



UMC Utrecht  
Julius Center

# Individualized prediction in pulmonary embolism; novel concepts and future ideas.

*Geert-Jan Geersing, MD PhD*

*Family Medicine specialist*

# Our thrombosis research

ARTICLE

## The Wells Rule Does Not Adequately Rule Out Deep Venous Thrombosis in Primary Care Patients

Ruud Oudega, MD; Arno W. Hoes, MD, PhD; and Karel G.M. Moons, PhD

Since then:

→ 50+ papers

→ Guidelines primary care

R.Oudega, et.al. Ann Int Med 2005;143:100-107



# And beyond ...

## DIAGNOSIS, PROGNOSIS AND TREATMENT?!



SVT

distal DVT

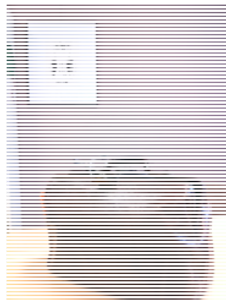
proximal DVT

atrial fib

PE

AF + ...

Mild thrombosis



Severe thrombosis



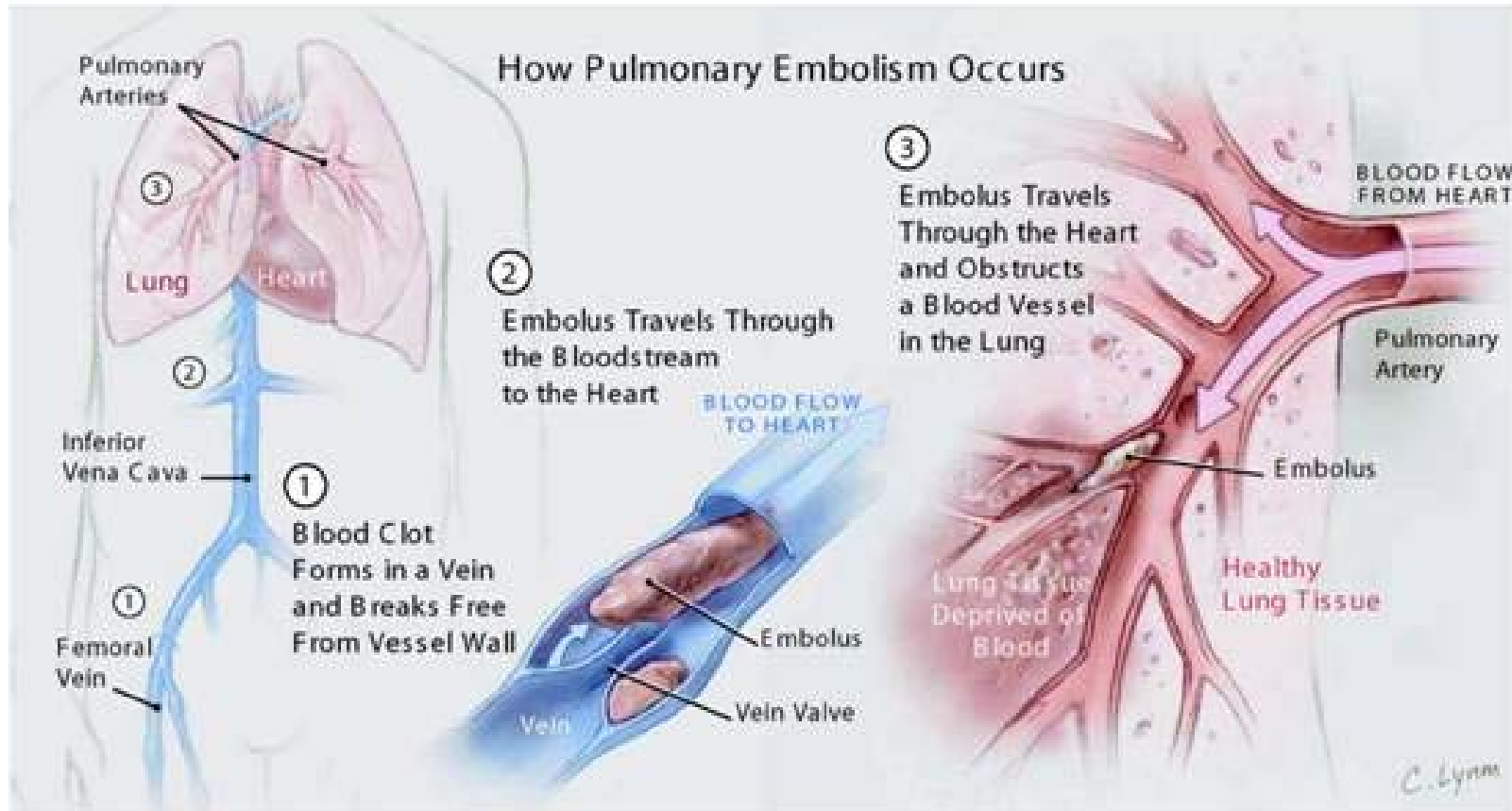
# Talk of today

Management of (acute) pulmonary embolism

→ Primary Care



# Pulmonary embolism



Europe: 500.000+ deaths per year



# Our patient of today

Home visit:

82 years

Heavy smoker

COPD, HT



Shortness of breath

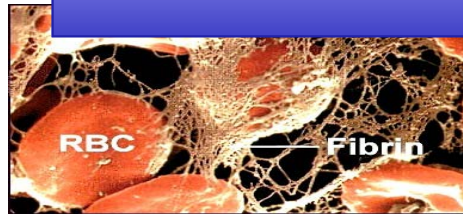
‘not like it usually is, doc ...’



