AMERICAN COLLEGE OF OSTEOPATHIC INTERNIST
PULMONARY EMBOLISM & RELATED STUFF

Timothy J. Barreiro, DO, MPH, FCCP, FACP, FACOI
Section Chair, Pulmonary & Critical Care Medicine
Associate Professor of Internal Medicine
NIH Health Minority & Harvard Macy Scholar
Ohio University Heritage College of Osteopathic Medicine
Northeast Ohio Medical University
Director, St. Elizabeth Pulmonary Health & Research Center

Disclosures

2016 ACOI Annual Convention and Scientific Sessions

- I have no relevant or non relevant financial relationship with a commercial interest in this subject or other subject matter.
- I have no financial relationships to disclose.
- I will not discuss off label use or investigational use in my presentation.
- I will discuss the following off label use and/or investigational use in my presentation:

Learning Objectives

- Describe issues related to VTE that occur frequently & frustrates everyone.
- Analyze the current data, formulate the best treatment for this problem.
- Review some new data that will help us make an improved decision on similar cases – which we will likely see tomorrow on the medical wards remembering not to go back to our old habits.

Case Presentation

Mr. Med al CoError is a 57-year- old man present with left-sided chest pain for the past 5 to 6 days. He has no history of cancer, but has HTN, OSA, DM, and CAD without MI. On questioning symptoms started gradually & progressively worsened; He reports pressure-like pain but no radiation, Pain Scale: 8/10; Cough or body movement make the pain worse; lying still feels better.

His vitals are BP: 134/87. P: 112. RR: 22. T:97⁴⁰ O_2: 97%. W: 264 #. MP III, macroglossia, normal thyroid exam. Symmetrical clear chest with some dullness on the left base. Regular; No clicks, gallops or rubs. Soft (-) organomegaly. No rebound or guarding. Trace edema on the right. A chest Radiograph show a small left pleural effusion.

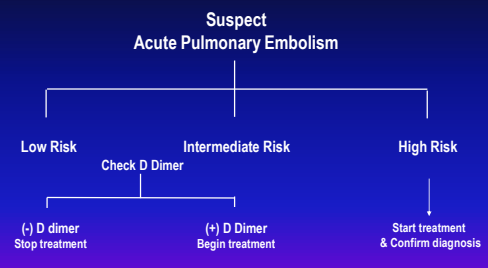
You suspect a pulmonary embolism.

Question 1

What is the next best step in the evaluation of this patient?

A. Do nothing
B. Risk stratification
C. Yell for help
D. Start Treatment and order D-Dimer

Risk Stratification



Nick van Es et al. *Ann Intern Med*. 2016;165(4):253-261. doi:10.7326/M16-0031.
Clive Kearon et al. Blood 2014;123:1794-180
European Heart Journal (2014) :doi 10.1093

Venous Thromboembolism Primary Care Criteria

***Primary Care Diagnostic Rule to Estimate the Probability of Deep Vein Thrombosis (DVT)**

Clincial Features	Score
Male Gender	1
Oral Contraceptive Use	1
Presence of cancer/malignancy	1
Recent surgery (4 wk)	1
Absence of trauma	1
Vein distension	1
Calf circumference >3	2
Abnormal D – dimer	6

*Large cross sectional study of 1295 consecutive adults. Greater than 18 years old who visited one of the 110 primary care doctors in the Netherlands suspected of DVT

Oudega R et al. Semin Thromb Hemost 2006; 32: 673.

Venous Thromboembolism Modified Wells Criteria

*Modified Wells Rule for Use to Estimate the Probability of Venous Thrombosis

Clincial Features	Score
Active Cancer	1
Clincial Symptoms of DVT	3
Immobilization or major surgery < 4 wks	1.5
Heart Rate > 100	1
Hemoptysis	1
Previously documented deep vein thrombosis	1.5
Alternative diagnosis as likely than that of DVT	- 3

Traditional Clincial Probability Assessment

High	**> 6 points**
Intermediate	**2 to 6 points**
Low	**< 2 points**

Simplified Clincial Probability Assessment

*Scores of > 4 indicated that the probability of pulmonary embolism is likely.
*Score of < 4 indicated that the probability of pulmonary embolism is unlikely.

Wells PS et al. Ann Intern Med 2001, 135:98
*Van Belle A et al. JAMA 2006;295:172

Thrombosis Risk Factor(s) Sirius Study

Risk Factor(s)	OR	95% CI
Malignant neoplasm	18	13.4 - 22
History of VTE	15	6.77 – 35.8
Pregnancy	12	1.40 – 93.2
Congestive heart failure	10	3.3 – 15.8
Neurologic disease with paresis	7	3.5 – 10.2
*Exogenous female hormones	5.75	2.2 – 15.0
Immobilization	5.61	2.30 – 13.6
Venous insufficiency	5	3.10 – 6.3
Obesity (BMI>30)	2.39	1.48 – 3.87

OR = Odds Ratio

Samama MM. Arch Intern Med 2000; 160: 3415-3420.
Rosendaal FR. Thromb Haemost.1999;82:610-619.

