

Home Sweet Home?

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OUTLINE

Pulmonary Embolism

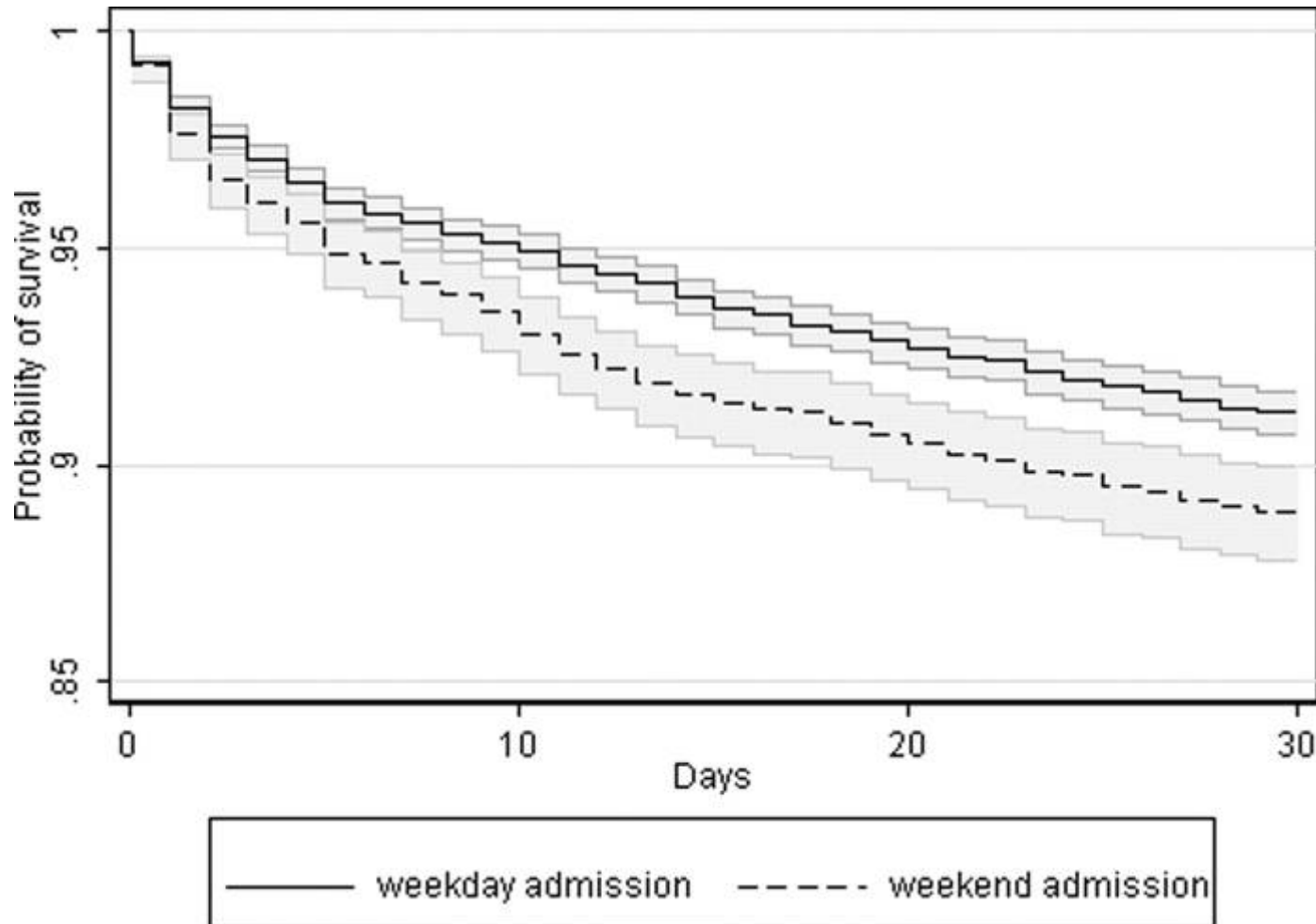
- Diagnosis of PE
- Clinical spectrum
- Prediction of outcome
 - CDR
 - Radiology
 - Biomarkers
- Management studies and the future



Clinical Decision Rules

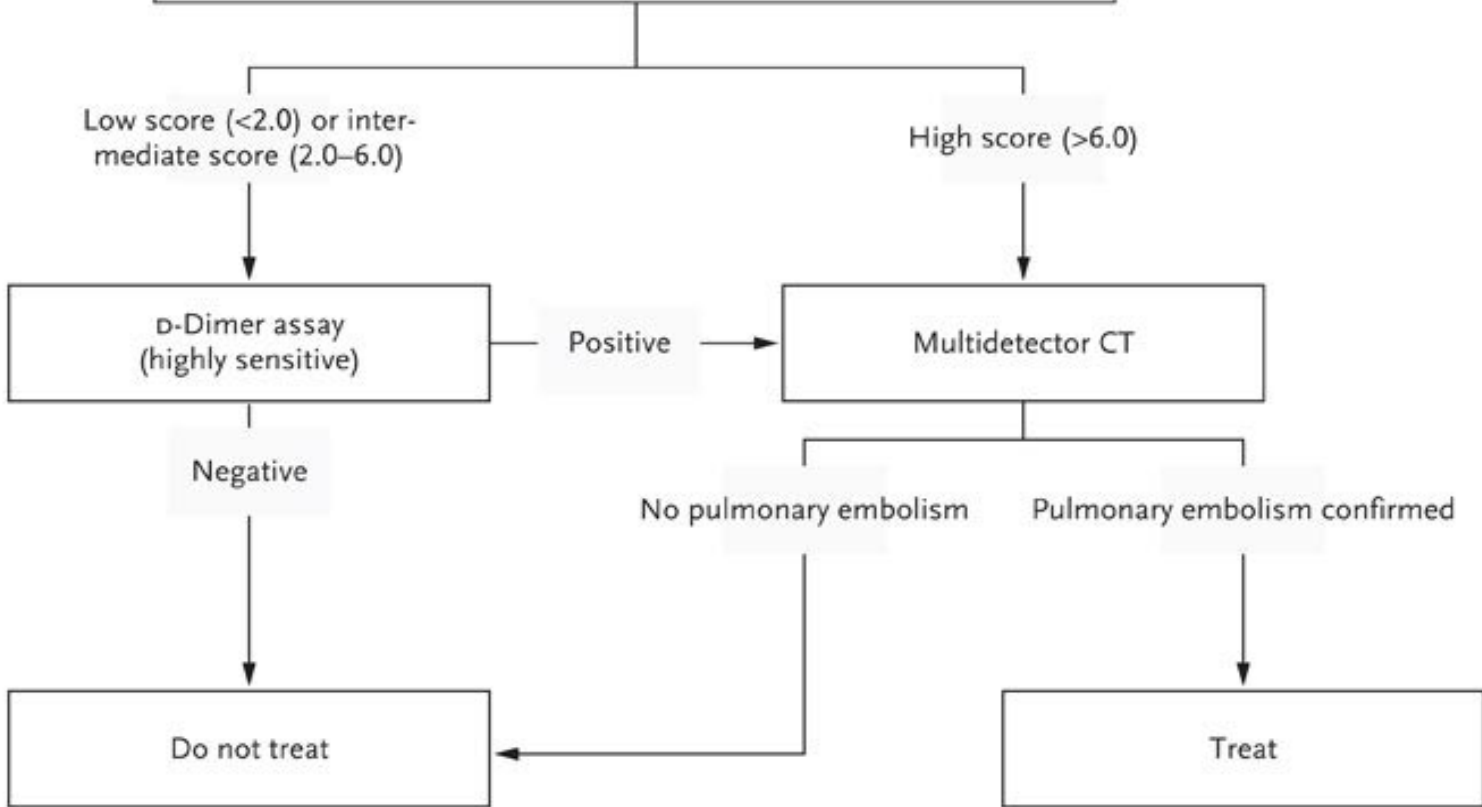
- Easy to collect clinical parameters
- Easy to interpret clinical parameters
- Most patients with suspicion of PE are seen by **inexperienced/junior doctors**

