Age-dependent cut-off values for D-dimer testing

Fred Haas 08-11-2012
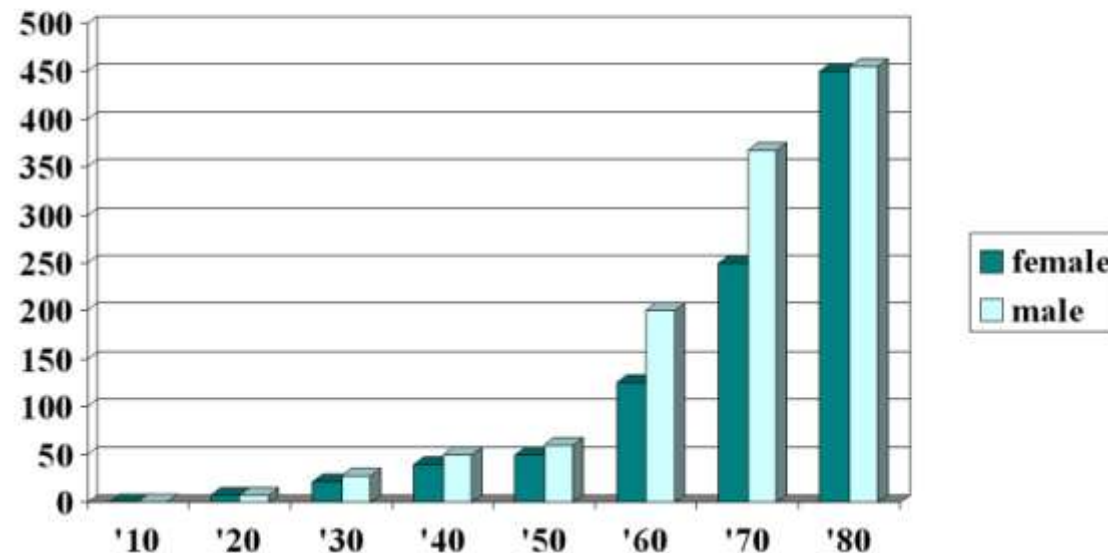
Why special interest for D-dimer in elderly?

❏ **Prevalence DVT / PE in elderly?**

   - Chance for recurrence and / or bleeding

❏ **Comparison performance D-dimer assays related to age**

   - Sensitivity and specificity

❏ **What is the "reference" value?**

   - Use of a variable cut-off value related to age

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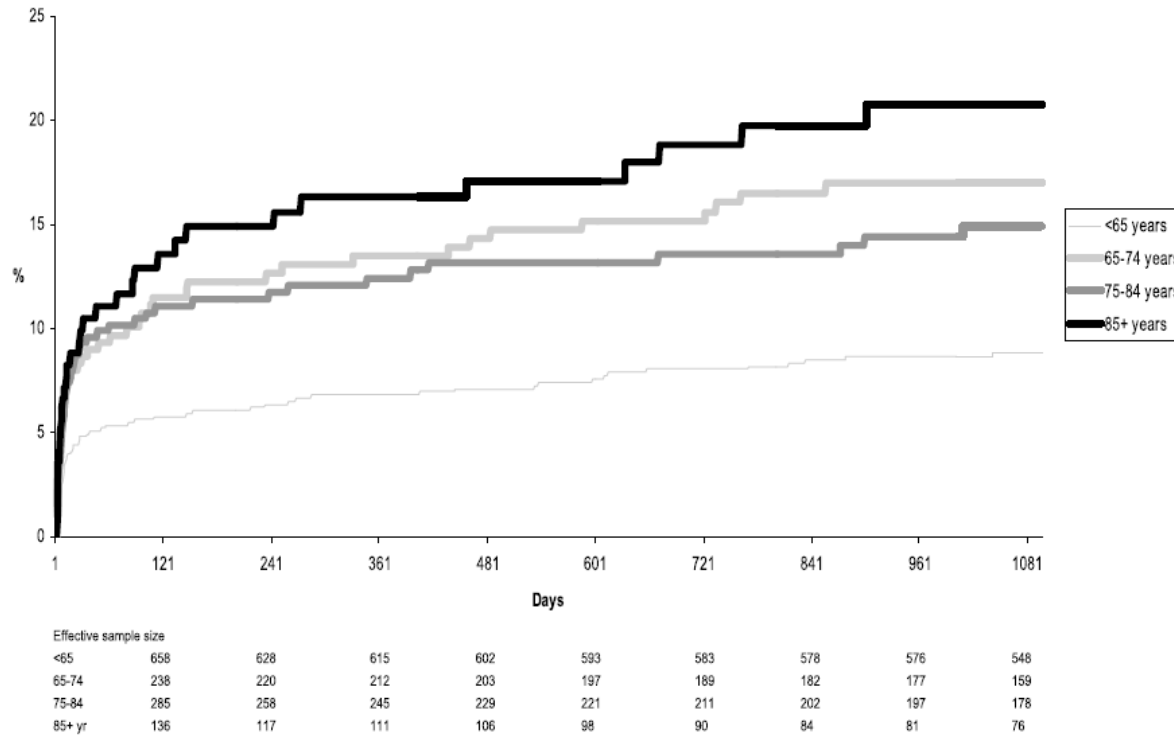ST ANTONIUS