# Our patient of today



**Suspicion**



**Testing**

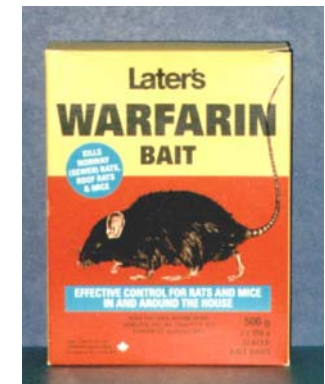


**Reference**



**to diagnosis**

**Rx**



# Suspected of PE...



COPD exacerbation?

Heart failure?


“not like usually...” → PE...





# Misdiagnosis is common

**Table 1. Most Frequently Missed Diagnoses  
Among 583 Physician-Reported Cases of Diagnostic Error**

<b>Diagnosis</b>	<b>No. (%)</b>
 Pulmonary embolism	26 (4.5)
Drug reaction or overdose	26 (4.5)
Lung cancer	23 (3.9)
Colorectal cancer	19 (3.3)
Acute coronary syndrome	18 (3.1)

G.Schiff, et.al. Arch Intern Med 2009;169(20):1881-7



# Not a new problem

## **Clinical Features**

Unless doctors and nurses become more “thrombosis-minded” venous thrombosis will too often remain undiagnosed until it has spread to the femoral vein and produced an obvious swelling of the leg or sudden death through pulmonary embolism has occurred. The key to effective treatment is early diagnosis while the process is limited to the calf.



# What do we know

Common; estimates 30-50%

- Higher age/comorbidity
- Non-specific symptoms
- May increase mortality

J. Alonso-Martinez, et.al. Eur.J.Int.Med. 2010;278-82

J. Torres-Macho, et.al. Am.J.Emerg.Med. 2013;1646-50



# More research needed

- Determinants in primary care
- Consequences
- Evaluate awareness strategies

*Journal of Thrombosis and Haemostasis*, 2: 1244–1246

## COMMENTARY

### Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients

G. LE GAL and H. BOUNAMEAUX

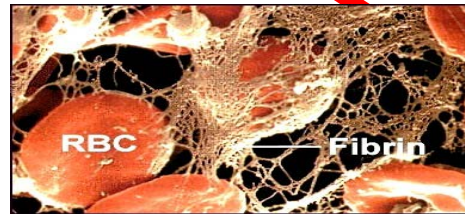
*Division of Angiology and Hemostasis, Department of Internal Medicine, Geneva University Hospitals, Geneva, Switzerland*



