PE MANAGEMENT

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PE MANAGEMENT

Objectives

- **Pathophysiology**
- **Risk stratification**
- **Diagnosis**
- **Anticoagulation**
  - UFH VS LMWH
- **Thrombolytics in PE**
  - Hemodynamiclly stable vs unstable pt.
- **Other TTT options**
- **Complications**

PE MANAGEMENT

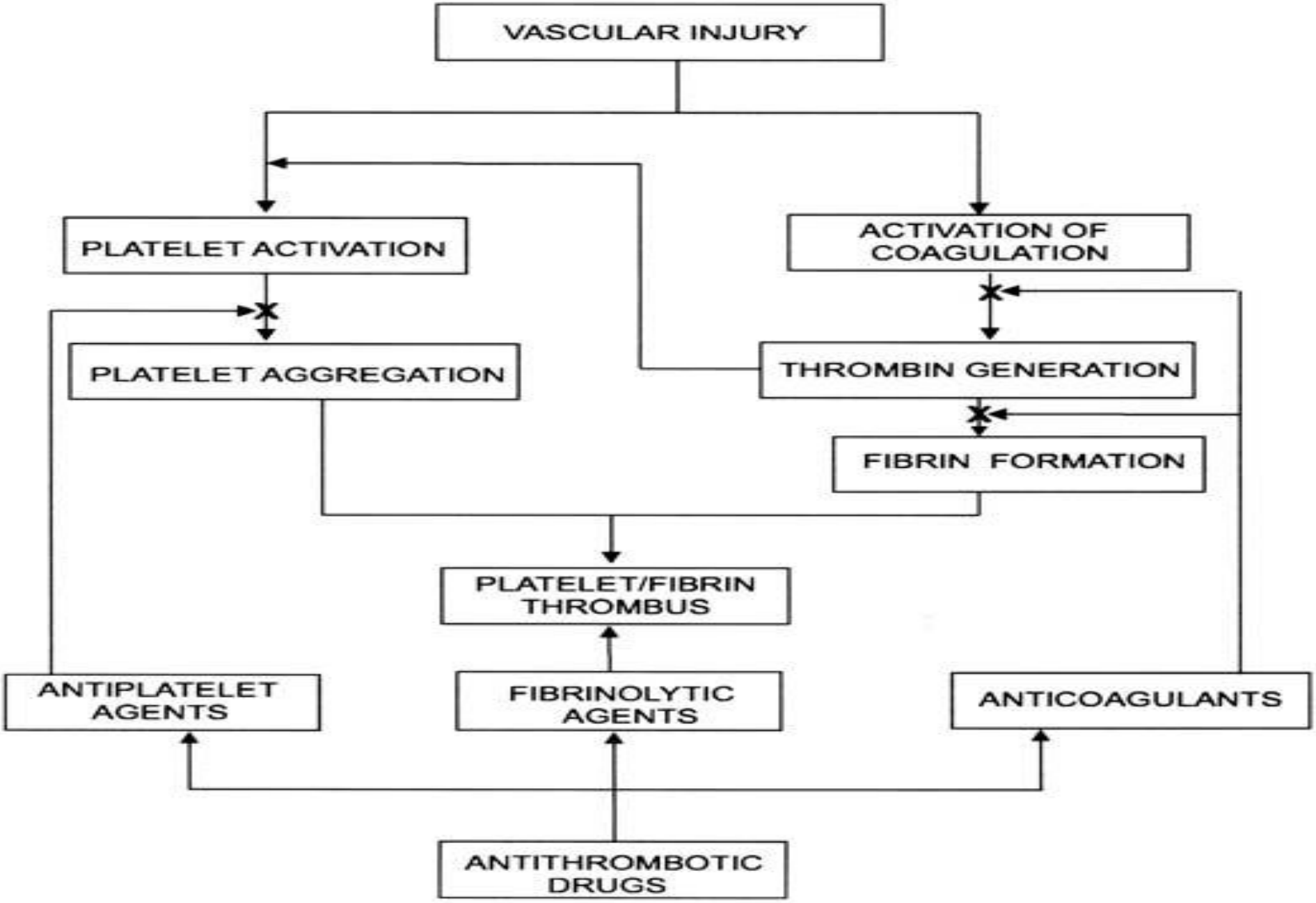
Mortality

The management strategy and prognosis of PE Registry included 1001 patients from 204 German centre divided into 4 subgroups based on cardiac performance.

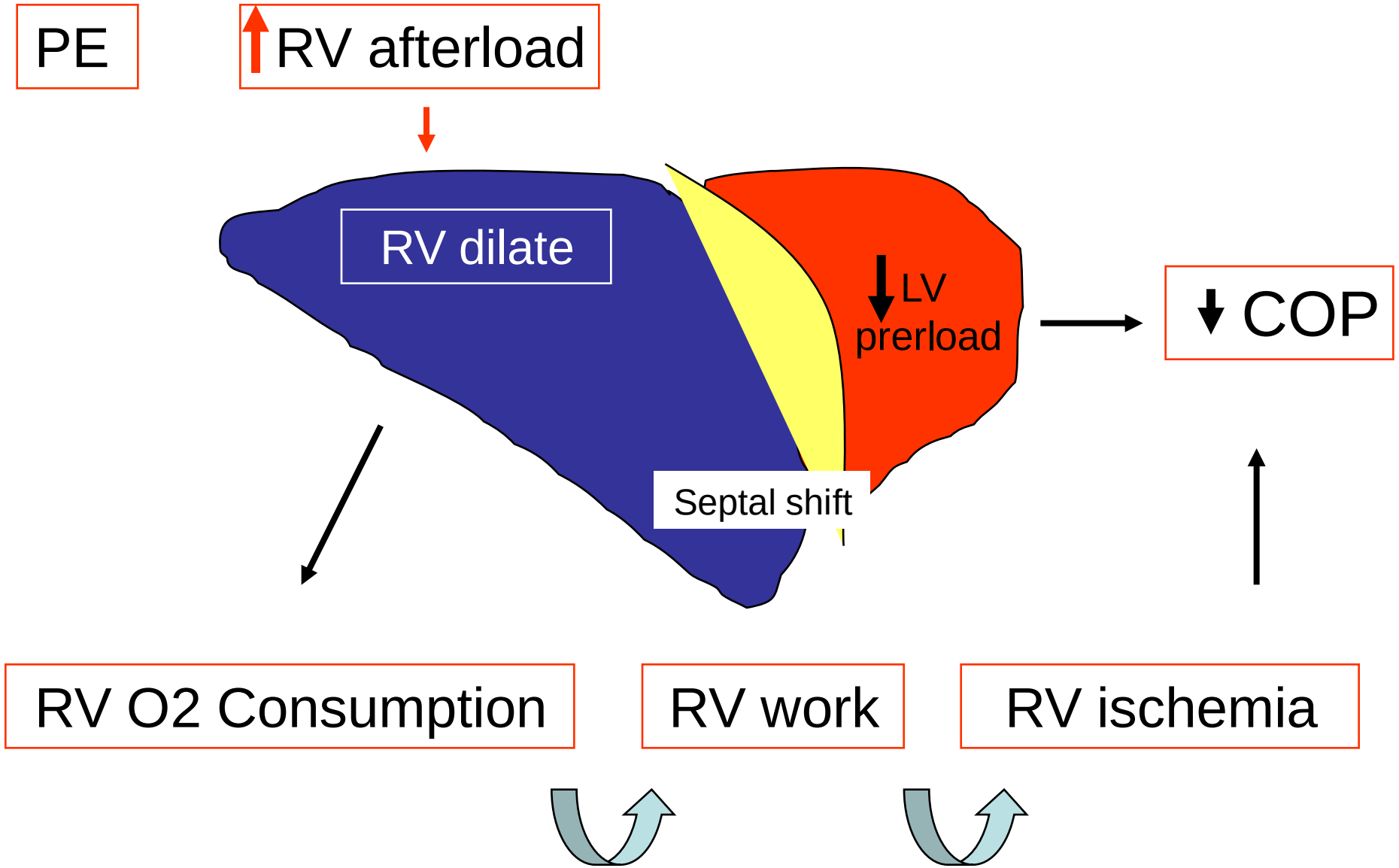
Overall mortality was as follows:

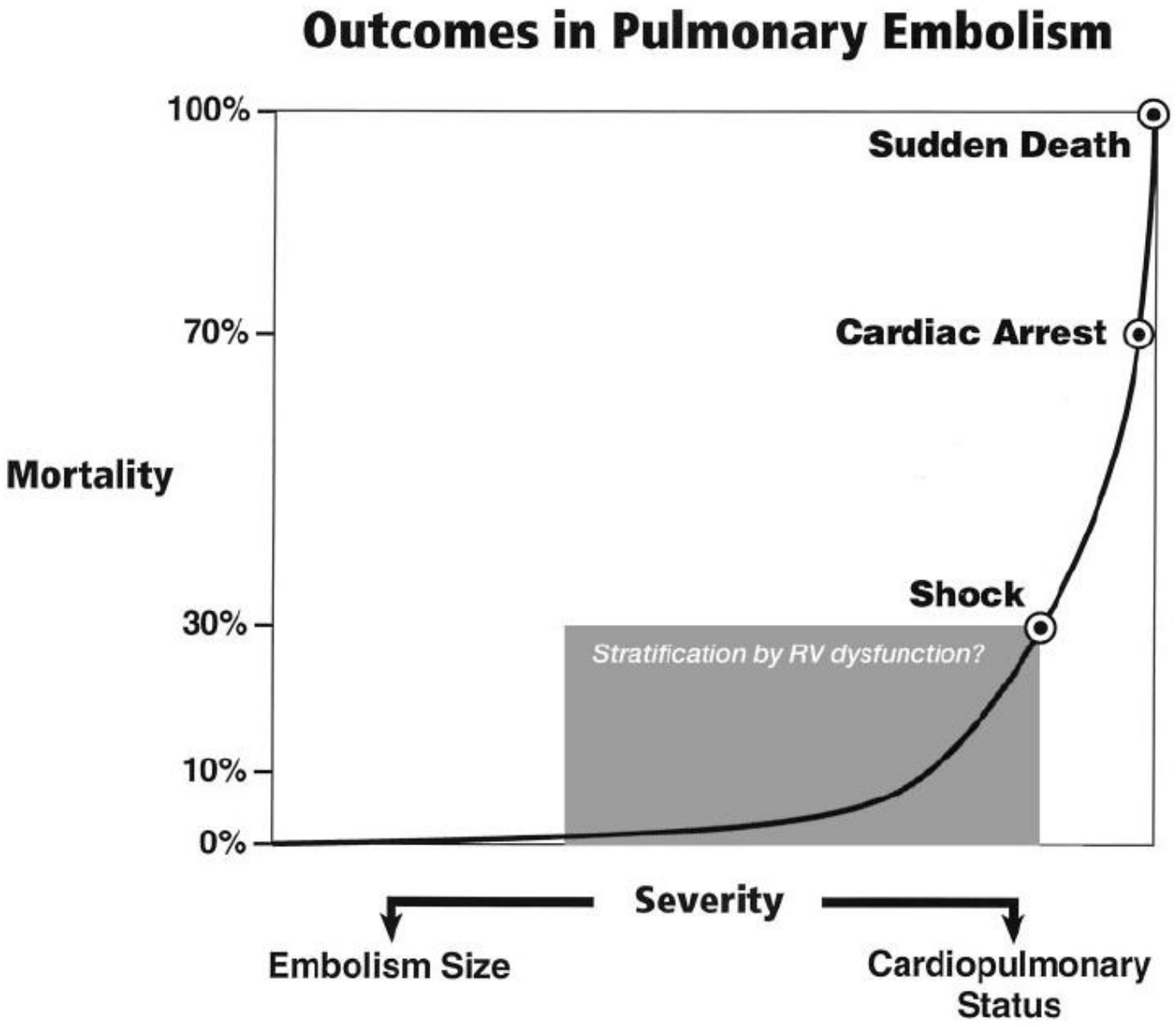
- Group 1: normotensive group but with pulmonary hypertension or RV dysfunction on echocardiogram. Mortality 8.1%.
- Group 2: systemic hypotension (systolic blood pressure <90 or pressure drop >40). Mortality 15%.
- Group 3: cardiogenic shock. Mortality 25%.
- Group 4: those requiring cardiopulmonary resuscitation. Mortality 65%.

Pulmonary Embolism Pathophysilogy



Hemodynamic Effects PE MANAGEMENT





The relationship of severity and mortality in patients with MPE.

Risk Factors Pearls

- Risk Factors increase your suspicion
- However 20% of patients with PE have no known Risk Factors
- Therefore Lack of Risk Factors by no means excludes PE

Symptoms

syncope

- 8% to 13% of all patients who have PE
- caused by right ventricular outflow obstruction and subsequent decreased left ventricular ejection fraction & shock

PE

Symptoms

Dyspnea

- There may be only on exertion
- The onset usually, but not always, rapid.
- Orthopnea may occur.
- Less frequent in elderly patients with no previous cardiopulmonary disease.
- Dyspnea may be absent even in patients with circulatory collapse

Paul D. Stein. Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II
The American Journal of Medicine - Volume 120, Issue 10 (October 2007)

Symptoms of PE	PE All Patients N = 184-191 n (%)
Dyspnea	
Dyspnea (rest or exertion)	151 (79)
Dyspnea (at rest)	117 (61)
Dyspnea (exertion only)	31 (16)
Orthopnea (≥2-pillow)	69 (36)
Pleuritic pain	89 (47)
Chest pain (not pleuritic)	33 (17)
Cough	82 (43)
Wheezing	58 (31)
Calf or thigh swelling	72 (39)
Calf and thigh swelling	15 (8)
Calf or thigh pain	78 (42)
Calf and thigh pain	30 (16)

Paul D. Stein. Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II The American Journal of Medicine - Volume 120, Issue 10 (October 2007)

Conclusion

- Symptoms may be mild, and generally recognized symptoms may be absent

- A high or intermediate-probability objective clinical assessment suggests the need for diagnostic studies
- a low-probability objective clinical assessment does not exclude the diagnosis.