Question 2

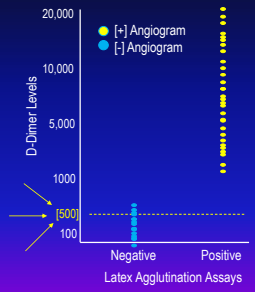
Your colleague asks you, *"What are you thoughts on a D-dimer test."* for this patient for which you reply….

A. Come on dude, D dimer are useless
B. The D dimer test is < 500 (negative) but you know your going to do a CTA anyway. (as you laugh and walk away)
C. The D dimer test confirms a diagnosis
D. A D dimer test is reasonable in low /intermediate risk patient but it should be above the age-adjusted cutoff

Thromboembolism Cutoff Level

Study:
103 patients suspected of PE
34% confirmed via angiogram.

Latex Agglutination Assays
Sensitive of > 97%
Specificity of 29%
Negative predictive value >94%



Schluger N et al. J Thoracic Imaging 1994; 9: 180.
Quinn DA et al. AJRCCM 1999; 159: 1445.

Age-Adjusted D-Dimer Cutoff Levels The ADJUST-PE Study

2898 patient
pulmonary embolism unlikely
or
non-high clinical probability

817	337 patient	1744 Patients
D Dimer <500	D Dimer > 500 but < age adjusted cutoff	Levels > age adjusted cut-off

Prospective ! Study Results According to D-Dimer Assays

To prospectively validate whether an **age-adjusted D-dimer cutoff, defined as age × 10 in patients 50 years** or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.

JAMA. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135

Age-Adjusted D-Dimer Cutoff Levels The ADJUST-PE Study

Therefore, the use of the age-adjusted cutoff resulted in an 11.6% absolute increase (95% CI, 10.5%-12.9%) or a **41.2% relative increase** (95% CI, 31.3%-52.0%) **in the proportion of negative D-dimer results**.

Wells /Geneva Scores / D-Dimer Assay	Low/Intermediate or Unlikely Clinical Probability, No. of Patients	D-Dimer <500 µg/L	3-mo Thromboembolism Risk: No. of Events/ Total Patients	3-mo Thromboembolism Risk: % (95% CI)	D-Dimer ≥500 µg/L and <Age-Adjusted Cutoff	3-mo Thromboembolism Risk: No. of Events/ Total Patients	3-mo Thromboembolism Risk: % (95% CI)
VIDAS D-Dimer Exclusion	1345	423	0/417	0.0 (0.0-0.9)	130	0/127	0.0 (0.0-2.9)
Innovance D-Dimer	838	202	1/202	0.5 (0.1-2.8)	103	1/103	1.0 (0.2-5.3)
STA-Liatest D-Dimer	389	132	0/132	0.0 (0.0-2.8)	49	0/47	0.0 (0.0-7.6)
D-Dimer HS 500	185	32	0/31	0.0 (0.0-11.0)	23	0/23	0.0 (0.0-14.3)
Second-generation Tina-quant	128	26	0/26	0.0 (0.0-12.9)	32	0/31	0.0 (0.0-11.0)
Cobas h 232	13	2	0/2	0.0 (0.0-65.8)	0		
Total	2898	817 (28.2%)	1/8	0.0.1 (0.0-0.7)	337 (11.6%)	1/331	0.3 (0.1-1.7)

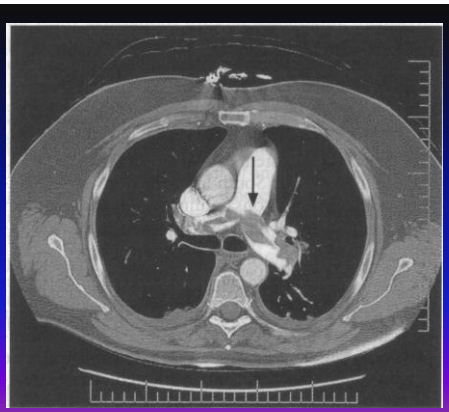
JAMA. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135

Question 3

The patient age adjusted D-dimer was 680 (+), what is the best next step in the management of your patient?

A. No more testing is needed
B. Order a CT Angiogram
C. Admit & Start Apixaban [Eliquis]
D. Discharge home with NOAC agent
E. Order a V/Q and US legs bilaterally

Case Presentation Radiographic Images



Question 4

What is the next best step in for this patient?