# Our patient of today



**Suspicion**

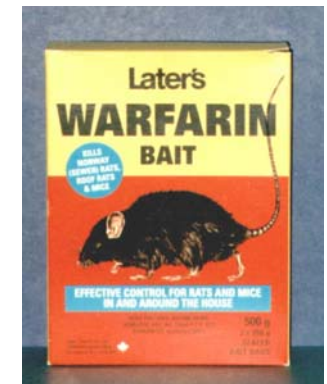


**Testing**



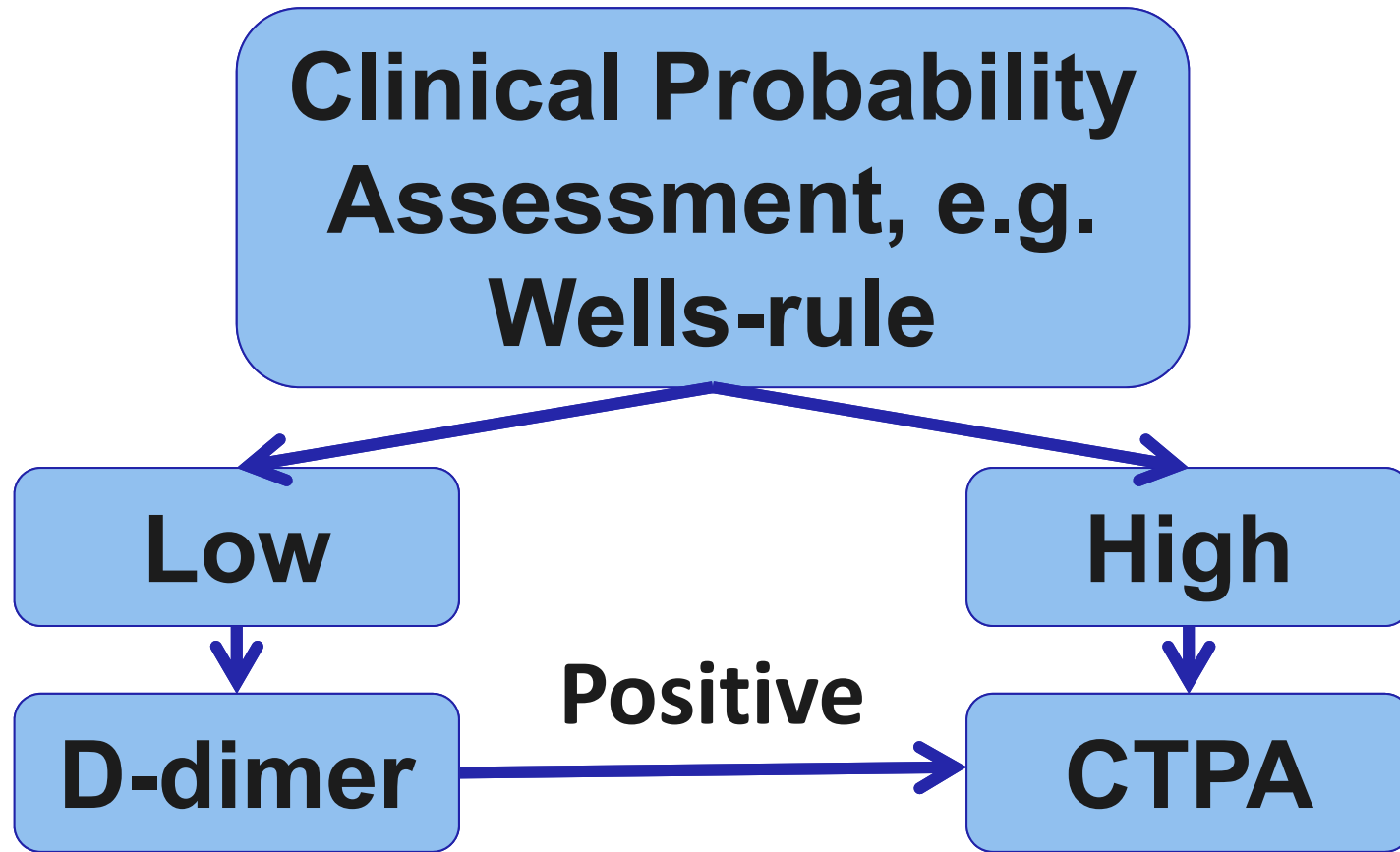
**Reference**

**Rx**



**Pathway to diagnosis**

# Testing



**Negative:  
rule-out**



# Good news: Wells-rule

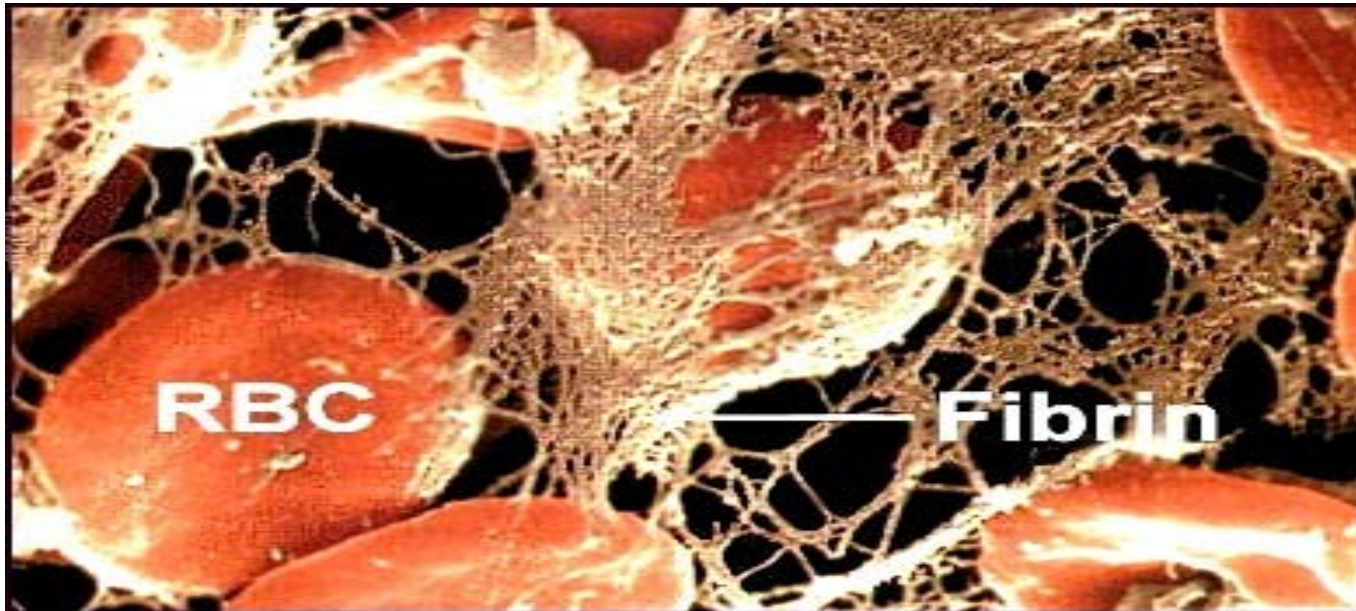
Variable	Points
Signs of DVT	3.0
PE most likely	3.0
Heart rate > 100	1.5
Immobilization	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Score  $\leq 4$   
defines  
low risk

Score  $>4$   
defines  
high risk



# Add D-dimer



Good for rule-out  
Yet, low specificity





# More good news

**Table 2. Failure Rate and Efficiency of Gestalt and the Clinical Decision Rules When Combined With Either Quantitative or Qualitative D-Dimer Testing\***