Survival among patients admitted on weekdays and weekends



Aujesky, D. et al. *Circulation* 2009;119:962-968

Clinical Probability Score	
Symptoms and signs of deep-vein thrombosis	3.0
Heart rate >100 beats/min	1.5
Recent immobilization or surgery (≤ 4 wk)	1.5
Previous deep-vein thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Cancer	1.0
Pulmonary embolism more likely than alternative diagnosis	3.0



Reagent (1): D-dimer buffer (1)

Reagent (2): D-dimer latex test solution (2)

Sample 12 μL
Reagent (1) 100 μL

Reagent (2) 100 μL

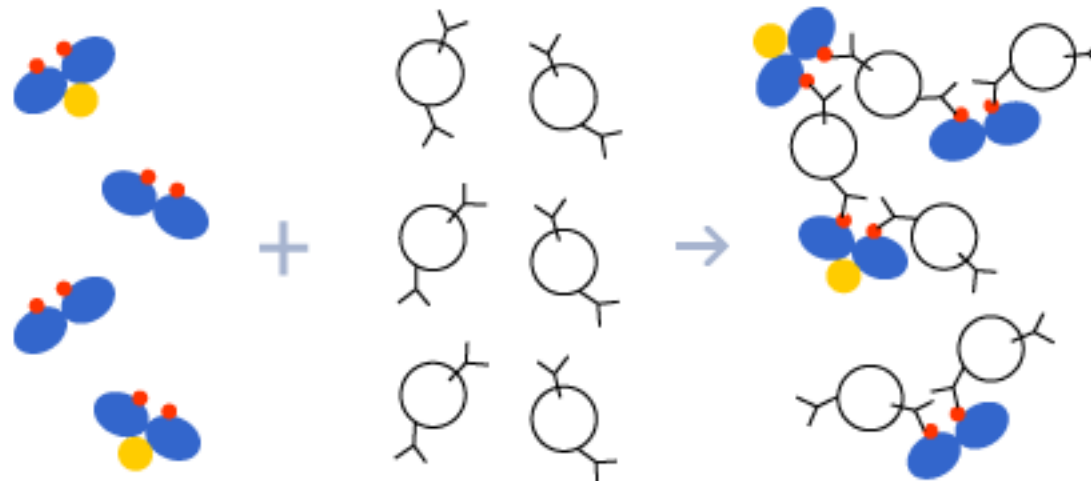
37°C, 5 minutes

Measurement*

Measurement*

*Difference of absorbance
between 570 nm and 800 nm

(Hitachi 7170 type)



D-dimer (various fractions)