Relation VTE, age and gender

Age Adjusted VTE (per 100,000) pop

From Ennis 2009

Relation VTE and age
cumulative rate of major bleeding episodes stratified by age
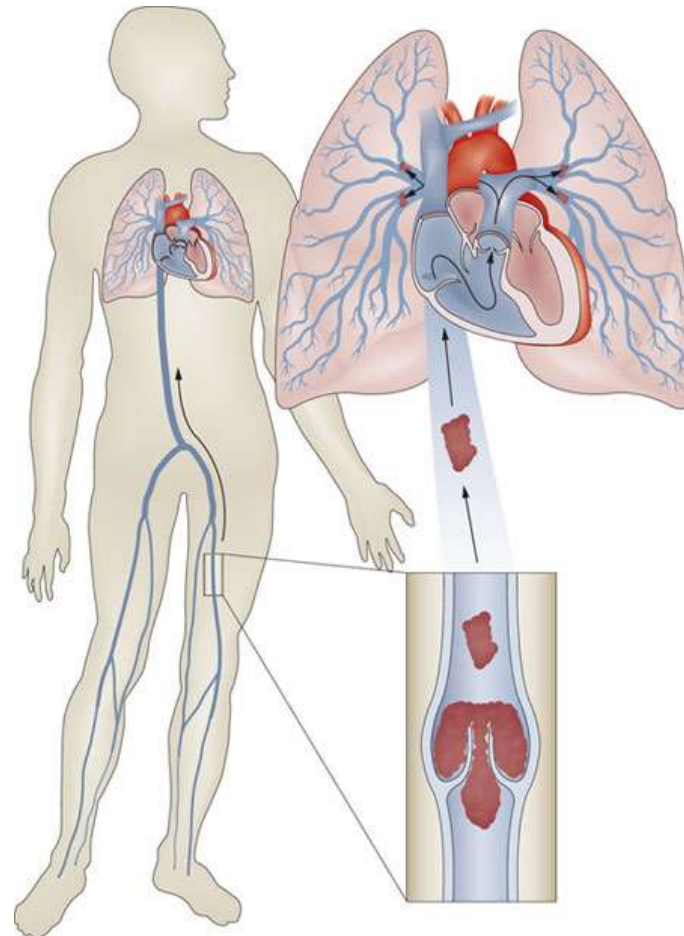

Spencer TH 2008

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DVT

PE

DVT en PE

~ 90% of PE's orginate in lower extremity DVT

~ 50% of proximale DVT embolize to lung

~ 20% of calf vein DVT embolize to proximale veins

~ only 10% cause PE

Diagnosis DVT / PE

International / national guidelines:

➢ **D-dimer (funtion of rule out!)**

➢ **Clinical decision rule**

➢ **Imaging**

Simplified scheme elevated D-dimer

➢ **Aorta dissection**

➢ **Bleeding** (trauma)

➢ **Hart, liver and kidney disease** (ACS, AF, LV aneurysm)

➢ **Inflammation**

➢ **Malignancy**

➢ **Preeclampsia**

➢ **Thrombosis**
  - ➢ Venous (DVT, PE)
  - ➢ Arterial (MI, stroke, PAD)
  - ➢ Microvasculair (DIC)
  - ➢ Intravascular (because of "strange body")

➢ **False positive** (age, cigarette smoking, pregnancy, race)

Clinical probability or clinical decision rule (CDR)