- Maintenance of a high level of suspicion is critical.

Signs

- Tachypnea absent in 5% to 13% of cases.
- Tachycardia absent in
  - 70% of patients under age 40 with PE
  - 30% of patients over age 40
- What is the point?

Much of what has been taught about traditional vital signs is wrong. Use of these as a guide to rule in or rule out the disease is not helpful

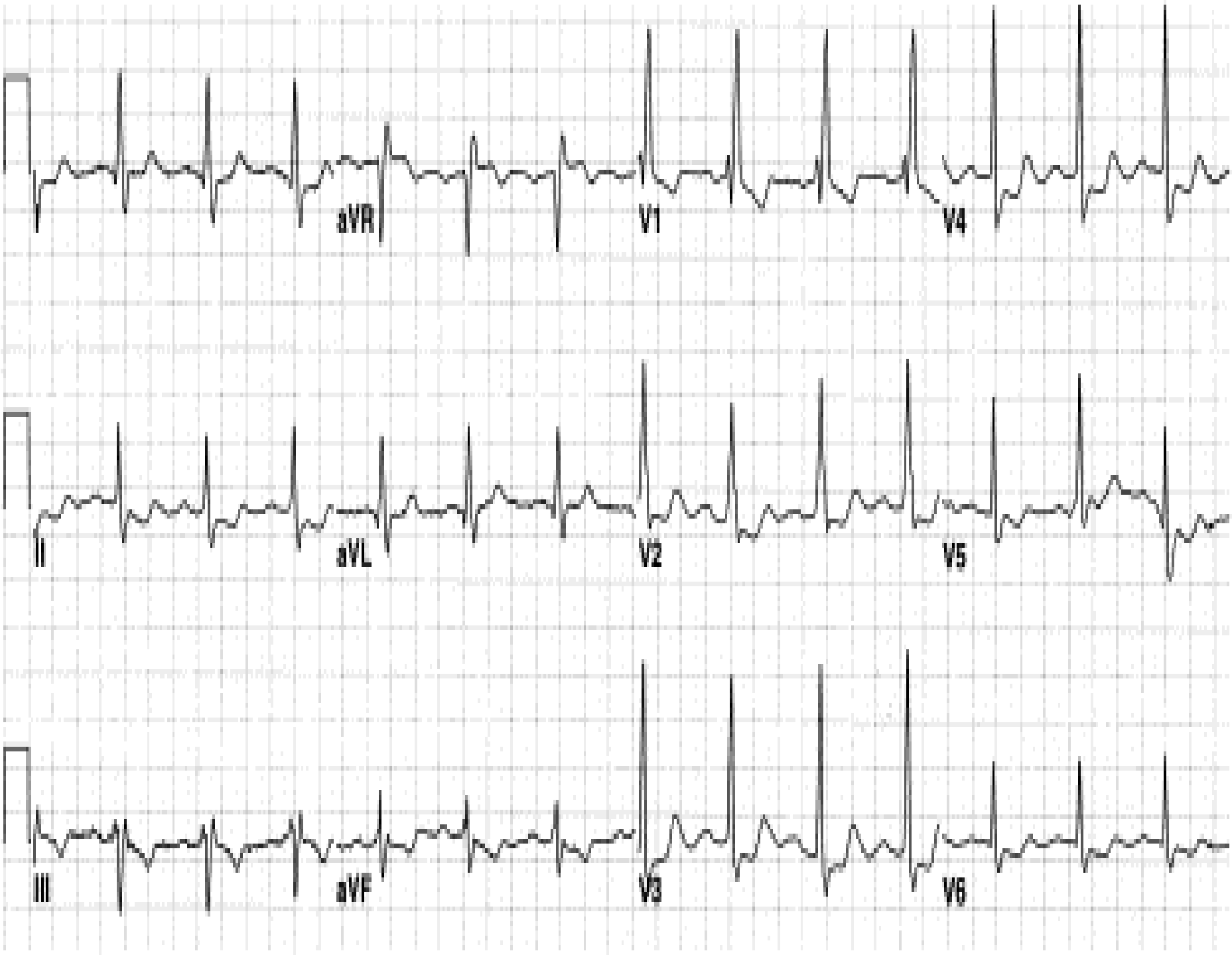
Signs of Pulmonary Embolism	PE All Patients N = 184-191 n (%)
Tachypnea (≥20/min)	108 (57)
Tachycardia (>100/min)	49 (26)
Diaphoresis	8 (4)
Cyanosis	1 (1)
Temperature > 38.5°C	3 (2)
Cardiac examination (abnormal)	42 (22)
Increased P2	22 (15)
Right ventricular lift	8 (5)
Jugular venous distension	25 (13)
Rales (crackles)	40 (21)
Wheezes	6 (3)
Decreased breath sounds	40 (21)
Pleural friction rub	2/ (1)
Calf or thigh dvt signs	90 (47)
Calf and thigh dvt signs	23 (12)

PE

Relationship between DVT & PE

autopsy studies indicates that

- many patients who have documented DVT have asymptomatic PE.
- many patients who have PE have silent or asymptomatic DVT.


aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

EKG -- Pearl

- Only useful if it provides an alternate diagnosis

PE

Investigation

D-Dimer

a degradation product of a cross-linked fibrin blood clot.

sensitive but non-specific markers for venous thromboembolism.

There are qualitative and quantitative D-dimer assays.

PE

Investigation

D-Dimer

Qualitative D-dimer assays

- by visual inspection to be positive or negative.
- The first tests developed were latex agglutination assays
- The second was a whole blood agglutination assay (SimpliREDTM
- The SimpliREDTM is the qualitative test with the most clinical data.
- have the advantages that they are simple to perform

PE

Investigation

Imaging procedures

In the PIOPED study, 1.6% of patients with normal pulmonary angiograms developed PE in a one year follow-up period.

- Most of these events occurred within a month of the procedure
- A normal perfusion lung scan essentially excludes the diagnosis of PE
- a high probability lung scan has an 85% to 90% predictive value for PE

PE

Investigation

Imaging procedures

- largest study of MDCT accuracy for PE—are 90% to 95%

Stein P.D., Fowler S.E., Goodman L.R., et al: Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 354. 2317-2327.2006

Investigation

V/Q

Consider it if:

- Normal CXR
- Contrast Allergy
- Pregnancy

Investigation

Blood Gases

The PaO2 while breathing room air was 80 mm Hg or more in 32% of all patients with pulmonary embolism

The A-a oxygen difference was 20 mm Hg or less in 32% of all patients with pulmonary embolism

Investigation

Echo

PATIENTS IN EXTREMIS

- The sensitivity of transthoracic echo for RV enlargement or dysfunction in patients with massive PE or unstable patients, combining data from 3 case series, was 33 of 33 (100%).