Gestalt or Rule	Studies, <i>n</i>	Patients, <i>n</i>	Prevalence of Pulmonary Embolism, %	Failure Rate (95% CI), %	Efficiency (95% CI), %
<b>All</b>	23	24 384	14.0	0.7 (0.5–1.0)	35 (30–41)
<b>Quantitative D-dimer testing</b>					
All	12	10 941	21.1	0.4 (0.2–0.7)	27 (22–34)
Wells, cutoff value $\leq 4$	4	5320	19.2	0.5 (0.2–0.9)	39 (31–47)
Geneva	2	1224	24.4	0.0 (0.0–1.3)	21 (14–31)
Simplified Geneva	2	1856	23.3	0.3 (0.0–1.7)	23 (15–33)
<b>Qualitative D-dimer testing</b>					
All	11	13 443	8.3	1.0 (0.8–1.3)	45 (39–52)
Gestalt	2	3495	4.4	0.7 (0.4–1.2)	52 (40–64)
<b>Wells</b>					
Cutoff value $\leq 4$	3	2337	16.0	1.7 (1.0–2.8)	42 (32–52)
Cutoff value $< 2$	5	5309	9.0	0.9 (0.6–1.5)	40 (33–48)

\* Separate results shown only when  $\geq 2$  studies were available.

W. Lucassen, et.al. Ann Int Med 2011; 155:448-60



# Also true for primary care

BMJ

BMJ 2012;345:e6564 doi: 10.1136/bmj.e6564 (Published 4 October 2012)



RESEARCH

## Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study

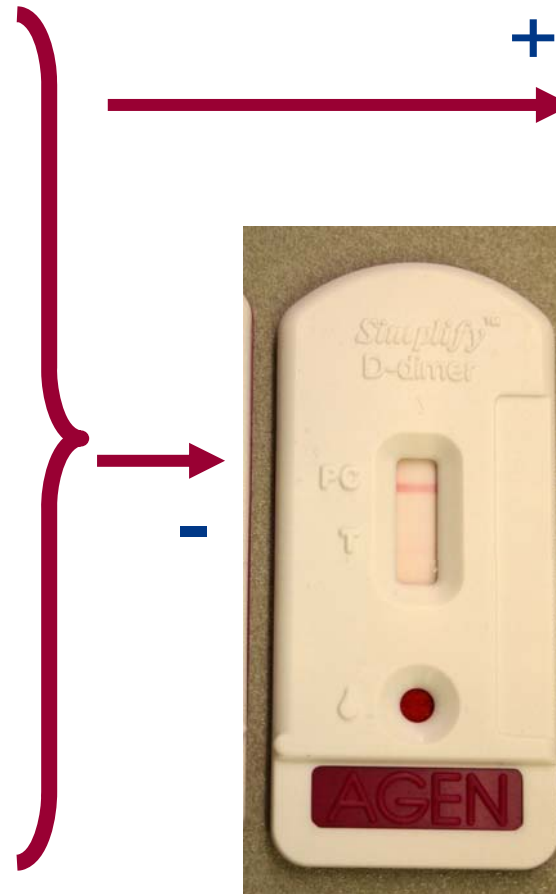
OPEN ACCESS

Geert-Jan Geersing *general practitioner*<sup>1</sup>, Petra M G Erkens *clinical epidemiologist*<sup>2</sup>, Wim A M Lucassen *general practitioner*<sup>3</sup>, Harry R Büller *professor of medicine*<sup>4</sup>, Hugo ten Cate *professor of medicine*<sup>5</sup>, Arno W Hoes *professor of general practice*<sup>1</sup>, Karel G M Moons *professor of clinical epidemiology*<sup>1</sup>, Martin H Prins *professor of clinical epidemiology*<sup>2</sup>, Ruud Oudega *general practitioner*<sup>1</sup>, Henk C P M van Weert *professor of general practice*<sup>3</sup>, Henri E J H Stoffers *general practitioner*<sup>2</sup>



# Point-of-care D-dimer

Clearview Simplify®, Inverness Medical, Bedford, UK

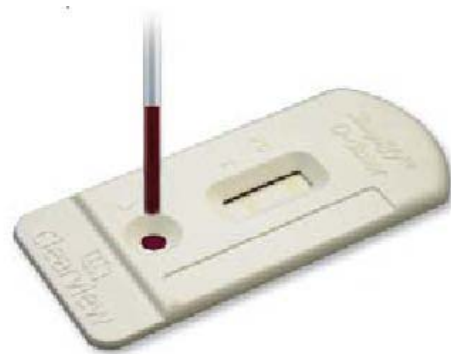


# More POC tests

Sensitivity lower (around 90%)