- **A. Do nothing**
- **B. Start Treatment with a thrombolytic**
- **C. Again, Risk stratification**
- **D. Now, yell for help (really loud)**

Risk Assessment Score
Pulmonary Embolism Severity Index

Pulmonary Embolism Severity Index [PESI]

Age	1 point / yr
Male sex	+10 points
Cancer	+30 points
CHF/Chronic HF	+10 points
Chronic lung dis.	+10 points
Δ mental status	+ 60 points
Pulse > 110 b/p/m	+ 20 points
Systolic BP <100 mmHg	+ 30 points
Respiratory Rate >30 b/min	+ 20 points
Temperature <36 C	+ 20 points
Arterial Oxygen SaO_2 <90%	+ 20 points

85 pionts or less = low risk of fatal PE – NPV = 99%

Our case
Age 57
SBP 135
SaO_2 >90 %
+ COPD
P = 112
RR = 22

Risk Class for Mortality	Points
Class I	< 66
Class II	66-85
Class III	86-105
Class IV	106-125
Class V	>125

Aujesky D et al. Am J Resp Crit Care Med 2005;172:1041–6
External validation in: J Intern Med 2007;261:597-604

Risk Assessment Score
Pulmonary Embolism Severity Index

- **Risk Strata PESI Scores**

Class I <65 points	Very low 30 day mortality risk (0 -1.6%)
Class II >66 - 85 points	Low mortality risk (1.7-3.5%) NPV 99%
ClassIII >86 - 105 points	Moderate mortaltiy risk (3.2-7.1%)
Class IV >106 -125 points	High mortality risk (4.0 – 11.4%)
Class V >125 points	Very high risk (10 to 24.5%)

Our case	Our case	Our case
Age 57	= + 57	
SBP 135	= 0	= + 87 CLASS III
SaO_2 >90 %	= 0	
+ COPD	= + 10	
P = 112	= +20	
RR = 22	= 0	

Aujesky D et al. Am J Resp Crit Care Med 2005;172:1041–6
External validation in: J Intern Med 2007;261:597-604

Risk Assessment Score
Simplified PESI

- **sPESI = Retrospective analysis of RIETE registry**

Age >80	1 point
History of Cancer	1 point
Chronic cardiopulmonary disease	1 point
Pulse > 110 b/p/m	1 point
Systolic BP <100 mmHg	1 point
Arterial Oxygen SaO_2 < 90%	1 point

Risk Class for Mortality	Points
Low risk	0
High risk	>1

- **Risk Strata sPESI Scores**
  - 0 points = low 30 day mortality risk (1.0% 95% CI 0.0-2.1%)
  - >1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5-13.2%)

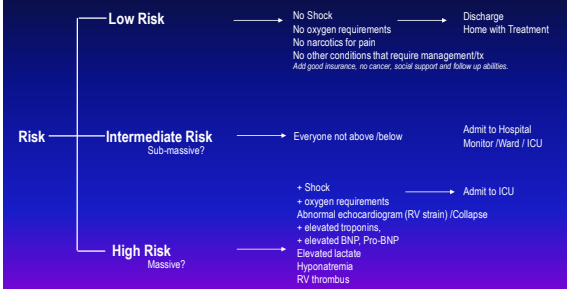
Jiménez D et al. Arch Intern Med. 2010;170:1383-9.
Konstantinides SV et al. Thrombosis & Haemostasis 2015; 113:1202-1209.

Question 5

Based on this information where would you admit the patient?

A. **The Palm Springs 'Bates' Hotel**
B. **General Medical Ward**
C. **Hospital (Step down/ICU)**
D. **Discharge home with treatment**

Risk Stratification
Acute Pulmonary Embolism



Wells PS. Arch Intern Med. 1998; 158: 1809 -1812.
Piran S et al. A Systemic Review and Meta-analysis. Thromb Res 2013; 132: 515 - 519.
Stein PE et al Am J Med. 2016; 129 (9): 974 - 977.