Anti-human D-dimer mouse
Monoclonal antibody sensitization latex

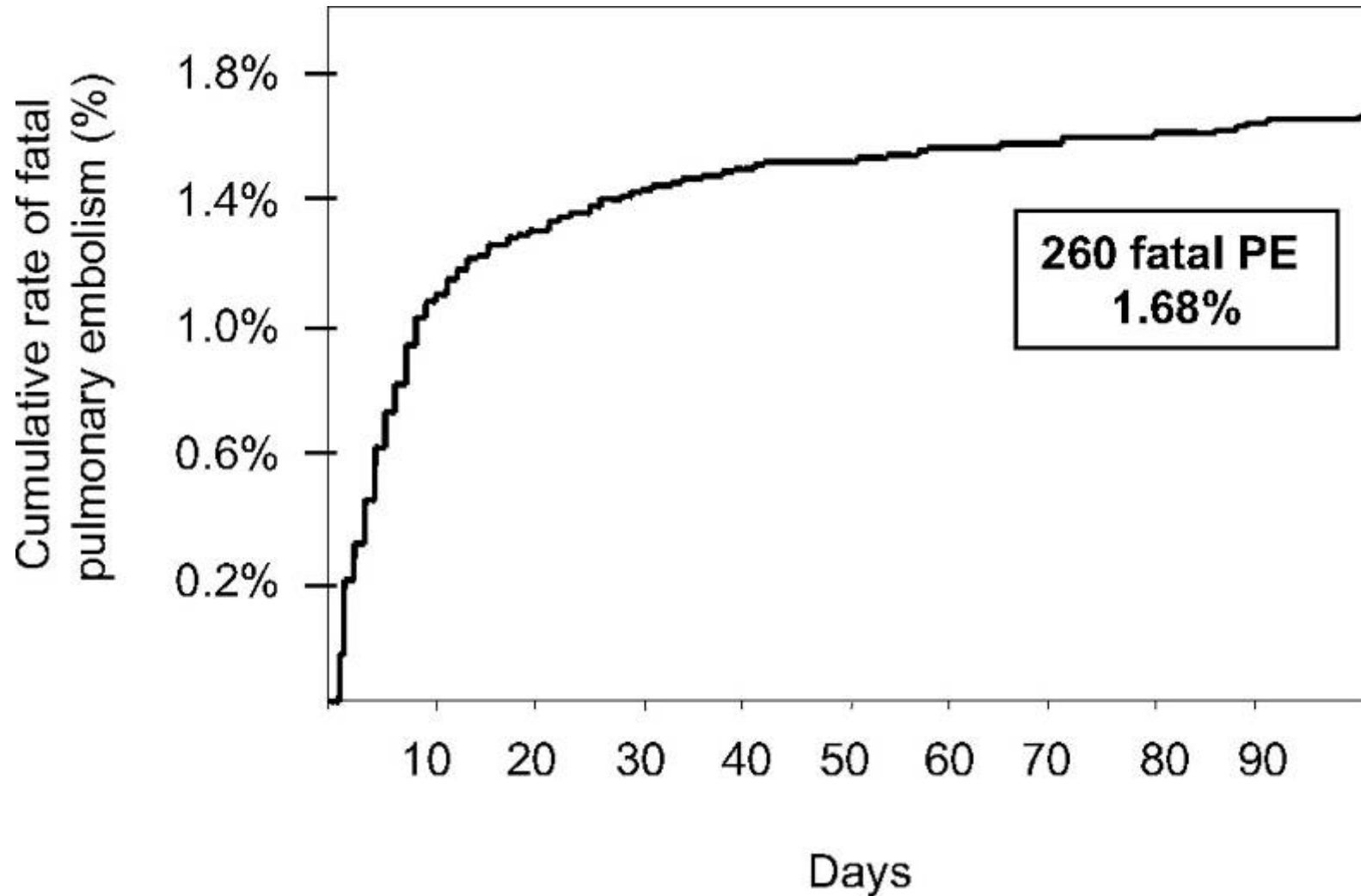




Pulmonary Embolism

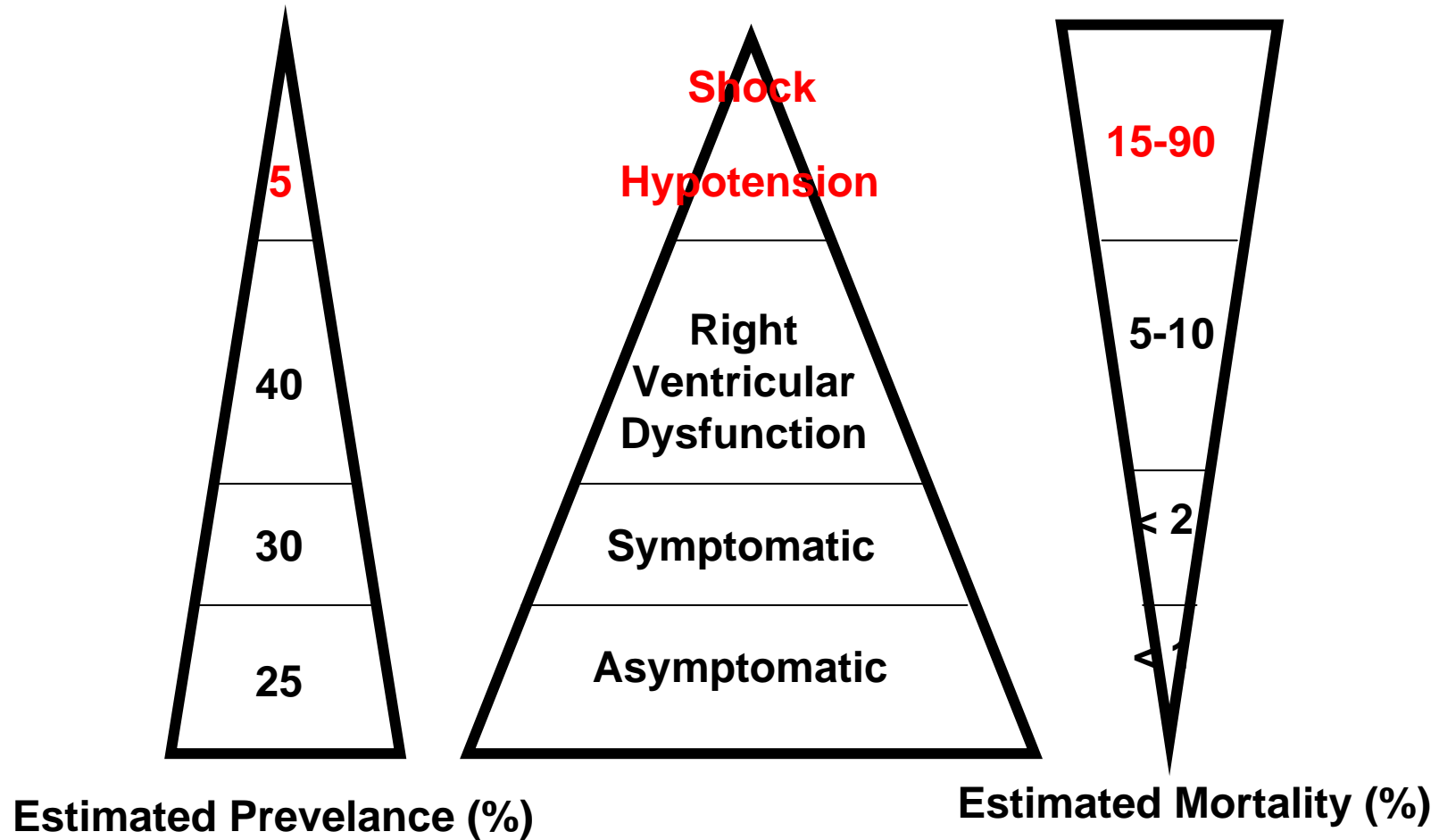
- *PIOPED* study 1990
 - 1 out of 3 patients
- *CHRISTOPHER* study 2006
 - 1 out of 5 patients