Good NPV combined with CDR

Cost-effective



G.J. Geersing, et.al. BMJ; 2009:b2990

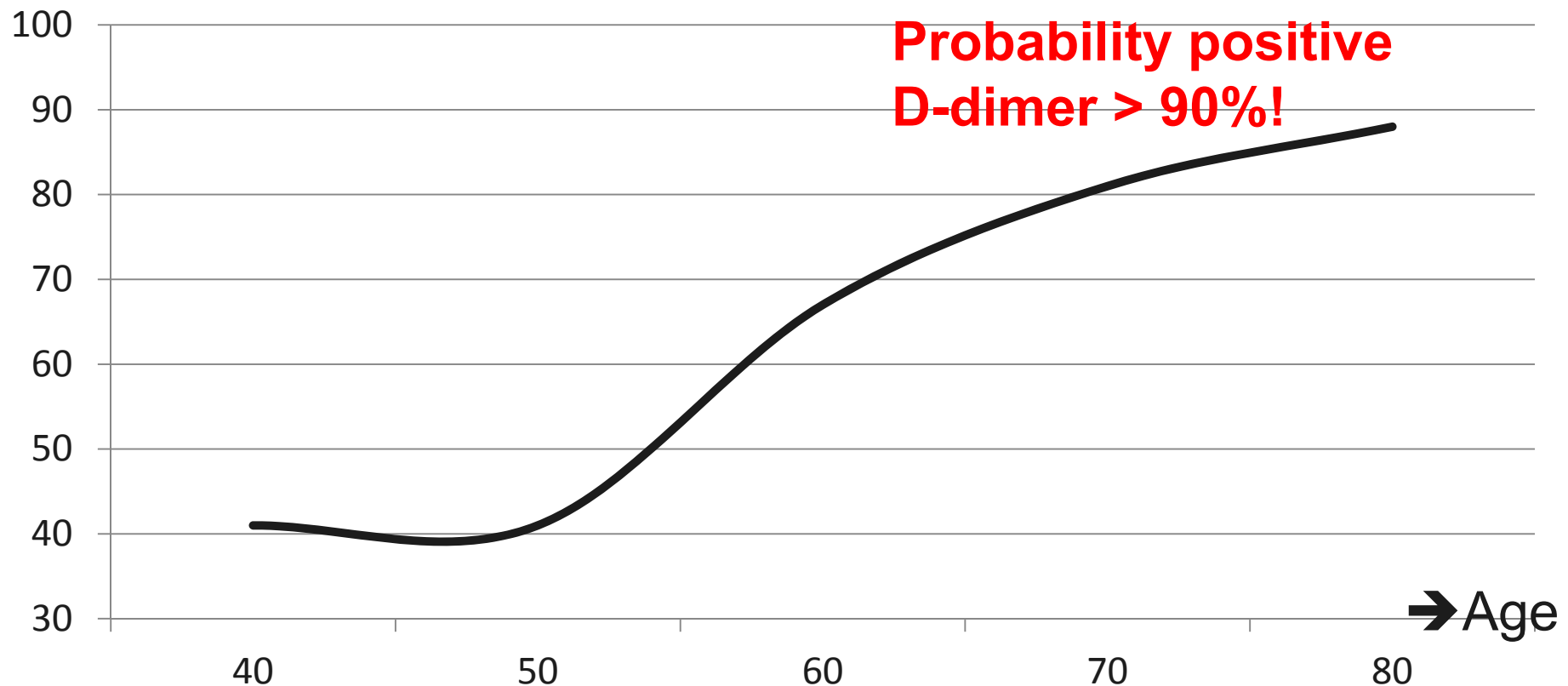
J. Hendriksen, et.al. Expert Rev Mol Diagn; 2015:125-36



# Back to our patient



↑ % D-dimer positive



H. Schouten, et.al. BMJ; 2013:346; f2492

R. Douma, et.al. BMJ; 2010:340; c1475





# Decisions to Withhold Diagnostic Investigations in Nursing Home Patients with a Clinical Suspicion of Venous Thromboembolism

Henrike J. Schouten<sup>1,2\*</sup>, Huiberdina L. Koek<sup>2</sup>, Marije Kruisman-Ebbers<sup>1</sup>, Geert-Jan Geersing<sup>1</sup>, Ruud Oudega<sup>1</sup>, Marijke C. Kars<sup>1</sup>, Karel G. M. Moons<sup>1</sup>, Johannes J. M. van Delden<sup>1</sup>

<sup>1</sup> Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands, <sup>2</sup> Department of Geriatrics, University Medical Center Utrecht, Utrecht, the Netherlands

**423 nursing home patients**  
**322 ‘high risk’**  
**39% of those: not referred**

H. Schouten, et.al. PloS one;2014: e90395



# Mortality non-referred

**126 non-referred:** mean age: 82 years

75% blind initiation of anticoagulants (!)

Mortality at 3 months: 31%

**199 referred:** mean age: 82 years

60% confirmed VTE (!)

Mortality at 3 months: 17%

**adjusted OR mortality 1.99 (1.09-3.62)**



“In many of my years of experience, I have seen so much misery: people going to the hospital and either dying there, tremendously delirious, tied up to the bed, or returning in a condition that makes you say: “Oh my, I wish we had never started this.”



# Interim summary

Getting a suspicion difficult ...