Home Treatment of Pulmonary Embolism In the Era of Novel Oral Anticoagulants

Study	Design	N	Cancer (%)	Risk Stratification	Rx & Tx	Mortality (%)	Fatal PE (%)	Fatal ICH (%)	Recurrent Event (%)	Major Bleeding (%)
Agterpf, 2010	Cohort	152	20(13.2)	Low NR-ProBNP	Outpatient	0(0)	0(0)	0(0)	0(0)	0(0)
Aujesky, 2011	RCT	171	1(1)	PESI(Class I or II)	Outpatient	1(0.6)	0(0)	0(0)	1(0.6)	3(1.8)
Beer, 2003	Cohort	43	NA	Geneva (<2)	Outpatient	0(0)	0(0)	0(0)	1(2.3)	0(0)
Davies, 2007	Cohort	157	NA	Clinical gestalt	Early Discharge	3(1.9)	0(0)	0(0)	0(0)	0(0)
Kovas, 2000	Cohort	108	24 (22)	Clinical gestalt	Outpatient	4(3.7)	0(0)	0(0)	6 (5.6)	2(1.9)
Olsson, 2006	Cohort	102	NA	Clinical gestalt	Outpatient	NA	0(0)	NA	NA	NA
Otero, 2010	RCT	72	6 (4.5)	Uresandi Score (>2)	Outpatient	3(4.2)	1(1.4)	0(0)	2(2.8)	1(1.4)
Siragusa, 2005	Cohort	36	36(100)	Clinical gestalt	Outpatient	NA	NA	NA	NA	NA
Wells, 2005	RCT	90	NA	Clinical gestalt	Outpatient	3(3.3)	0(0)	0(0)	2(2.2)	0(0)
Zondag, 2011	Cohort	297	28 (9.4)	Hestia Criteria	Outpatient	3(1)	0(0)	1(0.3)	6(2)	2(0.67)

NA = Not Available; PE = Pulmonary Embolism; PESI = Pulmonary Embolism Severity Index; RCT = Randomized Control Trial; VTE = Venous Thromboembolism

Home Treatment of Pulmonary Embolism

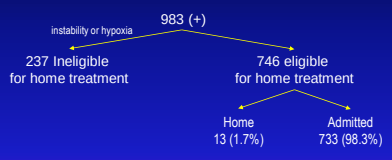
Outcomes Event Rates after 3 months of Follow-Up

Outcome	Event Rate %, (95% CI)
Recurrent PE/DVT	1.47%, (0.47 to 3.0%)
Fatal Pulmonary Embolism	0.47%, (0.16 to 1.0%)
Major Bleeding	0.81%, (0.37 to 1.4%)
Fatal ICH	1.29%, (0.06 to 0.6%)
Overall Mortality	1.58%, (0.71 to 2.8%)

Piran S et al. A Systemic Review & Meta-analysis. Thromb Res 2013; 132: 515 – 519.

Home Treatment of Pulmonary Embolism In the Era of Novel Oral Anticoagulants

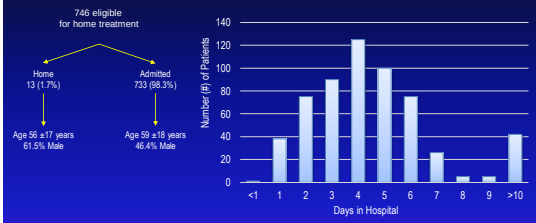
Retrospective Cohort Study
18 years age w / pulmonary embolism
5 Emergency Departments.



- Anticoagulant treatment for those treated at home was low-molecular weight heparin or warfarin in 9 (69.2%) and novel oral anticoagulants in 4 (30.8%).
- Discharge in 2 days was in 119 patients (16.2%).
- Treatment of these patients was low-molecular-weight heparin or warfarin in 76 (63.9%), novel oral anticoagulants in 34 (28.6%), and in 9 (7.6%), anticoagulants were not given because of metastatic cancer or treatment was not known.

Stein PE et al. Am J Med. 2016; 129 (9): 974 – 977.

Home Treatment of Pulmonary Embolism In the Era of Novel Oral Anticoagulants



CONCLUSION: Even in the era of novel oral anticoagulants, the vast majority of patients with acute pulmonary embolism were hospitalized, and only a small proportion were discharged in 2 days. Although home treatment has been found to be safe in carefully selected patients, and scoring systems have been derived to identify those at low risk of adverse events, home treatment was infrequently selected.

Stein PE et al Am J Med. 2016; 129 (9): 974 - 977

Home Treatment Be Careful

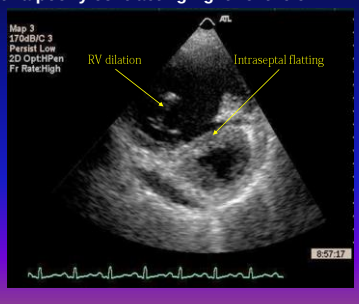
- In patients with acute thrombosis whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).
- **Remarks:** The recommendation is conditional on the adequacy of home circumstances:
  - well-maintained living conditions,
  - strong support from family or friends,
  - phone access, and
  - ability to quickly return to the hospital if there is deterioration.
  - It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe symptoms or comorbidity).

Antithrombotic Therapy For VTE Disease: Chest Guideline And Expert Panel Report
Kearon C, Akl EA, Ornelas J, et al. Chest. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.

Risk Stratification Echocardiogram

Transthoracic echocardiograph reveals evidence of acute right heart strain , with a poorly contracting right ventricle

Also, tricuspid regurgitation with pulmonary hypertension (PSP 55 mm Hg) and bowing of the interventricular septum towards the left ventricle



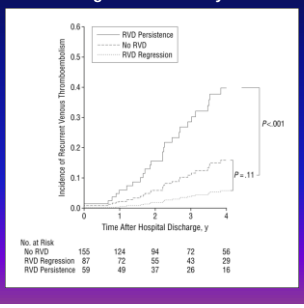
Question 6

Based on the abnormal echocardiogram, You are able to tell the patient and family what important information?