Cheriex EC, Sreeram N, Eussen YF, et al. Cross-sectional Doppler echo as the initial technique for the diagnosis of acute PE. *Br Heart J.* 1994;72:52-57.

Mansencal N, Redheuil A, Joseph T, et al. Use of transthoracic echo combined with venous ultrasonography in patients with PE. *Int J Cardiol.* 2004;96:59-63.

Rudoni RR, Jackson RE, Godfrey GW, et al. Use of two-dimensional echo for the diagnosis of pulmonary embolus. *J Emerg Med.* 1998;16:5-8.

PE

Investigation

Echo

If any 2 of the following 3 assessments were positive

1. Clinical probability high
2. Echo
3. U/S

the sensitivity for massive PE was 33 of 34 (97%) and the NPV was 98%.

Grifoni S, Olivotto I, Cecchini P, et al. Utility of an integrated clinical, echocardiographic, and venous ultrasonographic approach for triage of patients with suspected pulmonary embolism. *Am J Cardiol.* 1998;82: 1230-1235.

Rules

use of clinical prediction rules allows reasonably accurate stratification of patients into different risk categories.

Table 2

Wells' Criteria for Assessment of Pretest Probability

The Wells Criteria for assessing pretest probability is important for diagnosing DVT and PE. Below describes the criteria and scoring system:

Criteria	Points
Suspected DVT	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate > 100 beats per minute	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the past six months or palliative)	1.0

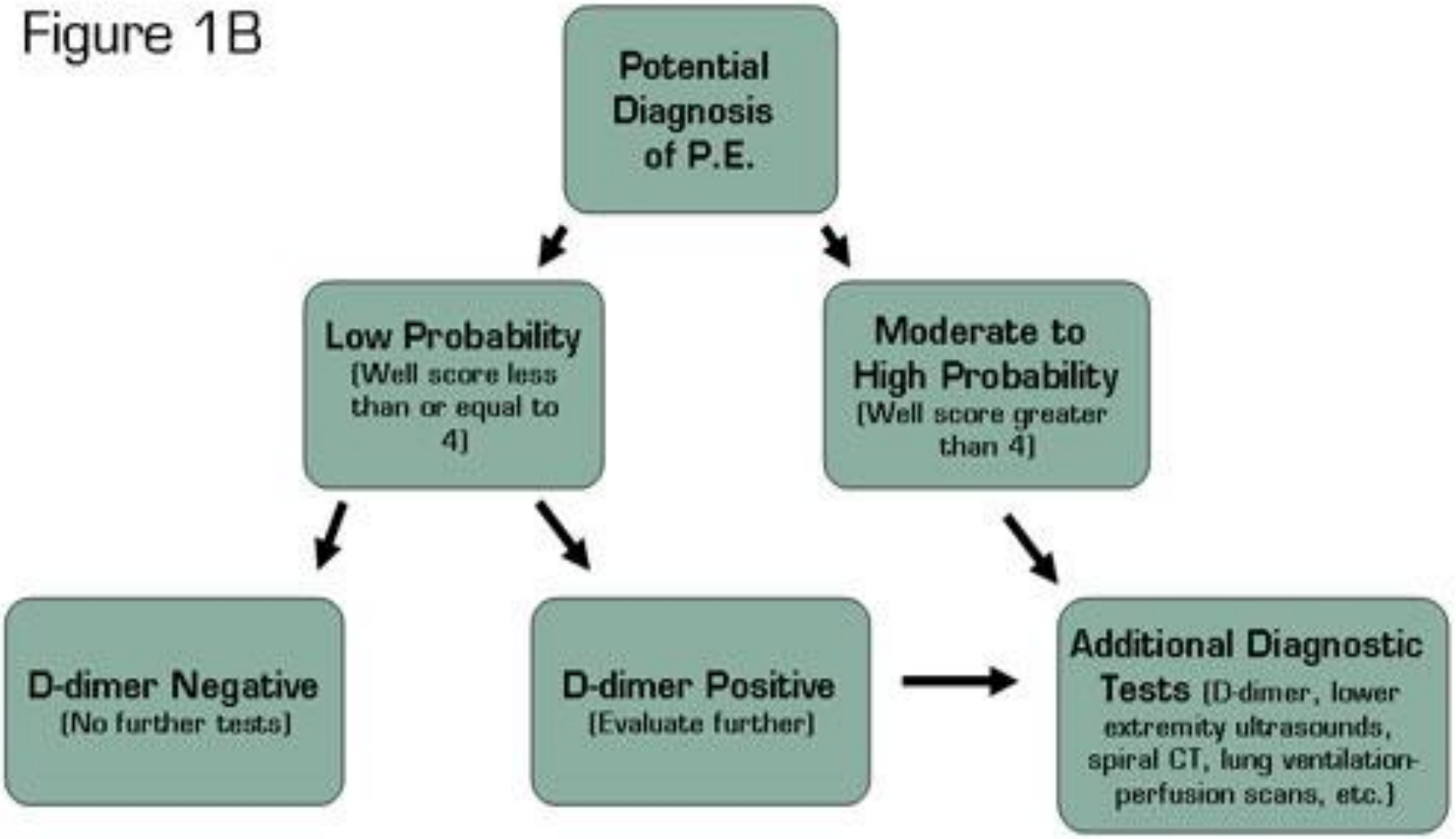
Score range	Mean probability of PE	% with this score	Interpretation of risk
<2 points	3.6%	40	Low
2 to 6 points	20.5%	53	Moderate
>6 points	66.7%	7	High

Source: Adapted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83:416-420.

Recommendations for patients with low probability clinical assessment :

- Perform a D-dimer rapid ELISA.
- No further testing is required if normal.
- If is positive, CT.
- If CT angiography or CT angiography/CT venography is negative, treatment is unnecessary.