Cumulative rate of fatal PE



Laporte et al. *Circulation* 2008;117:1711-1716

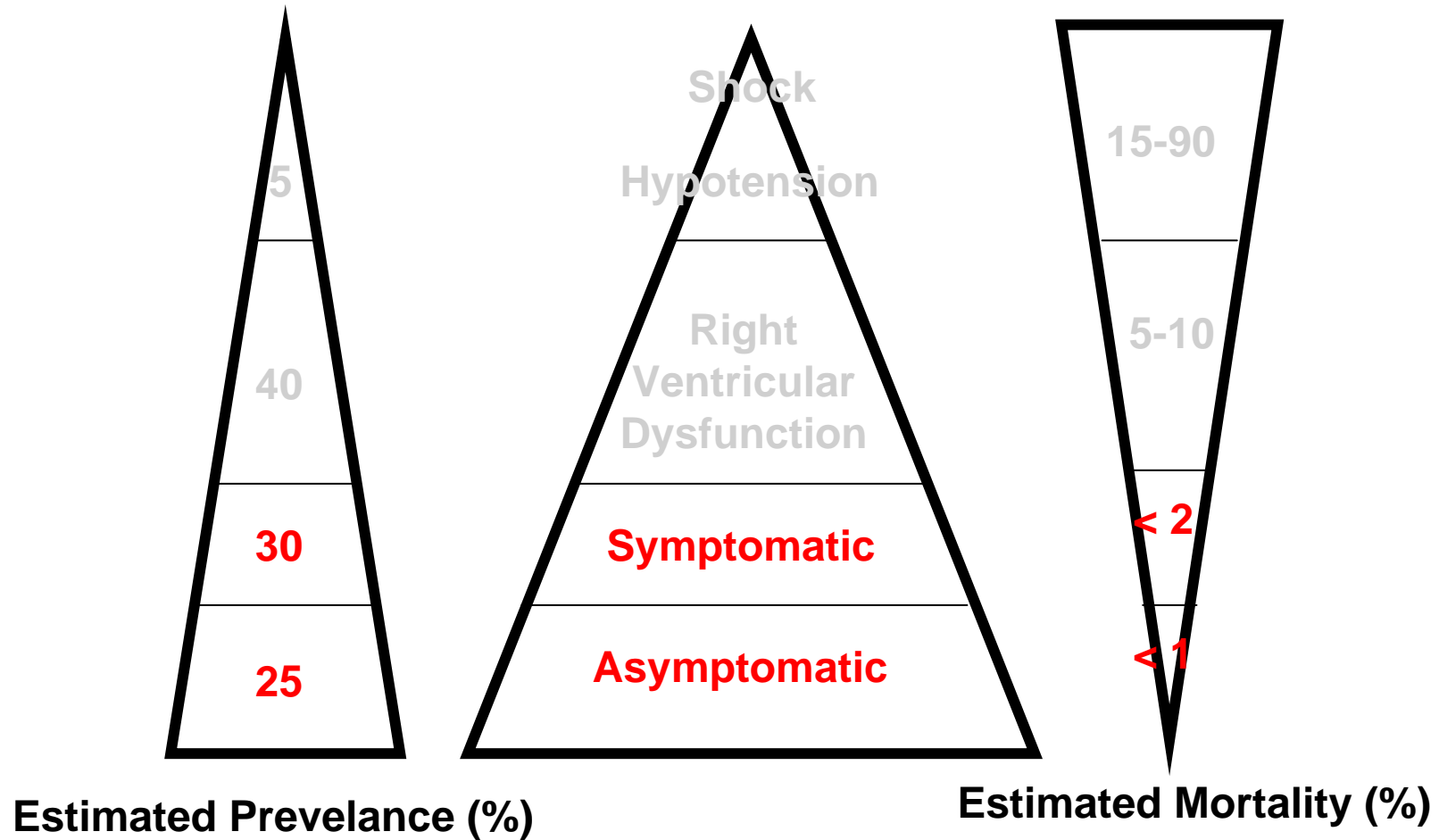
PE Clinical features



Short term prognosis PE

- † < 2 % in hemodynamically stable, non-massive PE
- † 15% in massive PE with shock (5 % total)
- † 95 % in patients with cardiorespiratory arrest
- Inpatient mortality directly related to thromboembolic event
- **RISK STRATIFICATION**

PE Clinical features



Clinical Decision Rules

- Easy to collect clinical parameters
- Easy to interpret clinical parameters
- Most patients with suspicion of PE are seen by **inexperienced/junior doctors**

Pulmonary Embolism Severity Index

N = 15 531 patients

Predictors	Points assigned
<i>Demographic characteristics</i>	
Age, per year	Age, in years
Male gender	+ 10
<i>Comorbid illnesses</i>	
Cancer	+30
Heart failure	+10
Chronic Lung disease	+10
<i>Clinical findings</i>	
Pulse \geq 110/min	+20
SBP < 100 mm Hg	+20
Respiratory rate \geq 30/min	+20
Temperature < 36 °C	+20
Altered mental status	+60
Art oxygen saturation < 90 %	+20

Pulmonary Embolism Severity Index

N = 15 531 patients

Class	Points assigned
I	66-85
II	86-105
III	106-125
IV	106-125
V	> 125

Low Risk: Class I and II: 30-day all cause mortality of 0.9-2.6 %

High Risk: Class V: 30-day all cause mortality of 24.5 %

Aujesky et al. Am J Respi Crit Care Med 2005;172:1041-6

Aujesky et al. Eur Heart J 2006;27:476-81

Pulmonary Embolism Severity Index

N = 15 531 patients

Dichotomized as LOW (classes I-II) vs
HIGH (classes III-V)

Sensitivity > 90 %

Negative predictive value 98-100 %

Positive predictive value < 15 %

Aujesky et al. Eur Heart J 2006;27:476-81
Jimenez et al. Chest 2007;132:24-30

Geneva Risk Score

N = 296 patients

Predictors	Adjusted odds ratio (95 % CI)	Points assigned
Cancer	9.5 (3.5-25.8)	+ 2
Heart failure	2.6 (1.0-6.6)	+ 1
Previous DVT	2.8 (1.0-7.6)	+ 1
Systolic BP < 100 mm Hg	15.1 (2.4-96.4)	+ 2
PaO ₂ < 8 kPa	2.6 (1.0-6.5)	+ 1
Presence of DVT on CUS	3.8 (1.3-11.4)	+ 1

Low Risk \leq 2 points

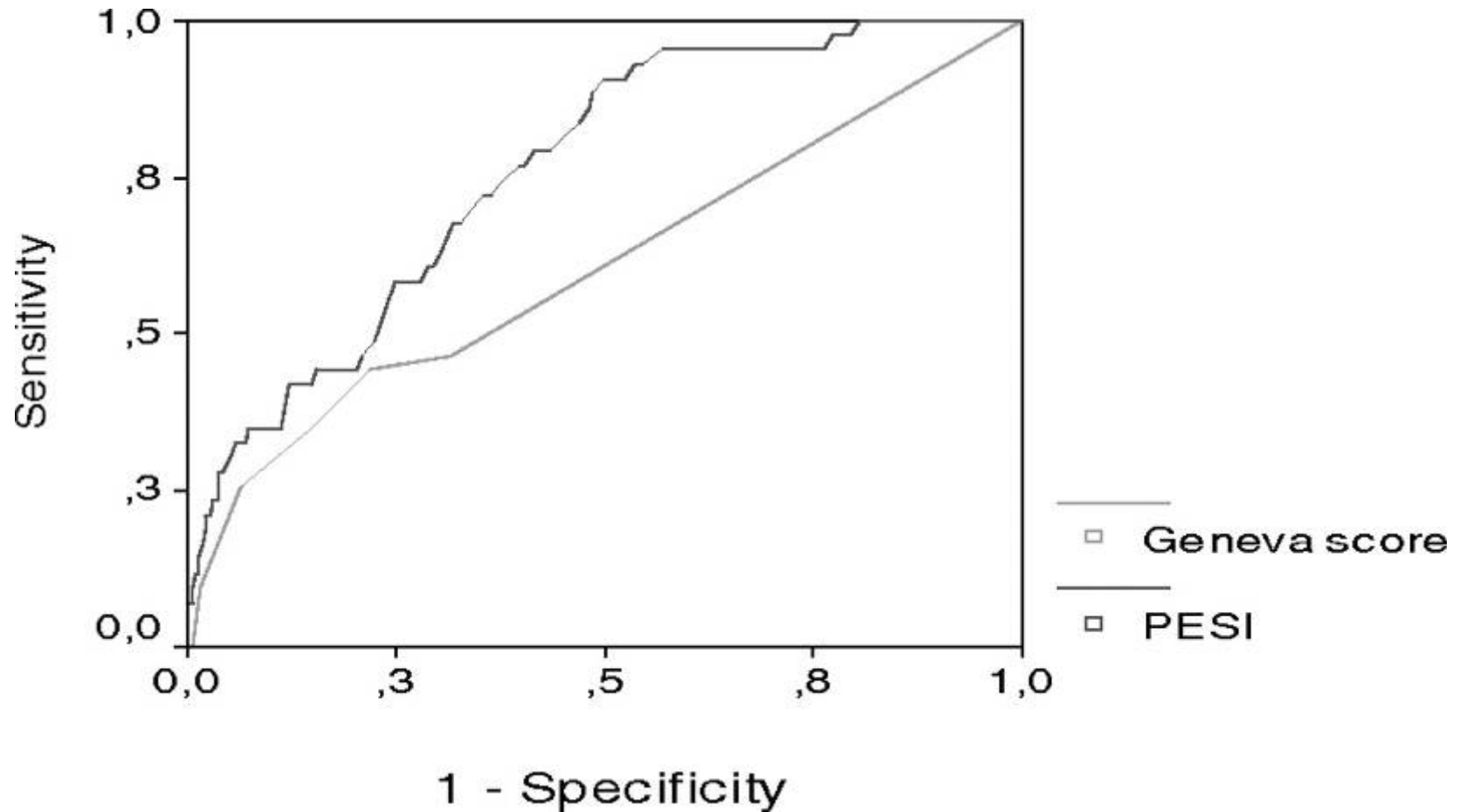
Direct Comparison of PESI with Geneva Score