A. Risk of fatal & non-fatal embolism is high
B. The risk of recurrent events is low
C. Risk of death from pulmonary embolism is low
D. He will be 'Ok' in 3 months

Case Questions Discussion

Cumulative incidence of recurrent venous thromboembolism. RVD indicates right ventricular dysfunction.



Echocardiography was used to assess RVD on admission and before hospital discharge in 301 consecutive patients with the first episode of acute pulmonary embolism.

Right ventricular dysfunction was diagnosed in the presence of 1 or more of the following: right ventricular dilation (without hypertrophy), paradoxical septal systolic motion, and Doppler evidence of pulmonary hypertension.

Patients were followed up at 2, 6, and 12 months and yearly thereafter.

The primary end point was symptomatic, recurrent fatal or nonfatal VTE.

Arch Intern Med. 2006;166(19):2151-2156.
doi:10.1001/archinte.166.19.2151

Case Questions Discussion

Table 2. Follow-up Outcomes in Study Patients Based on In-Hospital Course of RVD*

Outcome	No RVD (n = 155) [51.5%]	RVD Regression (n = 87) [28.9%]	RVD Persistence (n = 59) [19.6%]	Overall *P* Value
Follow-up, mean ± SD, y	3.2 ± 2.8	3.2 ± 2.7	2.6 ± 2.6	.39
OAT duration				.30
<1 y	75 (48)	35 (40)	21 (36)	
1-2 y	34 (22)	21 (24)	20 (34)	
>2 y	46 (30)	31 (36)	18 (30)	
Recurrent VTE	15 (10)	3 (3)	14 (24)†	.001
PE-related death	2 (1)	0	6 (10)†	.001
Fatal and nonfatal PE	6 (4)	2 (2)	12 (20)†	<.001
Isolated DVT	9 (6)	1 (1)	2 (3)	.24
Death	21 (15)	11 (13)	13 (24)	.20
Malignancy	11 (8)	5 (6)	5 (9)	.76
Coronary events	2 (1)	2 (2)	0	.66
Fatal hemorrhage	2 (1)	2 (2)	1 (2)	.85
Sepsis	2 (1)	1 (1)	0	>.99
Various‡	2 (1)	0	0	.70
Undefined	0	1 (1)	1 (2)	.24

Abbreviations: DVT, deep vein thrombosis; OAT, oral anticoagulant treatment; PE, pulmonary embolism; RVD, right ventricular dysfunction; VTE, venous thromboembolism.
*Data are presented as number (percentage) of patients unless otherwise indicated.
†*P*<.05 vs the other 2 groups by Fisher exact test.
‡Includes 1 suicide and 1 end-stage renal disease.

Arch Intern Med. 2006;166(19):2151-2156.
doi:10.1001/archinte.166.19.2151

Medication Options

Question 7

In this patient, what would be the best treatment to start?

A. Nothing
B. LMWH
C. High dose heparin gtt /per nomogram
D. Coumadin (Warfarin)
E. Altapace (tpa)
F. Surgical embolectomy

Treatment Options

- Enoxaparin (low molecular weight heparin)
  - Xa inhibitor
  - Weight-based dosing
  - Anti-Xa level for monitoring
  - Peak 3 - 5 hours, Half-life about 6 hours
  - Dosing in low weight, obese patients is challenging
  - Clearance reduced with renal disease (CrCl<30)

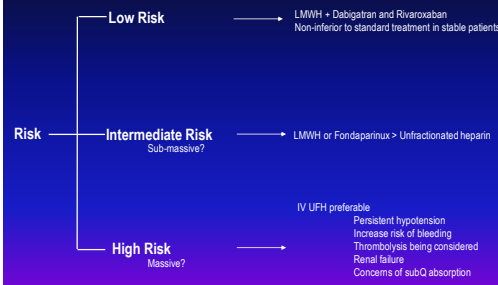
Antithrombotic Therapy For VTE Disease: Chest Guideline And Expert Panel Report
Kearon C, Akl EA, Ornelas J, et al. Chest. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.

Treatment Options

- Fondaparinux [Arixtra]
  - Binds anti-thrombin
  - Lowest risk of HIT (Heparin Induced Thrombocytopenia)
  - Peaks at 2 hours, half-life 17 hours
    - Stop 4 days before major procedure
    - No antidote
  - Clearance reduced with renal disease
    - Reduce 50% in CrCl < 50
    - Contraindicated in CrCl <30

Antithrombotic Therapy For VTE Disease: Chest Guideline And Expert Panel Report
Kearon C, Akl EA, Ornelas J, et al. Chest. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.