Figure 1B

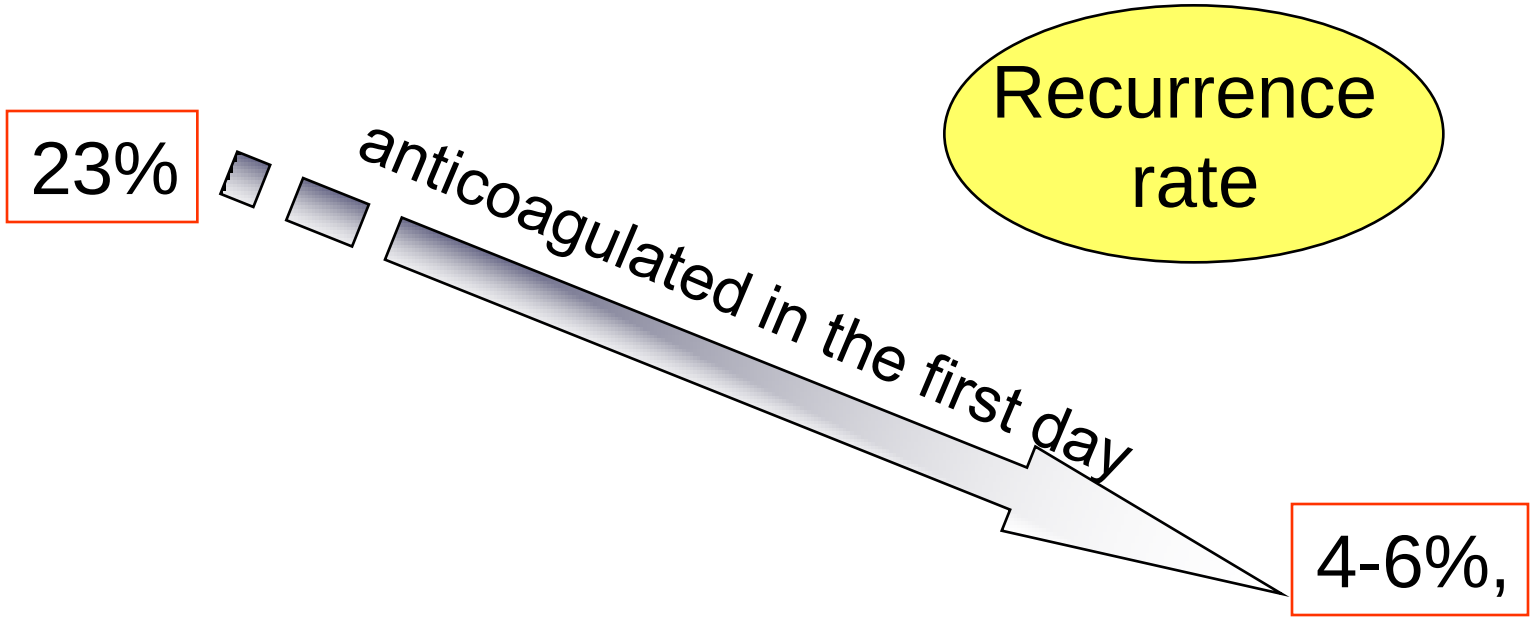


Kearon C, Ginsberg JS, Douketis J, et al.; Canadian Pulmonary Embolism Diagnosis Study (CANPEDS) Group. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 2006;144:812-21.

PE MANAGEMENT

Anticoagulation

Why earlier is better?



Hull RD, Raskob GE, Brant RF, et al. Relation between the time to achieve the lower limit of apt therapeutic range and recurrent venous thromboembolism during heparin treatment for deep venous thrombosis .*Arch Intern Med* .2568-157: 2562;1997

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Anticoagulation

Why earlier is better?

In a metaanalysis of 5 studies

only 1.5%.

Death rate

Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA*. 1998;279:458-462.

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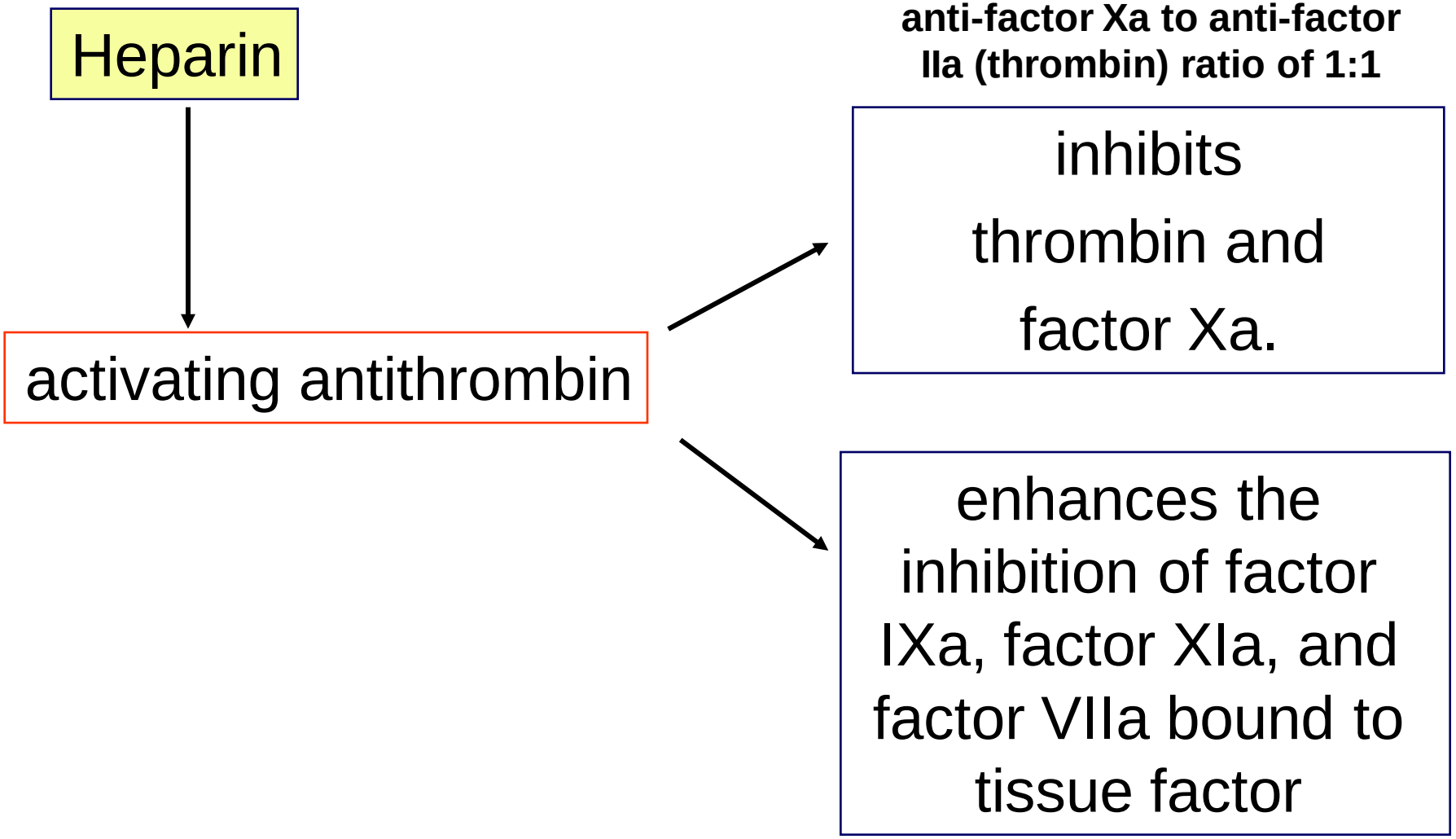
Anticoagulation

Why earlier is better?

- The risk of recurrent VTE with standard UFH treatment is 6.8%

Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;160:229-236.

PE Anticoagulation



PE Anticoagulation

Heparin Dosages

a bolus 80 IU/kg to 150 IU/kg.

followed by a drip 18 IU/ kg.

The goal is for the PTT to be 1.5 times the control value .