... but if we do:

- Validated prediction rules
- (POC) D-dimer testing
- Often false-positive = frustrating
- Leads to: non-referral in nursing homes



# Better tools needed

Improve “rule-in”

→ (serial) ultrasound testing



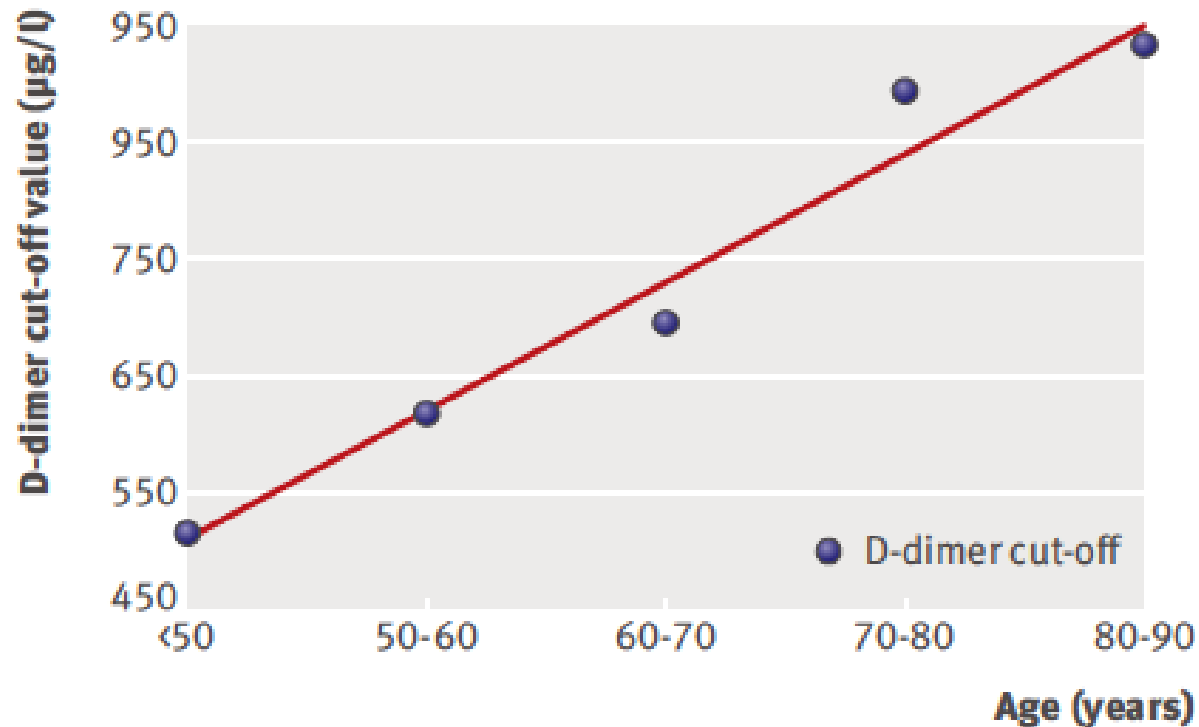
Improve “rule-out”

→ Age-adjusted D-dimer:

→ cut-off = age x 10 if age > 50 years



# Age-adjusted D-dimer



Cut-off:  
Age x 10

Fig 1 | Optimal cut-off values for D-dimer test for pulmonary embolism by age in patients with an unlikely clinical probability of pulmonary embolism (sensitivity set at 100%)