Risk Stratification
Acute Pulmonary Embolism



Antithrombotic Therapy For VTE Disease: Chest Guideline And Expert Panel Report
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Question 8

This patient appears to have a unprovoked pulmonary embolism thus would you recommend cancer screening.

A. I will ask Susan Stacy, she know everything
B. Yes
C. Maybe
D. No

Prevalence of Occult Cancer in Unprovoked Clot

Cochrane

= insufficient evidence

Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE (Review)

Robertson L, Yeoh SE, Stansby G, Agarwal R

*Robertson L[1], Yeoh SE, Stansby G, Agarwal R. Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE. Cochrane Database Syst Rev. 2015 Mar 6;3:CD010837. doi: 10.1002/14651858.CD010837.pub2.

Prevalence of Occult Cancer in Unprovoked Clot: SOME Study

- Prevalence of occult cancer was low.
- Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.
- CT included a virtual colonoscopy and gastroscopy, biphasic enhanced CT of the liver, parenchymal pancreatography, and uniphasic enhanced CT of the distended bladder.

Table 2. Occult Cancer Tumor Types.

Tumor Type	Limited Occult-Cancer Screening (N=14)		Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)		
During screening period	(3.2%)	P=0.28	(4.5%)
Acute leukemia	0/10		0/14
Gynecologic	3/10 (30)		0/14
Skin: melanoma	1/10 (10)		0/14
Colorectal	0/10		3/14 (21)
Prostate	2/10 (20)		0/14
Pancreatic	2/10 (20)		0/14
Cholangiocarcinoma	1/10 (10)		2/14 (14)
Lymphoma	1/10 (10)		3/14 (21)
Breast	0/10		2/14 (14)
Urologic	0/10		3/14 (21)
Unknown primary	0/10		1/14 (7)
During follow-up period			
Acute leukemia	1/4 (25)		1/5 (20)
Gynecologic	1/4 (25)		1/5 (20)
Skin: melanoma	0/4		1/5 (20)
Colorectal	1/4 (25)		1/5 (20)
Prostate	0/4		1/5 (20)
Pancreatic	1/4 (25)		0/5

Carrier M et al. N Engl J Med 2015;373:697-704

Kaplan–Meier Curves for Time to Detection of Missed Occult Cancer.

Group	Cancer	Percentage	95% CI
Limited Screening	14/431	3.2%	1.9 – 5.4
Limited (+) CT	19/423	4.5%	2.9 – 6.9

No significant between-group difference in the mean time to cancer diagnosis (4.2 m limited-screening group vs. 4.0 m in the limited-screening-plus-CT group. (P=0.88),

- Secondary outcome analyses:
  - Rate of recurrent events (3.3% and 3.4%, p=1.0),
  - Overall mortality (1.4% and 1.2%, p=1.0),
  - Cancer-related mortality (1.4% and 0.9%, p=0.75).
  - Rate of detection of early cancers (p=0.37).
    - 0.23% in the limited-screening group
    - 0.71% in the limited-screening-plus-CT group

Carrier M et al. N Engl J Med 2015;373:697-704

Question 9

What about Catheter related treatment for this patient?

A. Benefits (> 2 weeks) are in question.
B. Helps everyone who gets it.
C. Sure, there is no risk.
D. I really need to find Susan.

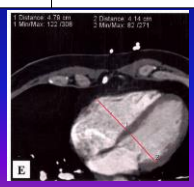
Interventions for Pulmonary Embolism

- Ultrasound Assisted Thrombolysis (EKOS)
  - Technically similar to catheter directed dripping.
  - Ultrasound potentially reduced drug administration time and tPA dose.
  - Potential lower rated of bleeding complications.

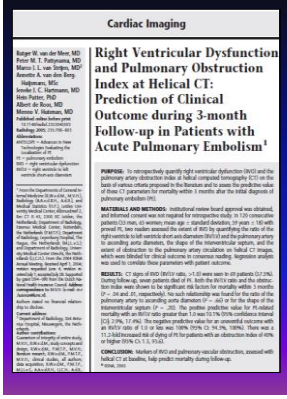
Back to Background Information

Massive PE	Submassive PE	Minor/Nonmassive PE
High risk	**Moderate/intermediate risk**	**Low risk**
• Sustained hypotension (systolic BP <90 mmHg for ≥15 min) • Inotropic support • Pulseless • Persistent profound bradycardia (HR <40 bpm with signs or symptoms of shock)	• Systemically normotensive (systolic BP ≥90 mmHg) • **RV dysfunction** • Myocardial necrosis	• Systemically normotensive (systolic BP ≥90 mmHg) • 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
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes:
  - new complete or incomplete RBBB
  - anteroseptal ST elevation or depression
  - anteroseptal T-wave inversion



Jaff et al. Circulation 2011;123(16):1788-1830.


