 1502 patients(0.9%) in the fondaparinux group and 88 of 1500 patients(5.9%) in the placebo group(relative risk reduction with fondaparinux, 85%;95% CI, 74 to 92; $P<0.001$).
- There was only 1 major bleed in each group.

Three Major Crimes in Acute VTE

1. Delay in diagnosis/ misdiagnosis

2. Failure to risk stratify

3. Delayed or inadequate therapy

SUMMARY:

1. In massive PE (hypotension), systemic thrombolytic therapy should be considered.
2. In submassive PE, there is no clear favored approach.

   Patients should be individualized.
4. Indications for IVC filter placement for acute VTE=contraindication to anticoagulation therapy, complications from anticoagulation, or failure of anticoagulation.
5. When there is high suspicion for acute PE, parenteral anticoagulants are suggested while awaiting test results.
6. Incidentally discovered acute PE should be treated.
7. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension, anticoagulation is suggested, rather than serial imaging of the deep veins.