PE Anticoagulation

Monitoring of the Anticoagulant Effect of Heparin

PTT or anti-factor Xa level

Monitoring of the Anticoagulant Effect of Hepartin

Anti-factor Xa

- therapeutic heparin levels range from 0.3 to 0.7 units/mL.
- **Indication** (heparin resistant) 25% of heparin-treated patients require doses in excess of 35,000 units/day to prolong the PTT into the therapeutic range

Limitation	Mechanism
Poor bioavailability at low doses	Binds to endothelial cells and macrophages
Dose-dependent clearance	Binds to macrophages
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets

Pharmacokinetic and Biophysical Limitations of Heparin

Side Effects of Heparin

Bleeding

- protamine sulfate to neutralize the heparin.
- 1 mg of protamine sulfate neutralizes 100 units of heparin.
- intravenously.
- Anaphylactoid reactions can occur

PE Anticoagulation

LOW-MOLECULAR-WEIGHT HEPARIN

Mechanism of Action

- by activating antithrombin.

- has greater capacity to catalyze factor Xa inhibition by antithrombin than thrombin inhibition

PE Anticoagulation

LOW-MOLECULAR-WEIGHT HEPARIN

FDA approved LMWHs for use in treating VTE

- Enoxaparin and Tinzaparin

PE Anticoagulation

Pharmacology of LMWH

- Subcutaneously
- can be administered intravenously when a rapid anticoagulant response is needed.
- LMWH cleared by the kidneys.

Advantages of LMWH over Heparin

Advantage	Consequence
Better bioavailability and longer half-life	Can be given subcutaneously once or twice after subcutaneous injection daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

PE Anticoagulation

LMWH Monitoring Indications???

Monitoring is necessary in

- renal insufficiency
- obesity
- pregnancy

PE Anticoagulation

LMWH Monitoring

anti-factor Xa levels

- 3 to 4 hours after drug administration.
- Therapeutic is 0.5 to 1.2 units/mL
- For prophylaxis doses 0.2 to 0.5 units/mL are desirable.

PE Anticoagulation

LMWH

Drug name	Mean molecular weight	Anti-Xa:anti-IIa ratio	Therapeutic dose
Enoxaparin	4200	3.8	or 150 100 IU/kg twice daily[a] IU/kg once daily[b]
Dalteparin	5800	2.8	or 200 100 IU/kg twice daily IU/kg once daily
Tinzaparin	5800	1.5–2	175 IU/kg once daily

a Current approved FDA dose for treatment of acute VTE .
b FDA approved for inpatient treatment .

Appropriate Starting Dosages of Anticoagulants for PE in Critically Ill Patients

Drugs	Dosages	Comments
Unfractionated heparin	80 U/kg IV bolus; 18 U/kg/h IV; titrate by aPTT	Avoid with HIT; dose by actual body weight
Fondaparinux	Subcutaneous qd; 5 mg if < 50 kg, 7.5 mg if 50 to 100 kg, and 10 mg if > 100 kg	Not tested in well-hydrated patients with creatinine levels > 2 mg/dL; no reliable monitoring
Enoxaparin	Subcutaneous, 1 mg/kg q12h	Uncertain whether to "cap" dosage > 120 kg or 150 kg; reduce to 1 mg/kg q 24 h fo calculated creatinine clearance < 30 mL/min
Dalteparin	Subcutaneous, 200 U/kg q24h	120 U/kg and 100 U/kg q12h have also been used; insufficient evidence in renal insufficiency
Tinzaparin	Subcutaneous, 175 U/kg q24h	Evidence exists for dosing by weight without "capping" and for standard dosage if calculated creatinine clearance > 20 mL/min

PE Anticoagulation

Side Effects of LMWH

Bleeding

- protamine sulfate incompletely neutralizes the anticoagulant activity of LMWH because it only binds the longer chains of LMWH.

- *patients at high risk for bleeding may be more safely treated with continuous intravenous unfractionated heparin*

SYNTHETIC HEPARIN ANALOGS

Fondaparinux

- binds antithrombin with an affinity similar to that of natural pentasaccharide.

is approved for thromboprophylaxis in high-risk orthopedic patients and may be a useful alternative to heparin or LMWH for initial treatment of patients with established venous thromboembolism.

idraparinux

- binds antithrombin with 50-fold higher affinity than fondaparinux (Kd values of 1 and 50 nM, respectively)

Fondaparinux

- 2213 patients
- Patients received fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing less than 50, 50 to 100, or more than 100 kg, respectively) subcutaneously once daily
- is at least as effective and as safe as adjusted-dose, intravenous administration of unfractionated heparin

Buller H.R., Davidson B.L., Decousus H., et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* (2003) 349 : pp 1695-1702.

PE MANAGEMENT

Warfarin

- Warfarin should be started within three days of initial heparin therapy

PE MANAGEMENT

Warfarin

- The first 24 hours of warfarin therapy are associated with a transient hypercoagulable state
- heparin should not be discontinued until (INR) has been in the therapeutic range for at least two days

PE & Thrombolysis

The US FDA has approved three thrombolytic agents for the treatment of PE:

- streptokinase
- urokinase
- recombinant tissue-type plasminogen activator (rt-PA).

Thrombolytics in PE

- limit further clot propagation
- dissolve clots.
- large decrease in right ventricular strain as compared to treatment with heparin.
- The difference seen on echo between the two treatment groups disappears after a week

Konstantinides S, Tiede N, Geibel A, et al. Comparison of Alteplase versus heparin for resolution of major pulmonary embolism .*Am J Cardiol* .970-82:966;1998

Thrombolytics in PE

Rapid:

- improvement in hemodynamic measurements and pulmonary perfusion.
- right ventricular function recovers quickly
- decrease in pulmonary hypertension.

•Arcasoy SM, Kreit JW. Thrombolytic therapy of pulmonary embolism .*Chest* .1706-115:1695;1999

•Nass N, McConnell MV, Goldhaber SZ, et al. Recovery of regional right ventricular function after thrombolysis for pulmonary embolism .*Am J Cardiol* .806-83:804;1999

Thrombolytics in PE

- Is it for all patient with PE???