Most used clinical score is the Wells score

- **Wells Score**

- **Wells Score, simplified**

Alternative clinical scores

- **Revised Geneva Score**

- **Revised Geneva Score, simplified**

- **Charlotte rule**
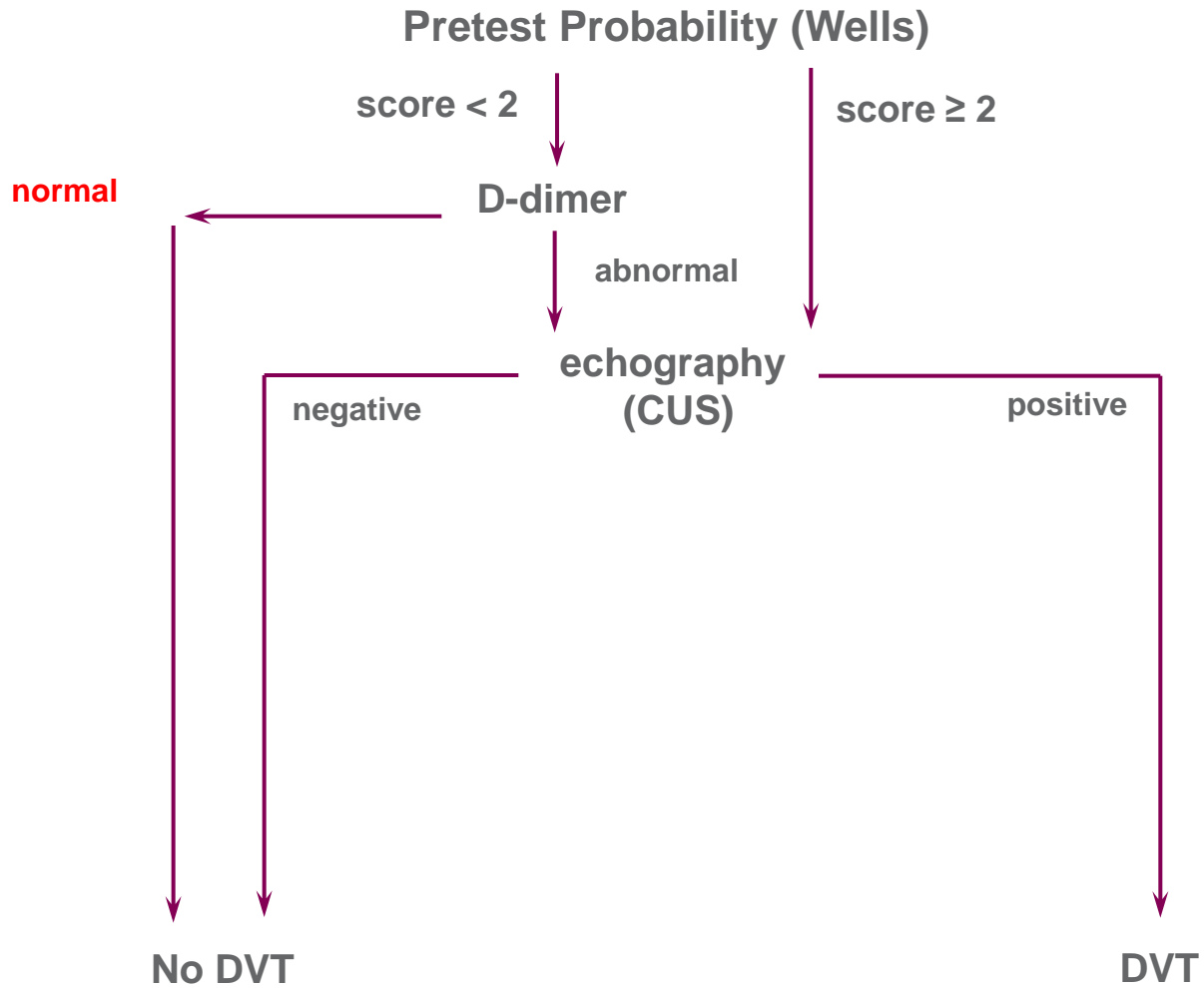
- **Pulmonary Embolism Severity Index (PESI)**

Oudega ("Utrecht") Score only for primary care

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CDR for DVT (level 1)

Level 1 CDR for DVT diagnosis: the dichotomised Wells' score for DVT [11].

Clinical characteristics	Points
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (nonvaricose)	+1
Previously documented deep-vein thrombosis	+1
Alternative diagnosis at least as likely as deep-vein thrombosis	−2

Total score	Clinical probability	Prevalence of DVT
<2 points	DVT unlikely	5.5% (95%CI: 3.8–7.6%)
≥2 points	DVT likely	27.9% (95%CI: 23.9–31.8%)

Algorithm suspicion DVT

Pretest Probability (Wells)