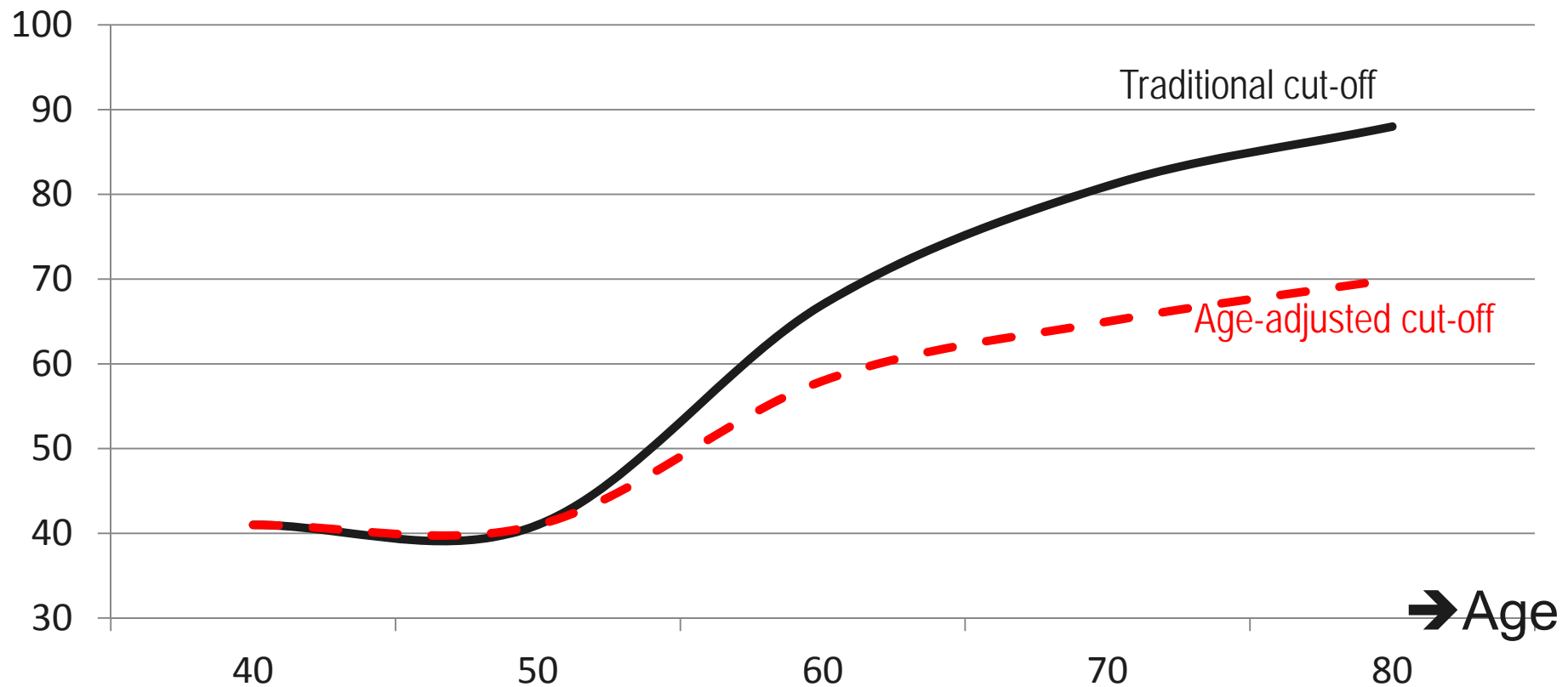
R. Douma, et.al. BMJ; 2010:340; c1475



# Back to our patient



↑ % D-dimer positive



H. Schouten, et.al. BMJ; 2013:346; f2492  
R. Douma, et.al. BMJ; 2010:340; c1475



# Age-adjusted D-dimer

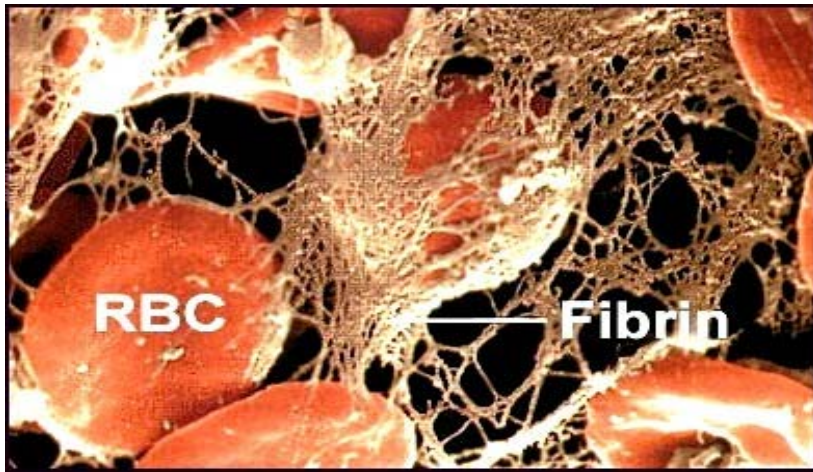
**Fewer false-positives D-dimer**

**Still:**  $\approx 70\%$  positive if age  $> 80$  years

Not incorporated: gender,  
comorbidity, cancer, etc.



# The next step



Personalized  
threshold based  
on age, gender,  
comorbidity,  
frailty, PTP, etc.



# IPD meta-analysis

Database  $\approx$  15.000 patients

Group: Canada-USA-Netherlands-  
Others?

- Advanced updating technique
- Interaction terms into the model
- Multilevel structure
- So aim  $\neq$  “new rule”!



# IPD meta-analysis

Many advantages

- Efficient use of existing data
- Gain in subgroup analyses
- Robust models, multiple validation option

**A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis**

**Thomas P. A. Debray,<sup>a\*†</sup> Karel G. M. Moons,<sup>a</sup> Ikhlaaq Ahmed,<sup>b</sup> Hendrik Koffijberg<sup>a</sup> and Richard David Riley<sup>b</sup>**

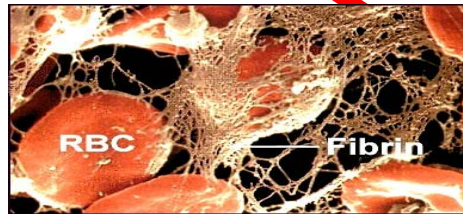




# Our patient of today



**Suspicion**

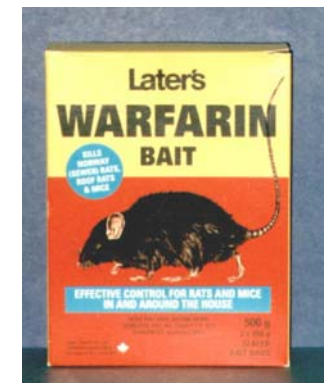


**Testing**



**Reference**

**Rx**



**Pathway to diagnosis**

# CTPA



- High sensitivity
- Easy to do
- Other diagnosis
- ...



# Flipside: Overdiagnosis

PERSPECTIVE

## Overdiagnosis and Overtreatment of Pulmonary Embolism: The Emperor May Have No Clothes

EUGENE D. ROBIN, M.D., F.A.C.P.; Stanford, California

Ann Int Med 1977



# Flipside: Overdiagnosis

SPECIAL ARTICLE

LESS IS MORE

## The Diagnosis and Treatment of Pulmonary Embolism

*A Metaphor for Medicine in the Evidence-Based Medicine Era*

*Vinay Prasad, MD; Jason Rho, MD; Adam Cifu, MD*

- Finding small clots
- Rx treatment benefit?