Cardiac Imaging

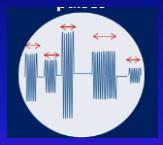
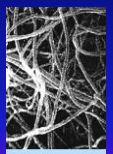
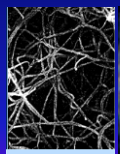
Right Ventricular Dysfunction and Pulmonary Obstruction Index at Helical CT: Prediction of Clinical Outcome during 3-month Follow-up in Patients with Acute Pulmonary Embolism[1]

- Retrospective analysis of 120 patients with hemodynamically stable PE based on CT
- PE-related mortality at 3 months:
  - **17%** if RV/LV ≥ 1.5
  - **8%** if 1.0 ≤ RV/LV < 1.5
  - **0%** if RV/LV < 1.0

Van der Meer et al. Radiology 2005; 235:798-803.

Ultrasound Accelerated Thrombolysis

Mechanism of Action

Ultrasound Pulses	Fibrin Separation		Active Drug Delivery by Acoustic Streaming
			
US delivered in: High freq (2.2Mhz) Low power (0.5 W/per element Pulses of varying waveforms	Fibrin without Ultrasound	Fibrin With Ultrasound	

Interventional Summary

- **Lysis vs. Placebo**
  - **13 placebo controlled, randomized trials of lysis vs placebo**
  - **Minority for massive PE, total 480 patients.**
  - **Variable drugs, dosing, timing and adjunctive therapies**
  - **No independent mortality effect**
  - **Meta-analyses reduction in death/recurrent PE**
  - **Improvement in RV size/function, mPA pressures**
- **EKOS vs. Heparin**
  - **No study large enough to evaluate death/recurrent PE**
  - **Improved RV size/function at 24hrs, catch up at 90days**
  - **Improved RV function at 90 days**

Question 10

How long would you recommend treatment for this patient.

A. Stop at hospital discharge
B. Life-long
C. Minimum of three month
D. Again, I will ask Susan

who should be treated for 3 months and who should indefinitely

Clive Kearon et al. Blood 2014;123:1794-180

Question 10

What would you do after three months? More importantly how would/do you decide?

A. Use a validated risk score
B. Rock, Paper, Scissors
C. Guess
D. Stop treatment after 3 months

VTE Recurrence Risk Assessment Scores

- **HERDOO-2 Score**

HERDOO-2 rule

HER =
- Hyperpigmentation or
- Edema or
- Redness

D = D-dimer positivity *(on warfarin)*

O = Obesity, BMI ≥ 30

O = Older age, ≥ 65 years

2 = score of ≥ 2: continue warfarin

Women = ≤ 1 Discontinue anticoagulation. Men, no matter what the score, need to continue anticoagulation.

- **DASH Score**

DASH Rule

D = D-dimer pos (off warfarin)	+ 2 points
A = age < 50 years	+ 1 point
S = sex (male)	+ 1 point
H = hormone use	- 2 points

Annual VTE recurrence rate:

<1	Discontinue anticoagulation
≤ 1:	3.1 %
2:	6.4 %
≥ 3:	12.3 %

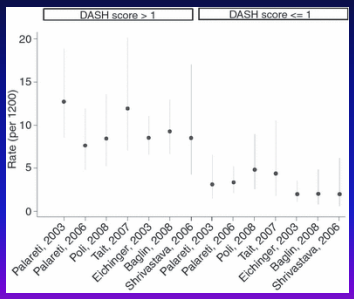
Tosetto A et al. J Thromb Haemost 2012 Jun;10(6):1019-25.
Rodger M et al; CMAJ 2008;179:417-426.

Predicting disease recurrence in unprovoked venous thromboembolism: a proposed prediction score (DASH)

DASH Score	Annualized Recurrence Rate (95% CI)	Cumulative Recurrence, %		
		1-year	2-years	3-years
-2	1.8 (0.5-7.6)	2.4	5.2	5.2
-1	1.0 (0.4-2.6)	1.9	1.9	5.7
0	2.4 (1.4-4.2)	4.2	5.4	9.5
1	3.9 (2.9-5.3)	5.1	8.7	15.9
2	6.3 (5.0-8.1)	8.4	12.8	25.3
3	10.8 (8.7-13.4)	14.6	20.5	40.9
4	19.9 (13.9-28.2)	21.9	33.6	61.3

Journal of Thrombosis & Haemostasis 2012; Volume10 (6): 1019-1025.