score < 2   score ≥ 2

normal ← **D-dimer**

abnormal

echography (CUS)
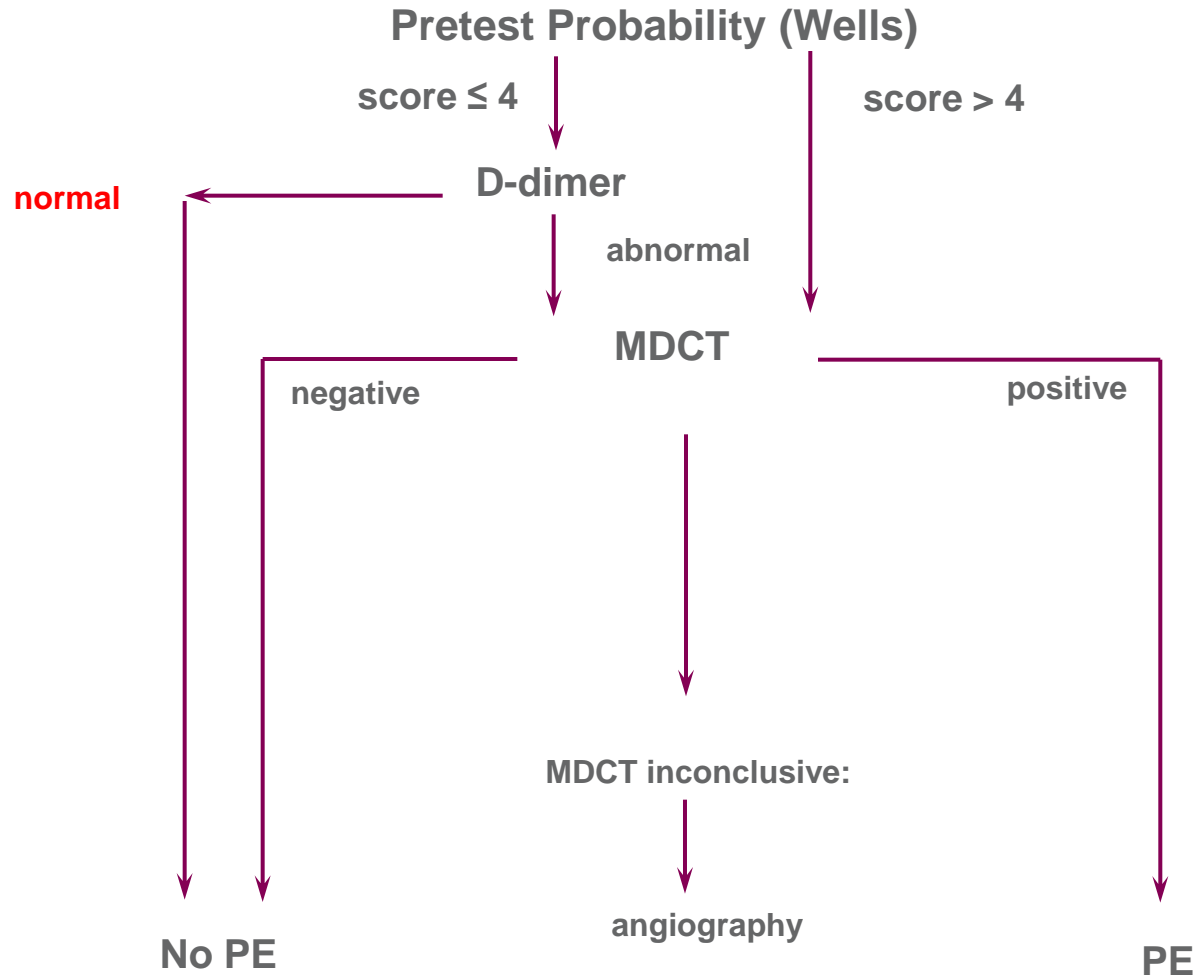
negative   positive

No DVT   **DVT**

CDR rules for PE (level 1)

Level 1 CDRs for PE.

Wells' score		Revised Geneva score		Charlotte rule	
Active cancer	+1	Age >65 years	+1	Age >50 years	+1
Hemoptysis	+1	Active cancer	+2	Surgery within one month	+2
History of previous DVT or PE	+1,5	Hemoptysis	+2	Hemoptysis	+2
Heart rate > 100 /min	+1,5	History of previous DVT or PE	+3	Unexplained hypoxemia (SpO2 < 95%)	+3
Surgery or bed rest ≥ 3 days within 1 month	+1,5	Surgery or lower limb fracture within one month	+2	Heart rate > systolic blood pressure	
Clinical signs or symptoms of DVT	+3	Unilateral edema and pain at palpation	+4	Unilateral leg swelling	
No alternative diagnosis as or more likely than PE	+3	Spontaneously reported calf pain	+3		
		Heart rate			
		75–94/min	+3		
		≥95/min	+5		

PTP	Points	PE (%)	PTP	Points	PE (%)	PTP	Points	PE (%)
Low	<2	5.7 (3.7–8.2)	Low	0–3	9.0 (7.6–10.6)	Safe	All of the previous absent	5.9 (3.3–9.3)
Intermediate	2–6	23.2 (18.3–28.4)	Intermediate	4–10	26.2 (24.4–28.0)			
High	>6	49.3 (42.6–56.0)	High	≥11	75.7 (69.0–81.8)	Unsafe	Any of the previous present	22.5 (11.4–36.2)
Unlikely	≤4	8.4 (6.4–10.6)						
Likely	>4	34.4 (29.4–39.7)						

Algorithm suspicion PE

Pretest Probability (Wells)

score ≤ 4 → D-dimer

score > 4

D-dimer → normal

abnormal → MDCT

MDCT: negative → No PE

MDCT: positive → PE

MDCT inconclusive: → angiography

No PE

PESI for PE (level 1)

Level 1 CDR for PE prognosis to determine eligibility for outpatient therapy: the pulmonary embolism severity index (PESI).

Predictors	Points assigned
Demographic characteristics	
Age, per year	Age, in years
Male sex	+10
Co-morbid illnesses	
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Clinical findings	
Pulse ≥110/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/min	+20
Temperature <36 °C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20

Score	Risk class	One month mortality
≤65	I: Very low	0.7–1.7%
66–85	II: Low	2.5–4.0%
86–105	III: Intermediate	5.5–7.6%
106–125	IV: High	9.0–11.9%
>125	V: Very high	22.7–26.4%

Exclusion PE with D-dimer and Wells score
inpatients and outpatients

		Inpatients					Outpatients			
Age group	N	Percentage of pts with a non-high CDR and a low d-dimer	Sensitivity (%)	Specificity (%)	NPV (%)	N	Percentage of pts with a non-high CDR and a low d-dimer	Sensitivity (%)	Specificity (%)	NPV (%)
< 65 years	123	22%	92 (75–99)	26 (17–36)	93 (76–99)	404	41%	100 (95–100)	50 (45–55)	100 (98–100)
65–75 years	40	22%	82 (48–98)	24 (10–44)	77 (40–97)	73	22%	100 (84–100)	31 (19–45)	100 (79–100)
>75 years	44	14%	90 (56–99)	15 (5–32)	83 (36–100)	63	14%	100 (85–100)	22 (11–38)	100 (66–100)
All ages	207	20%	91 (79–98)	23 (17–30)	88 (74–96)	540	36%	100 (97–100)	45 (40–50)	100 (98–100)