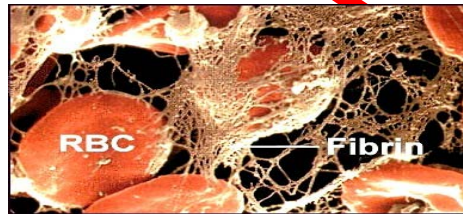
V. Prasad, et.al. Arch Int Med; 2012:172(12) 955-8



# Our patient of today



**Suspicion**



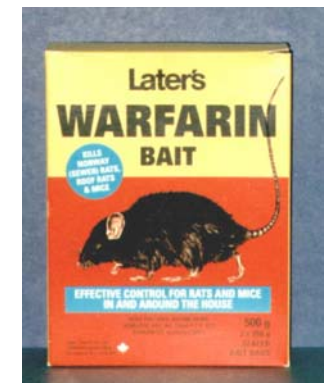
**Testing**



**Reference**

**Pathway to diagnosis**

**Rx**



# Treatment duration

Risk-benefit ratio:

Risk of recurrent event

**versus**

Risk of bleeding

Both for recurrence and bleeding →

Individualized Prediction models



# What we know

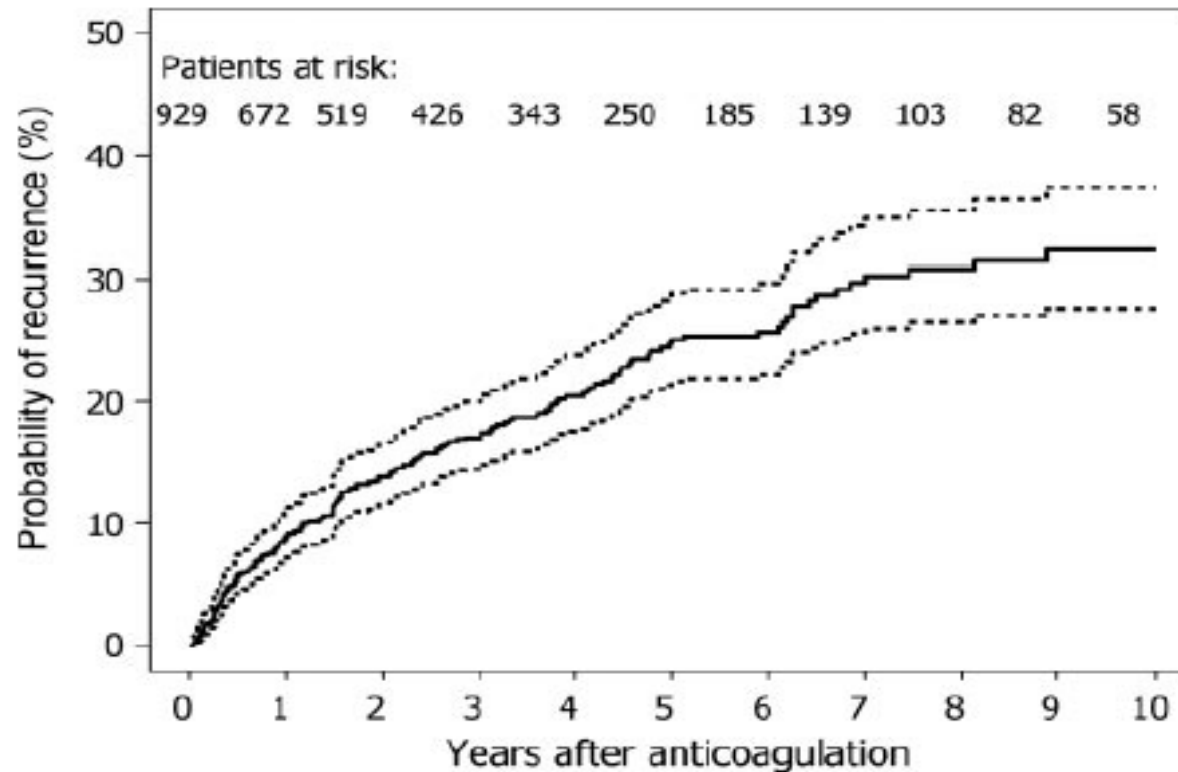
**Provoked:** low risk of recurrence

**Unprovoked:** ↑ recurrences, yet heterogeneous

**Bleeding:** ↑ in elderly, HT, history of bleeding, etc.



# Risk of recurrence



**Figure 1.** Overall cumulative recurrence rate in 929 patients with a first unprovoked VTE estimated by Kaplan-Meier analysis, with 95% CIs (dotted lines).

S. Eichinger, et.al. Circulation; 2010:121: 1630-6





# Research agenda

Several validation and impact studies ongoing (e.g. VISTA, VALID, REVERSE)

Validation bleeding risk scores

**Future challenge:** incorporate bleeding and recurrence in one (bivariate?) model



# Take home messages

PE challenging disease



Suspicion → Testing → Reference → Rx

→ In all steps: Prediction = personalized medicine

(one size does not fit all)



# Thanks for your attention

On behalf of my colleagues:

Prof. K.G.M. Moons, PhD

Prof. A.W. Hoes, MD PhD

F.H. Rutten, MD PhD

R. Oudega, MD PhD

J.M.T. Hendriksen, MD PhD

S. Van Doorn, MD

A.E.C. Kingma, MD

C. Van den Dries, MD

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