Predicting disease recurrence in unprovoked venous thromboembolism: a proposed prediction score (DASH)



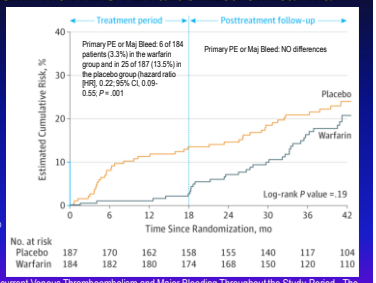
Journal of Thrombosis and Haemostasis 2012; Volume10 (6): 1019-1025.

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial

Randomized, double-blind trial (treatment period, 18 months; median follow-up, 24 months);

371 adult patients who had experienced a first episode of symptomatic unprovoked pulmonary embolism (ie, with no major risk factor for thrombosis) and had been treated initially for 6 uninterrupted months with a vitamin K antagonist were randomized and followed up between

Interventions Warfarin or placebo for 18 months.



Probability of the Composite Outcome of Recurrent Venous Thromboembolism and Major Bleeding Throughout the Study Period. The unadjusted hazard ratios for warfarin-placebo were 0.23 (95% CI, 0.09-0.55) during the treatment period and 0.74 (95% CI, 0.47-1.17) for the entire study period. The y axis that is shown in blue indicates the range of estimated cumulative risk from 0% to 10%.

JAMA. 2015;314(1):31-40. doi:10.1001/jama.2015.7046

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism: A Randomized Clinical Trial

Consecutive patients aged 18 years or older, hospitalized for acute, symptomatic clot. + at least 1 additional criterion for severity:

PREPRIC 2 Trail
399 patients Randomized

Standard care (UFH,LMWH or Fondaparinux +/–fibrinolytic treatment

IVC Filter Group + anticoagulation
<72 hours **n = 200**

Control [anticoagulation only] Group
n = 199

3 months IVC Removal

6 months = On anticoagulation
Data Analysis

JAMA. 2015;313(16):1627-1635. doi:10.1001/jama.2015.3780

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism: A Randomized Clinical Trial

Table 3. Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

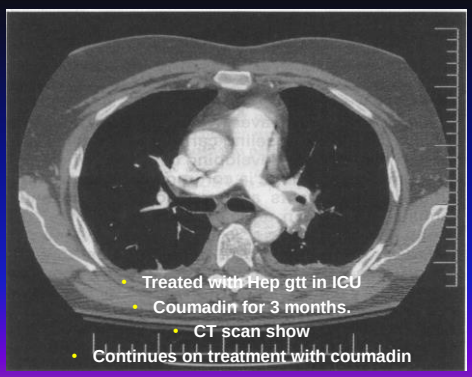
Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	P Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	> .99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	> .99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

JAMA. 2015;313(16):1627-1635. doi:10.1001/jama.2015.3780

Clinical Trials with DOAC in the Treatment of Venous Thromboembolism

Study (DOAC)	N (pts)	Age (yrs.)	Male Sex (%)	Index, PE n(%)	Clot Extent (%)	Drug Treatment	Control Treatment	Duration of Treatment	TTR (%)	Risk of Bias
Acute Treatment Venous Thromboembolism										
RE-COVER I (Dabigatran)	2,564	55 years	58%	786 (31%)	NR	Heparin >5 then DAB	UFH + Warfarin (INR 2-3)	6 month	60%	low
RE-COVER II (Dabigatran)	2,589	55 years	61%	816(32%)	NR	Heparin>5 then DAB	UFH + Warfarin (INR 2-3)	6 months	57%	low
EINSTEIN DVT (Rivaroxaban)	3,449	56 years	57%	23(1%)	NA	RIV15 mg BID. 3 weeks, RIV 20 mg QD	UFH+ Warfarin (INR 2-3)	3,6,12 months	57.7%	Unclear
EINSTEIN PE (Rivaroxaban)	5,400	57	59	4,833 (100%)	Extensive: 24 Intermediate 58	RIV 15 mg BID. 3 weeks; RIV 20 mg QD	UFH+ Warfarin (INR 2-3)	3,6,12 months	62.7%	Unclear
AMPLIFY (Apixaban)	5,400	57	59	1,836 (35%)	Extensive: 37 Intermediate 43	API 10 mg BID for 7 days, API 5 mg BID	Enoxaparin + Warfarin (INR 2-3)	6 months	63.5%	Low
HOKUSAI-VTE Edoxaban	8,292	56	57	3,319 (40%)	Extensive: 46 Intermediate 41	UFH 5 days + EDO 60 QD	UFH+ Warfarin (INR 2-3)	3 to 12 months	63.5%	Low



- Treated with Hep gtt in ICU
- Coumadin for 3 months.
- CT scan show
- Continues on treatment with coumadin

Conclusion

- There is no “ideal way” to diagnosis a VTE
- Can be managed safety when can't reach a definitive diagnosis.
- Risk stratification is need and often patients need to be followed longitudinally.
- Deliberate efforts are needed to assess thromboembolic risk in all patients.