Söhne TH 2005

Age and specificity D-dimer (Tina-quant)

Age	N	Prevalence of DVT	Sensitivity	Negative Predictive Value	Specificity
18-46.7	29 (59/203)	41	100 (95.7-100)	100 (93.9-100)	49.2 (40.2-58.1)
46.8-59.8	29 (58/203)	40	98.8 (93.3-100)	98.3 (90.8-100)	46.7 (37.9-55.6)
59.9-73.8	17 (35/203)	43	100 (95.9-100)	100 (90.0-100)	30.4 (22.0-38.8)
>73.8	12 (24/203)	32	100 (94.5-1000	100 (85.8-100)	17.4 (11.1-23.7)
Total	22 (176/812)	39	99.7 (98.3-100)	99.4 (96.9-100)	35.4 (31.1-39.6)

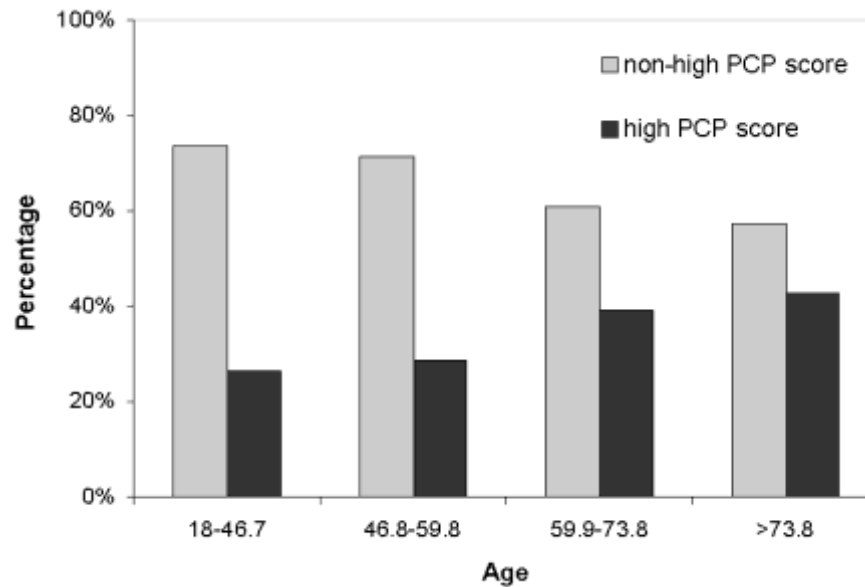(Values are presented as percentages)

Schutgens bjh 2005

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Age and clinical score

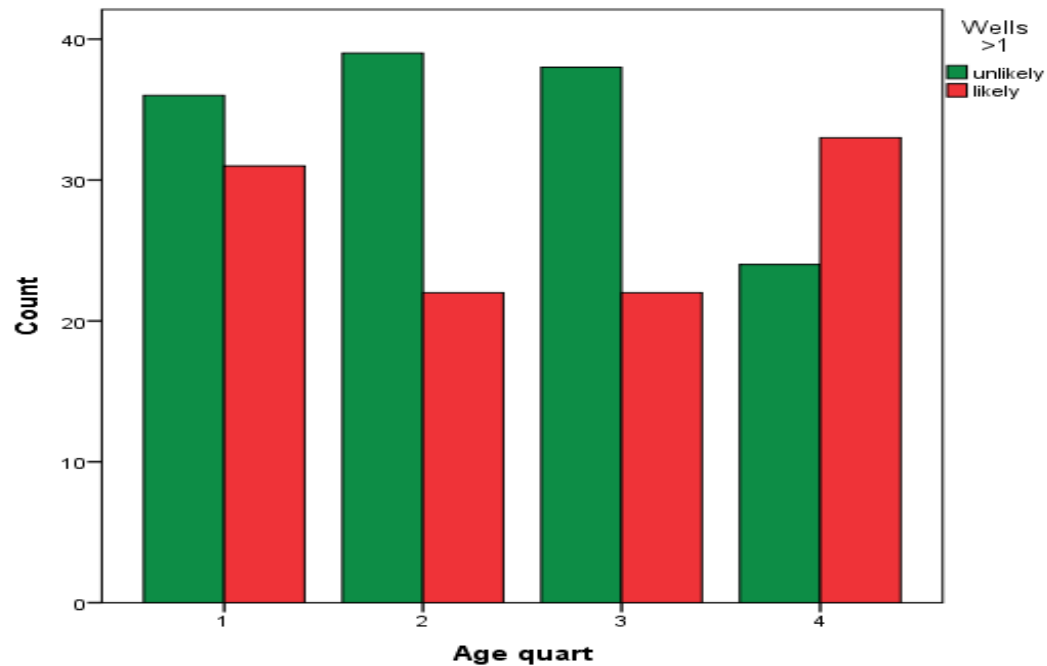| Age (years)	Non-high PCP score and normal D-dimer	High PCP score and normal D-dimer	Abnormal D-dimer
18-46.7	29 (59/203)	6 (12/203)	65 (132/203)
46.8-59.8	29 (58/203)	5 (10/203)	67 (135/203)
59.9-73.8	17 (35/203)	4 (9/203)	78 (159/203)
>73.8	12 (24/203)	4 (8/203)	84 (171/203)
Total	22 (176/812)	5 (38/812)	74 (597/812)