- N = 599 patients with PE
- Primary outcome was all-cause mortality at 30 days
- Secondary outcome was non-fatal recurrent VTE or non-fatal bleeding
- PESI low 36 % (41 %)
- Geneva low 84 % (67 %) $p < 0.0001$
- 30-day mortality: PESI 0.9 % (0.3-2.2)
- Geneva 5.6 % (3.6-7.6) $p <$

0.0001

Jimenez et al. Chest 2007;132:24-30

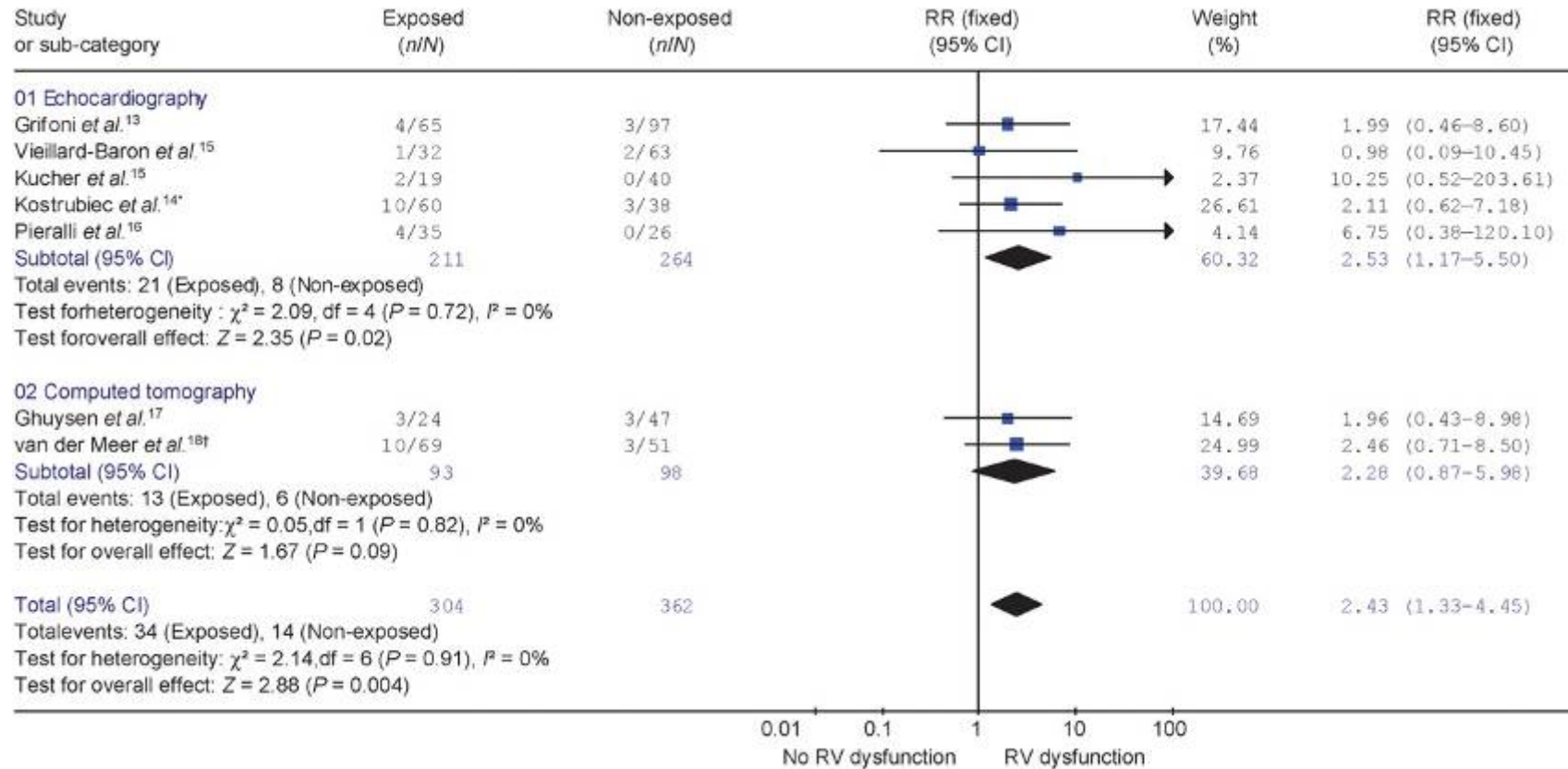
ROC curves for 30-day mortality for the PESI and the Geneva prediction rule in this validation cohort.