Thrombolytics in PE

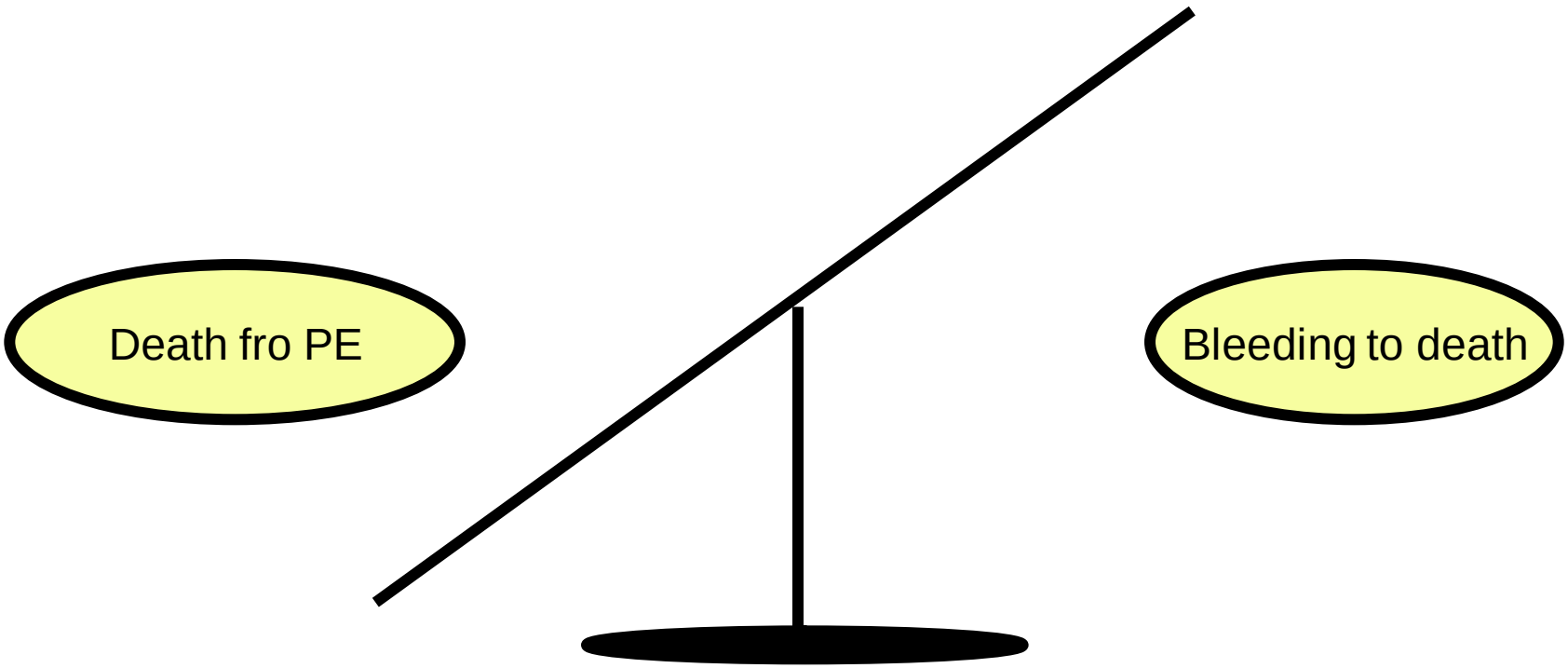
Shock due to PE small study

- none of the patients receiving thrombolysis died
- all who received heparin only died

Jerjes-Sanchez C, Ramirez-Rivera A, Garcia M de L, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: A randomized controlled trial .*J Thromb Thrombolysis.* 229-2:227;1995

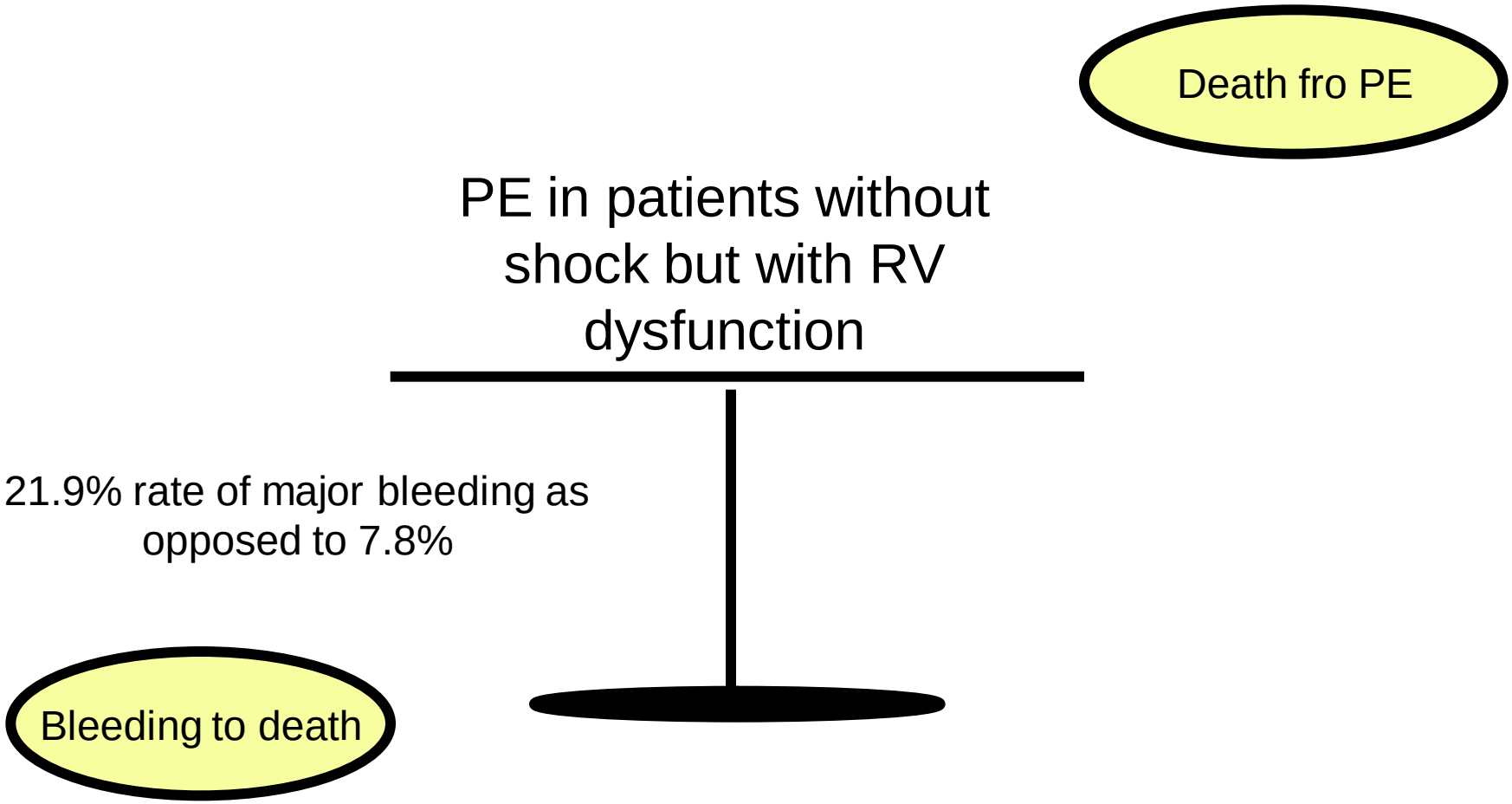
Thrombolytics in PE

Thrombolysis in massive PE with shock



Thrombolytics in PE

In the MAPPET trial



Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: Results of a multicenter registry *Circulation* 2500-2498:96;1997

Thrombolysis in hemodynamic stable PE

- no randomized controlled study available to answer this question.

Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation .*Chest* 125-120:120;2001

Thrombolysis in hemodynamic stable PE

Thrombolysis and heparin in patients with acute PE have been compared
in 11 randomized controlled trials (n=748)

Same Conclusions:

no clear benefit of thrombolysis over heparin was found

Thrombolysis in hemodynamic stable PE

Only 1 randomized controlled trial focused specificall on patients with RV dysfunction.

alteplase plus heparin and heparin alone in a double-blind trial of 256 patients with PE and RV dysfunction but not hypotension

The primary end point was death or need for escalation therapy,

Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347: 1143-1150.

Thrombolysis in hemodynamic stable PE

no significant differences

among the 2 treatment groups in

mortality rate and PE recurrence

Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347: 1143-1150.

Table 3. Efficacy End Points in the Study by Konstantinides et al[18]

End Point	Heparin Plus Alteplase (n = 118)	Heparin Plus Placebo (n = 138)	*P* Value*
Death, No. (%)	4 (3.4)	3 (2.2)	.71
Escalation of treatment, No. (%)	12 (10.2)	34 (24.6)	**.004**
Catecholamine infusion	3 (2.5)	8 (5.8)	.33
Secondary thrombolysis	9 (7.6)	32 (23.2)	**.001**
Endotracheal intubation	3 (2.5)	3 (2.2)	.85
Cardiopulmonary resuscitation	0	1 (0.7)	>.99
Embolectomy or thrombus fragmentation	0	1 (0.7)	>.99
Recurrent pulmonary embolism, No. (%)	4 (3.4)	4 (2.9)	.89

*Boldface indicates statistical significance.

Table 2. Main Characteristics and Results of 11 Trials Comparing Thrombolysis and Heparin in Patients With Acute Pulmonary Embolism

Source	Patients, Hep/TL, No.	Treatment Regimen	Patients With Shock Included	Follow-up, d	Recurrence of PE or Death, Hep/TL, No.	Major Hemorrhage,* Hep/TL, No.
UPET,[19] 1973	78/82	Heparin UK 2000 U/lb bolus, then 2000 U/lb per hour IV for 12 h	Yes	14	14/10	11/22
Tibbutt et al,[23] 1974	17/13	Intrapulmonary heparin Intrapulmonary SK 600 000 U bolus, then 100 000 U/h for 72 h	Yes	3	1/0	1/1
Ly et al,[24] 1978	11/14	Heparin SK 250 000 U bolus, then 100 000 U/h for 72 h	Yes	10	2/1	2/4
Dotter et al,[25] 1979	16/15	Heparin SK for 18-72 h	Yes	In hospital	3/1	1/0
Marini et al,[26] 1988	10/20	Heparin UK 800 000 U/d IV for 72 h UK 3 300 000 U IV for 12 h	Yes	7	0/0	0/0
PIOPED,[27] 1990	4/9	Heparin rt-PA 40-80 mg IV over 90 min plus heparin	No	7	0/1	0/1
Levine et al,[28] 1990	25/33	Heparin rt-PA 0.6 mg/kg IV over 2 min	No	10	0/1	0/0
PAIMS 2,[29] 1992	16/20	Heparin rt-PA 100 mg IV over 2 h	No	7	1/3	2/3
Goldhaber et al,[16] 1993	55/46	Heparin rt-PA 100 mg IV over 2 h	No	14	4/0	1/2
Jerjes-Sanchez et al,[3] 1995	4/4	Heparin SK 1 500 000 U IV over 1 h	Yes	3	4/0	0/0
Konstantinides et al,[18] 2002	138/118	Heparin, rt-PA 100 mg IV over 2 h	No	30	7/8	5/1

Abbreviations: Hep/TL, heparin/thrombolysis; IV, intravenous; PE, pulmonary embolism; rt-PA, alteplase; SK, streptokinase; UK, urokinase.
*Major hemorrhage was defined as intracranial or retroperitoneal hemorrhage or other bleeding requiring transfusion or surgery.

Thrombolysis for Pulmonary Embolism in Patients With Right Ventricular Dysfunction

Con

Gabriel Thabut, MD; Damien Logeart, MD

In conclusion, convincing evidence that thrombolysis should be administered to hemodynamically stable patients with PE and RV dysfunction is lacking. Consequently, we believe that thrombolytic therapy should only be considered in patients with massive PE complicated by shock.

PE MANAGEMENT

Thrombolytics in PE

- RCTs comparing the addition of thrombolytic therapy to standard heparin therapy for treatment of submassive PE fail to show any significant differences in clinically important outcomes.

Andrew Worster, Thrombolytic Therapy for Submassive Pulmonary Embolism?
Annals of Emergency Medicine - Volume 50, Issue 1 (July 2007)

Thrombolytics in PE

Drugs	Dosing
Streptokinase	250,00 U over 30 min; then 100,000 U/h for 24 h
Urokinase	4,400 U/kg over 10 min; then 4,400 U/kg/h for 12 h
Alteplase	10-mg bolus; then 90 mg over 2 h

Management of Lytic bleeds

	During infusion	Immediately after	6-36hrs after
Fibrinogen	Low	Nadir	Recovers
?Cryoprecipitate	20 units	20 units	20 units
Bleeding time	Long	Variable	Normal
?platelets	5 Units	5 units	No
Circulating lytic	Yes	Variable	Absent
?antifibrinolytic	Yes	Yes	Yes

MANAGEMENT

If serious noncompressible bleeding complications result from lytic therapy?????

- The infusion of lytic agent should be stopped.
- Fresh frozen plasma
- Cryoprecipitate
- *Aminocaproic acid* (an inhibitor of plasminogen activators) may be given as a 5-g IV bolus administered over 30 minutes, followed by a maintenance infusion of 1 g/hr until the bleeding has resolved.

PE MANAGEMENT

Vasopressors

In a canine model

- norepinephrine was superior to phenylephrine in increasing cardiac output and RV coronary blood flow
- both agents similarly improved mean arterial BP.

Hirsch LJ, Rooney MW, Wat SS, et al. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. Chest 1991; 100:796–801

PE MANAGEMENT

Fluids??????????????

13 free of previous cardiopulmonary disease with angiographically proven AMPE , with acute circulatory failure

Infusion of 500 mL of dextran 40 over 20 mins

CONCL. fluid loading can improve hemodynamic status in patients with acute circulatory failure caused by AMPE

Hemodynamic effects of fluid loading in acute massive pulmonary embolism.
Mercat A Crit Care Med. 1999 Mar;27(3):540-4

PE MANAGEMENT

Embolectomy

- patients who fail thrombolysis,
- patients who are too ill to attempt thrombolysis
- patients with contraindications to thrombolysis

PE MANAGEMENT

Summary

- **Pathophysiology**
- **Risk stratification**
- **Diagnosis,**

low probability & - dd done khalas

For moderat and high, anticoagulate and go for CT

- **Anticoagulation**
    - UFH VS LMWH, Fondaparinux
- **Thrombolytics in PE**
    - Hemodynamiclly stable vs unstable pt.
- **Other TTT options**
- **Complications**