(Values are presented as percentages)

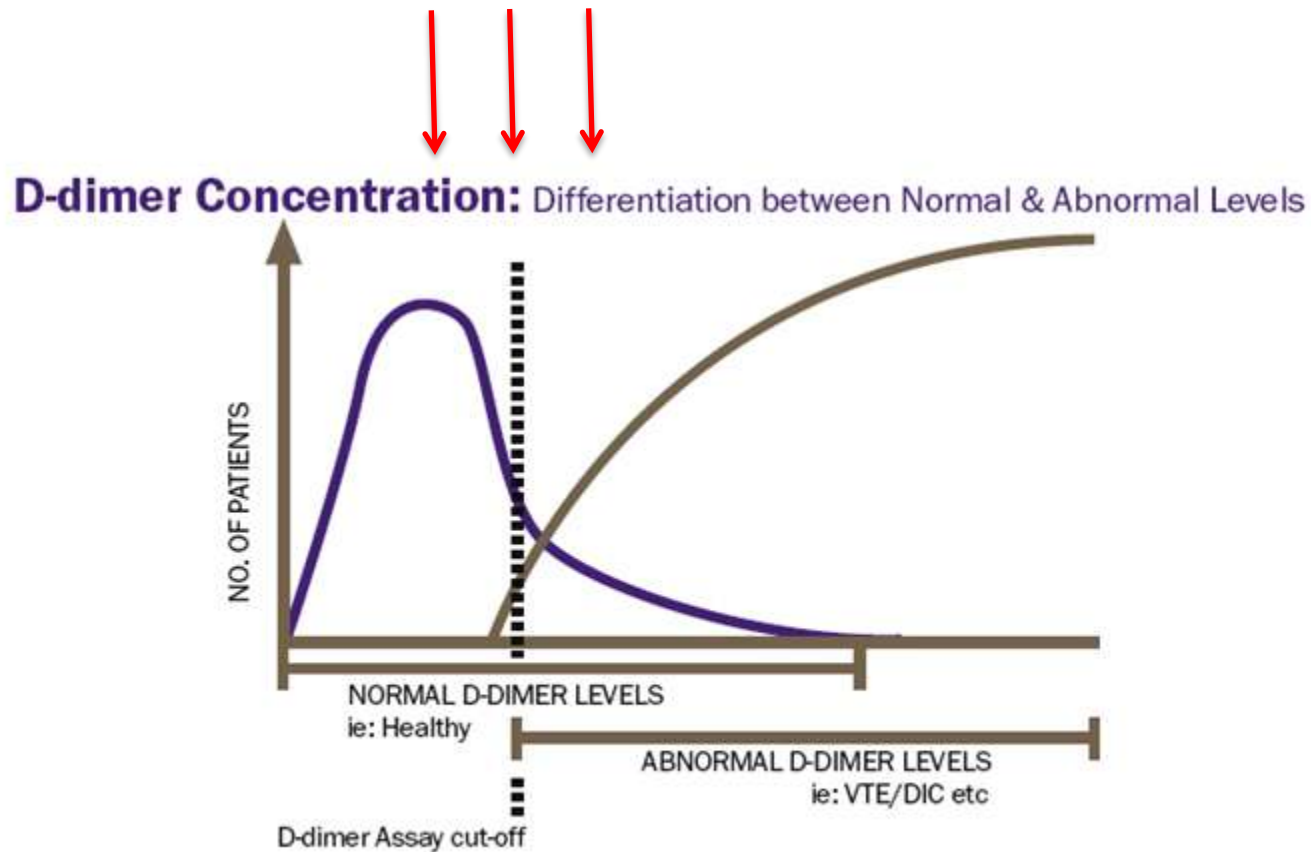Schutgens bjh 2005

Age and clinical score

Age and CDR

Conclusion

> **Decrease specificity with age**

> **Decrase non-high, increase high risk with age**

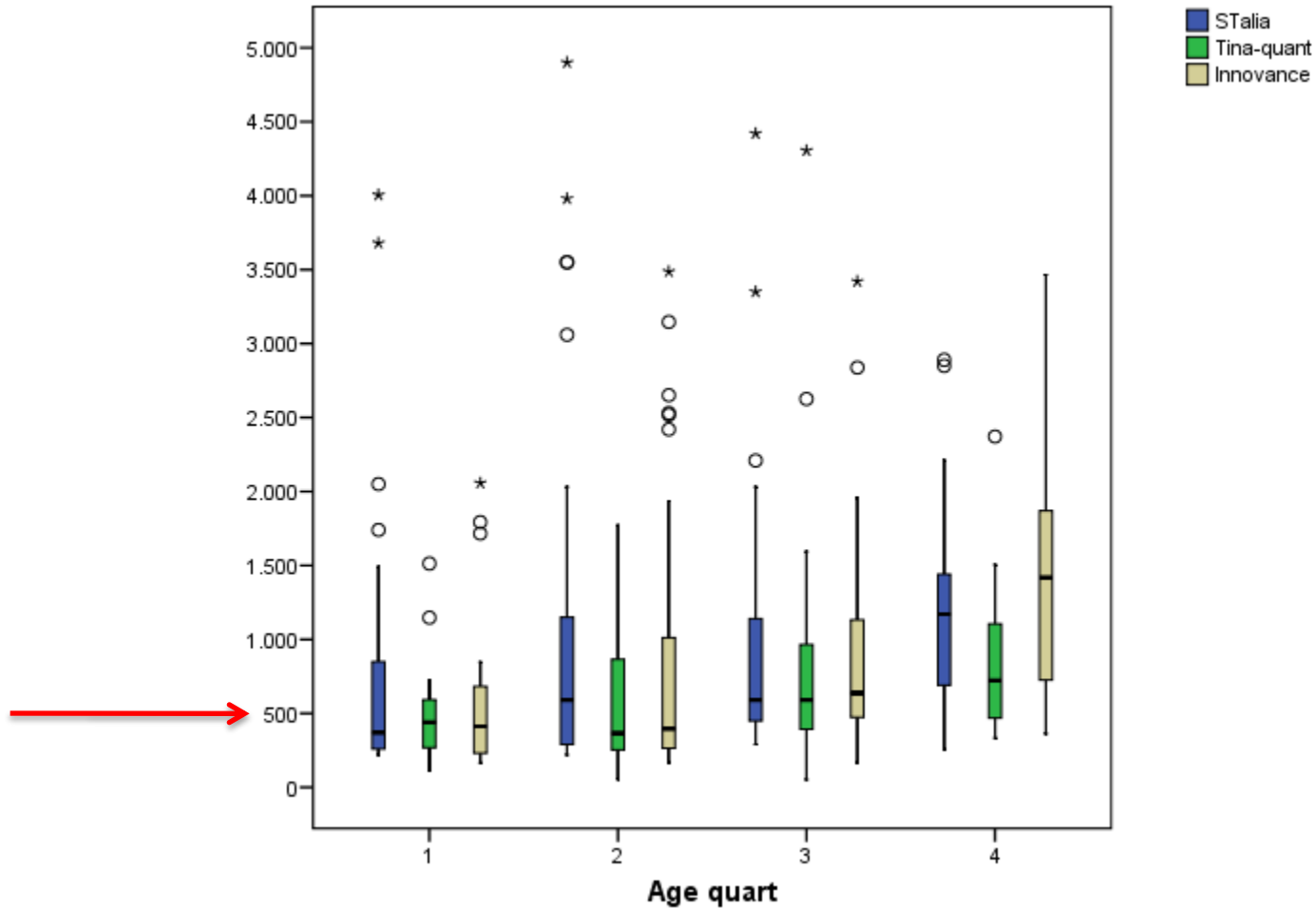> **Increase D-dimer value with age**

Use of cut-off value:
what is normal?

D-dimer Concentration: Differentiation between Normal & Abnormal Levels

NO. OF PATIENTS

NORMAL D-DIMER LEVELS
ie: Healthy

ABNORMAL D-DIMER LEVELS
ie: VTE/DIC etc

D-dimer Assay cut-off

D-dimer and age in DVT negative patients
PTP < 2

Age and D-dimer specificity cut-off 500 µg/L

Age [y]	STA Lia [%]	Tina-quant [%]	Innovance [%]
all	34.3	41.7	32.7