Jiménez D et al. Chest 2007;132:24-30



Imaging



Sanchez, O. et al. Eur Heart J 2008 29:1569-1577

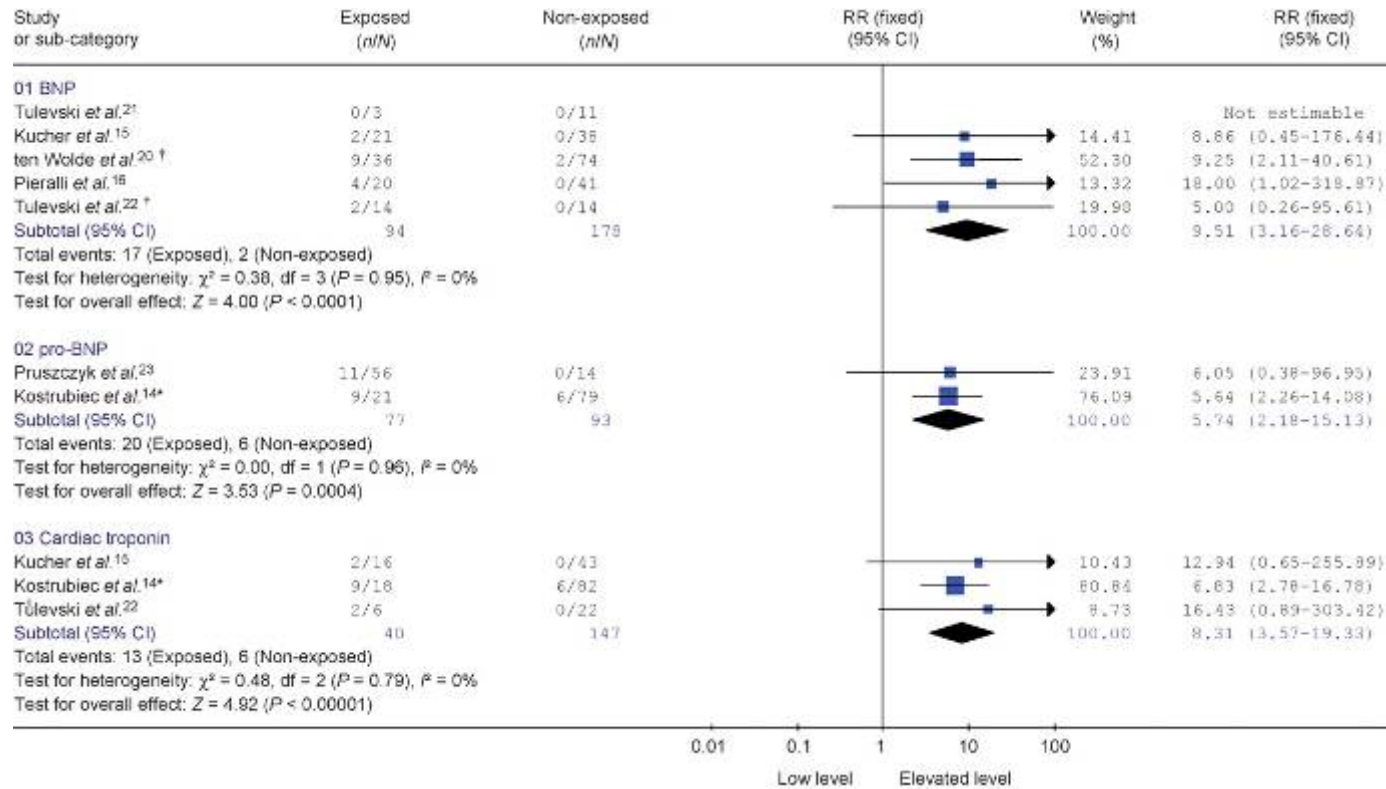
Echocardiography

In hemodynamically stable patients with PE:

- 44 % RV dysfunction
- Patients RVD + † 10 %
 RVD - † 3 %
- RVD significantly associated with mortality
 RR 2.5 (1.2-5.5)
 Sensitivity 70 %
 PPV 58 %
 NPV 60 %

No prospective trials to prove that patients with normal right ventricular function can be treated as out-patients

Cardiac Biomarkers



Sanchez, O. et al. Eur Heart J 2008 29:1569-1577

Cardiac Biomarkers

- **Troponin:** development of RV microinfarcts

Meta-analysis of 20 studies

- 31 % elevated troponin levels
- Patients Troponin = † 3.7 %
 Troponin > † 19.7 %
- Significantly associated with mortality
 - OR 5.2 (3.3-8.4)
 - Sensitivity 81 %
 - NPV 73 %
 - PPV 75 %

Becattini et al. *Circulation* 2007;116:427-33

Sanchez et al. *Eur Heart J* 2008;29:1569-77

Cardiac Biomarkers

- **Brain natriuretic peptides:** BNP/NT-pro-BNP, released in response to cardiomyocyte stretch