< 60	44.6	53.1	46.1
< 70	43.0	38.6	43.5
< 80	38.9	44.8	37.7
≥ 60	26.0	32.5	21.6
≥ 70	20.0	27.6	14.4
≥ 80	11.1	27.6	6.7

Haas AJH 2009

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Age, PTP and D-dimer

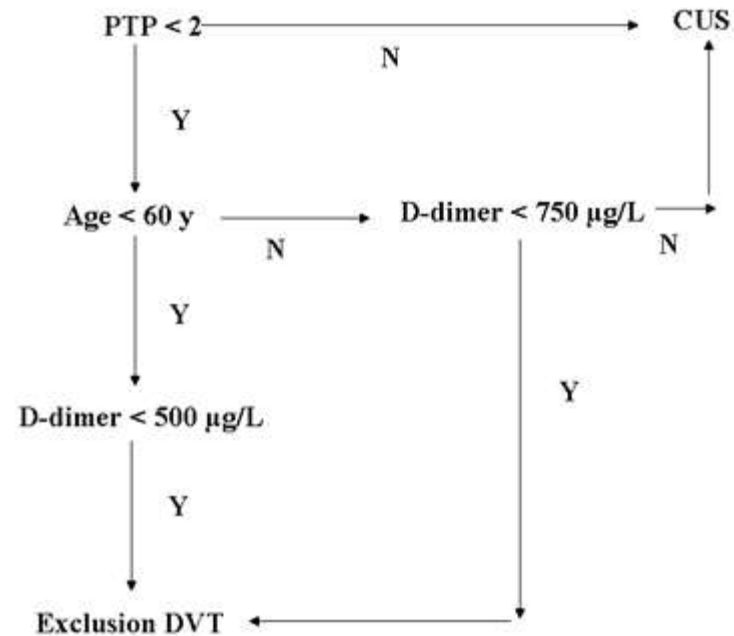| Age[y]	Remark	STA Lia [%]			Tina-quant [%]			Innovance [%]		
		sens	spec	NPV	sens	spec	NPV	sens	spec	NPV
all		97.3	34.3	95.1	98.4	41.7	97.5	100.0	32.7	100.0
< 60		97.8	44.6	96.7	98.9	53.1	98.6	100.0	46.1	100.0
≥ 60		97.7	26.0	95.2	98.9	32.5	98.0	100.0	21.6	100.0
All	PTP < 2	97.4	43.1	98.3	100.0	51.5	100.0	100.0	42.6	100.0
< 60	PTP < 2	95.7	50.0	97.2	100.0	62.0	100.0	100.0	59.2	100.0
≥ 60	PTP < 2	100.0	34.8	100.0	100.0	40.9	100.0	100.0	24.6	100.0