Meta-analysis of 13 studies

- 51 % elevated BNP/NT-pro-BNP levels

- Patients BNP = † 1.7 %

 BNP > † 16.8 %

- Significantly associated with mortality

Sensitivity 88-93 %

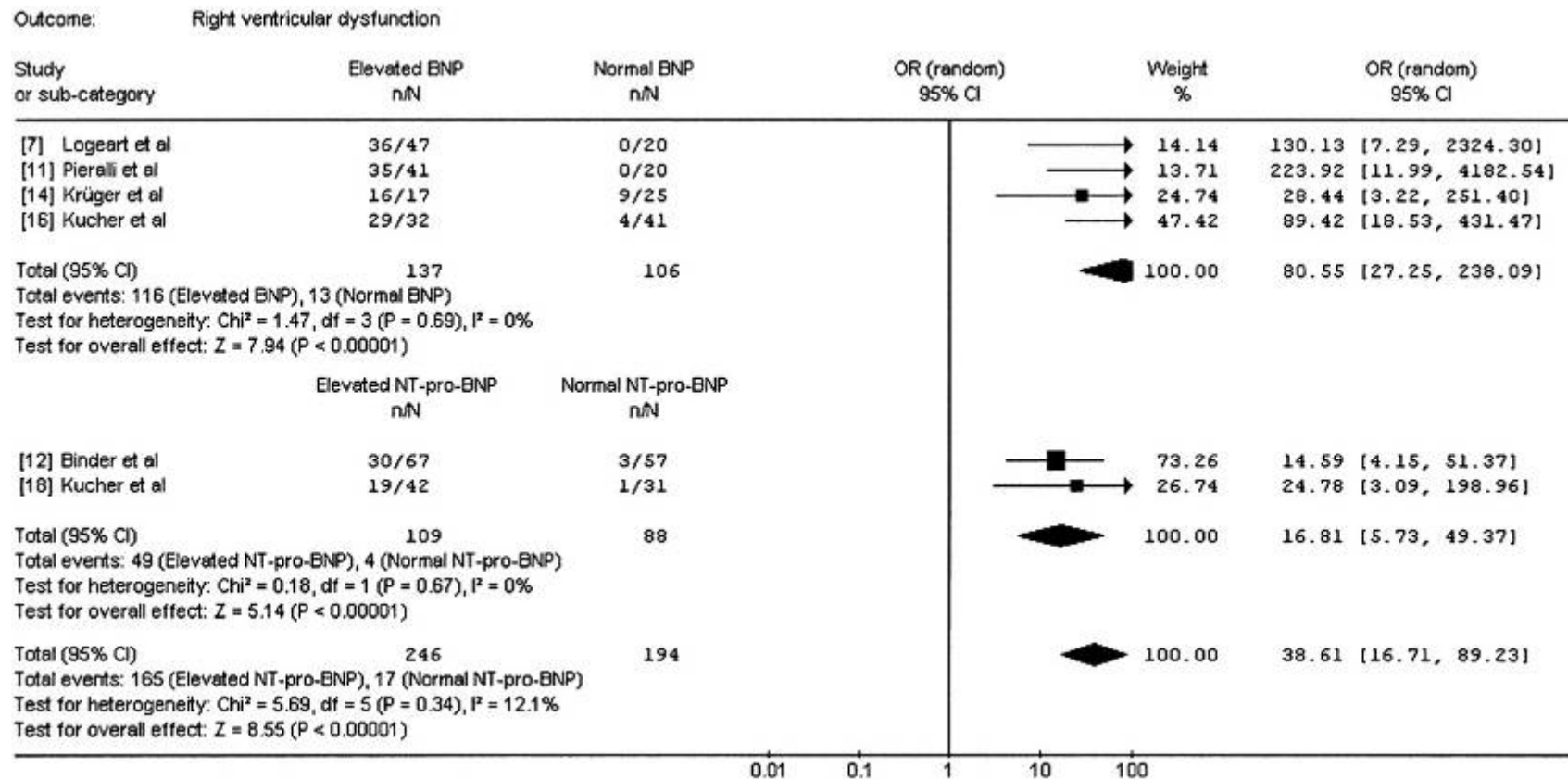
NPV 76-81 %

PPV 63-67 %

Klok et al. Am J Respir Crit Care Med 2008;178:425-30

Sanchez et al. Eur Haert J 2008;29:1569-77

OR for RVD on ECHO based on elevated (NT-pro) BNP



Klok et al. Am J Crit Care Med 2008;178:425

Pooled diagnostic indexes for echocardiography, CT, BNP, pro-BNP, and cardiac troponin

	Echocardiography	Computed tomography	BNP	Pro-BNP	Cardiac troponin
Sensitivity (%) (95% CI)	70 (46–86)	65 (35–85)	88 (65–96)	93 (14–100)	81 (23–100)
Specificity (%) (95% CI)	57 (47–66)	56 (39–71)	70 (64–75)	58 (14–92)	84 (77–90)
Negative predictive value (%) (95% CI)	60 (55–65)	58 (51–65)	76 (73–79)	81 (65–97)	73 (68–78)

Sanchez, O. et al. Eur Heart J 2008 29:1569

Imaging and Biomarkers usefull?

- CT and Echo findings of RVD are more likely to identify higher-risk than lower-risk patients
- Evidence on prognostic usefulness of CT-based pulmonary artery obstruction assays is non-conclusive
- For biomarkers:
 - Lack of test standardization
 - Absence of clinical studies demonstrating positive effect on patient care

Stratification of Risk of Death

Table 3. Stratification of Risk of Death Associated with Pulmonary Embolism and Severity-Adjusted Treatment.*

Early Risk of Death	Risk Factor			Recommended Treatment
	Shock or Hypotension (on Clinical Examination)	Right Ventricular Dysfunction (on Echocardiography or Multidetector CT)	Myocardial Injury (on Cardiac Troponin Testing)	
High	Present	Present†	NA‡	Unfractionated heparin plus thrombolysis or embolectomy
Non-high				
Intermediate§	Absent	Present	Present	Low-molecular-weight heparin or fondaparinux; as a rule, no early thrombolysis; monitor clinical status and right ventricular function
	Absent	Present	Absent	
	Absent	Absent	Present	
Low	Absent	Absent	Absent	Low-molecular-weight heparin or fondaparinux; consider outpatient treatment

* Adapted with modifications from the 2008 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology.¹³ NA denotes not applicable.

† If RV function is normal on echocardiography, or if a CT scan shows no RV dilatation in a patient with hemodynamic compromise and clinically suspected pulmonary embolism, an alternative diagnosis should be sought.

‡ Troponin test results do not influence risk assessment or treatment in hemodynamically compromised patients with acute pulmonary embolism.

§ Although it has been suggested that normotensive patients with both RV dysfunction and myocardial injury have a higher risk of death than those with only one of these risk factors, there is currently no definitive proof that they should receive more aggressive treatment.

Konstantinides S. N Engl J Med 2008;359:2804-2813



Conclusions

- Low risk patients may be treated in a **out-patient** setting
- **Pulmonary Embolism Severity Index** (PESI) is at this moment the best choice
- Absence of clinical studies demonstrating positive effect of **RV dysfunction/dilatation or elevated biomarkers** on patient care
- **NEW STUDIES**

HOME study

- Hemodynamically stable
- NT-proBNP < 500 pg/ml
- Primary endpoint: 10 days mortality
- Secondary endpoints: readmission rate, patient satisfaction and SAE
- 5 teaching hospitals in the Netherlands

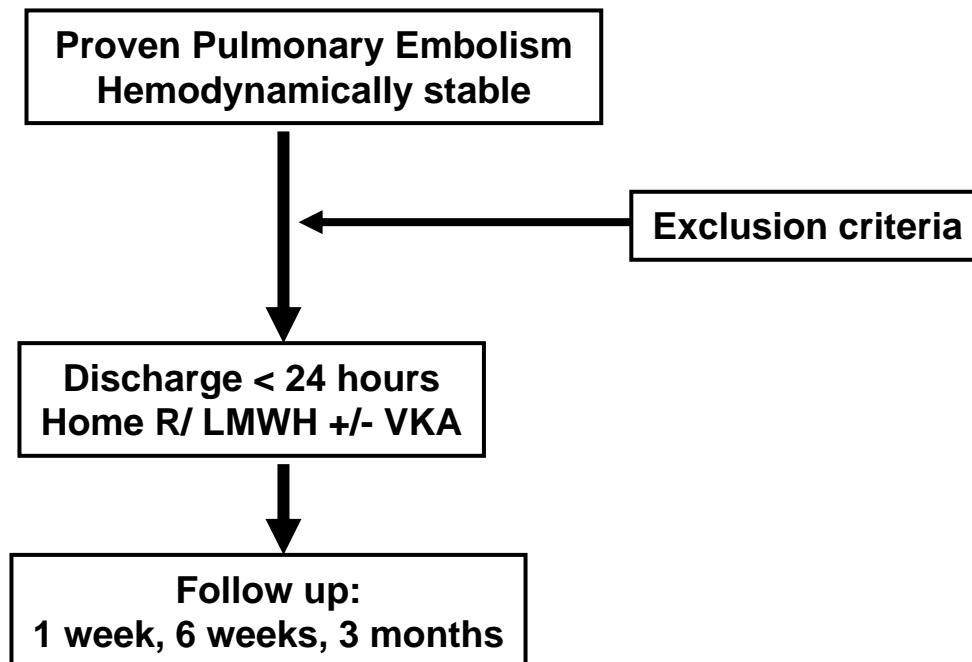
HOME study

- 351 patients with PE screened
- 152 patients included
 - 105 pt (70%) returned directly to home
 - 47 pt (30%) were discharged < 24 hours
- No death, VTE recurrence, major bleeding after 10 and 90 days follow up
- 7 pts readmitted:
 - 4 pts: illness unrelated to PE
 - 2 pts: anxiety and chest pain
 - 1 pt : dyspnoea and O2 sat 88%

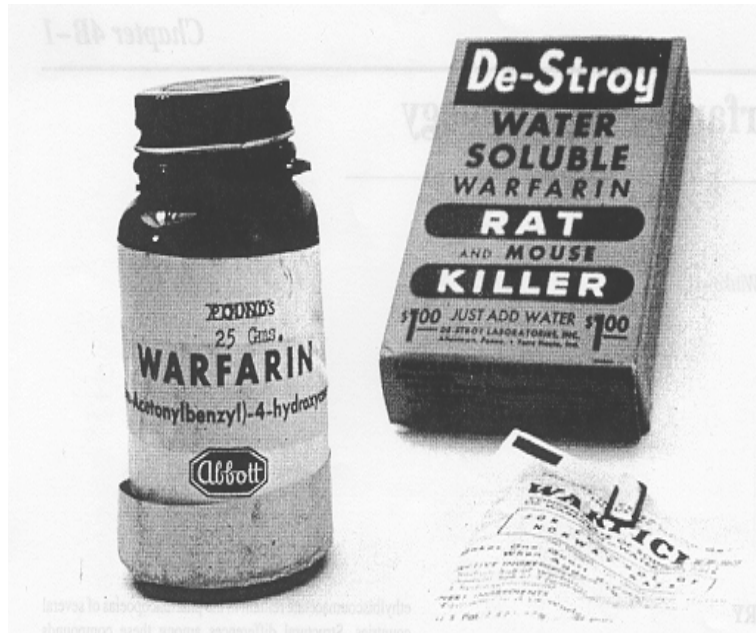
HESTIA study

prospective cohort investigation

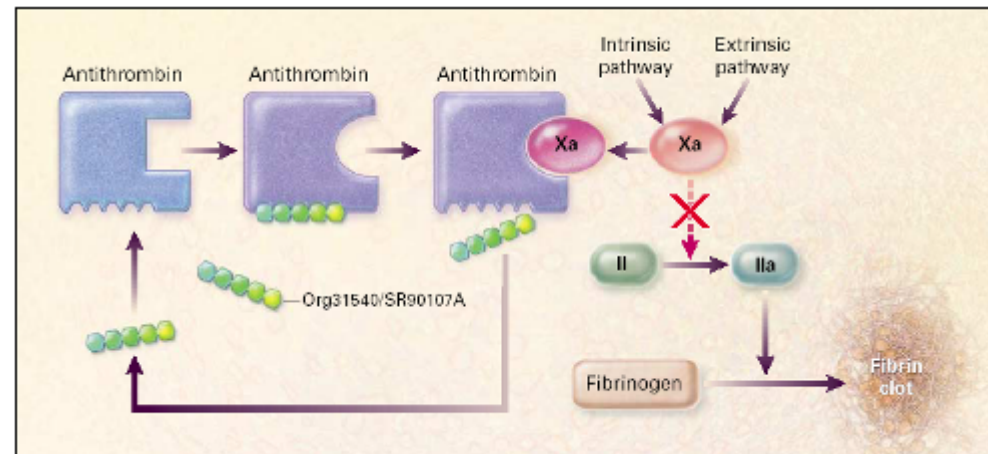
To investigate the efficacy and safety of home treatment of patients with **hemodynamically stable PE**



Treatment

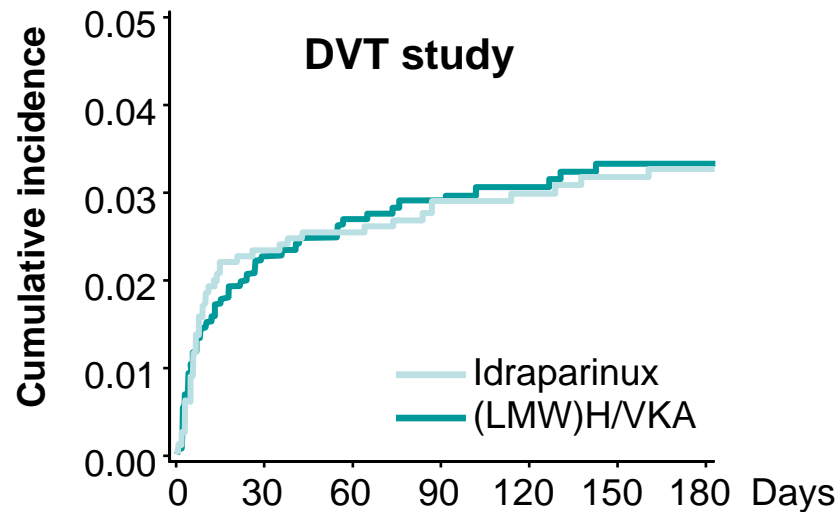


LMWH
Vitamin K antagonists



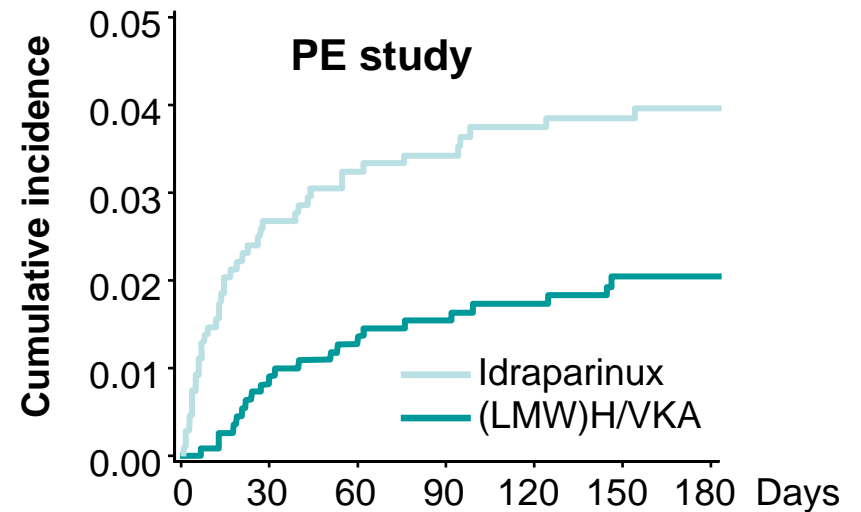
Factor Xa inhibitors
Thrombin inhibitors

Efficacy of Idraparinux for DVT vs PE



Number at risk:

Idraparinux	1,452	1,408	1,395	1,381	1,050	1,043	1,034
(LMW)H/VKA	1,452	1,409	1,389	1,378	1,067	1,057	1,054



Number at risk:

Idraparinux	1,095	1,050	1,029	1,016	906	904	897
(LMW)H/VKA	1,120	1,098	1,083	1,074	965	954	950

The van Gogh Investigators. *New Engl J Med* 2007;357:1094-1104