Haas AJH 2009

Age and D-dimer (PTP < 2)

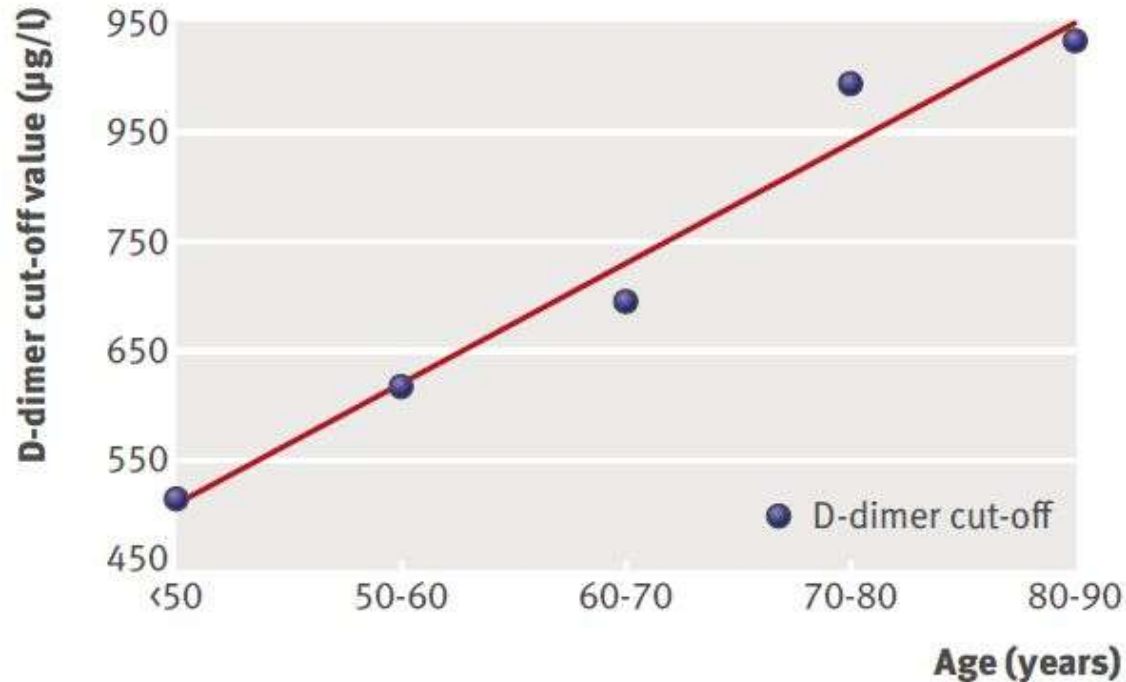| Age [y]	Cut-off	STA Lia [%]			Tina-quant [%]			Innovance [%]		
		sens	spec	NPV	sens	spec	NPV	sens	spec	NPV
All	500	**97.4**	**43.1**	**98.3**	**100.0**	**51.5**	**100.0**	**100.0**	**42.6**	**100.0**
		(93.7)	(28.7)	(88.9)	(90.7)	(43.5)	(94.9)	(90.7)	(34.3)	(93.8)
	750	97.3	58.4	98.8	94.7	69.3	97.9	94.6	61.0	97.6
	1000	94.6	66.2	97.9	89.5	78.1	96.4	94.6	67.6	97.9
< 60	500	**95.7**	**50.0**	**97.2**	**100.0**	**62.0**	**100.0**	**100.0**	**59.2**	**100.0**
		(78.0)	(23.5)	(85.2)	(85.8)	(49.7)	(92.0)	(85.8)	(46.8)	(91.6)
	750	95.7	67.6	98.0	91.7	77.5	96.5	91.7	71.8	96.2
	1000	91.3	73.2	96.3	87.5	84.5	95.2	91.7	78.9	96.6
≥ 60	500	100.0	34.8	100.0	100.0	40.9	100.0	100.0	24.6	100.0
	750	**100.0**	**48.5**	**100.0**	**100.0**	**60.6**	**100.0**	**100.0**	**49.2**	**100.0**
		(87.2)	(36.3)	(86.4)	(88.8)	(42.8)	(83.8)	(91.8)	(32.1)	(89.0)
	1000	100.0	58.5	100.0	92.9	71.2	97.9	100.0	55.4	100.0

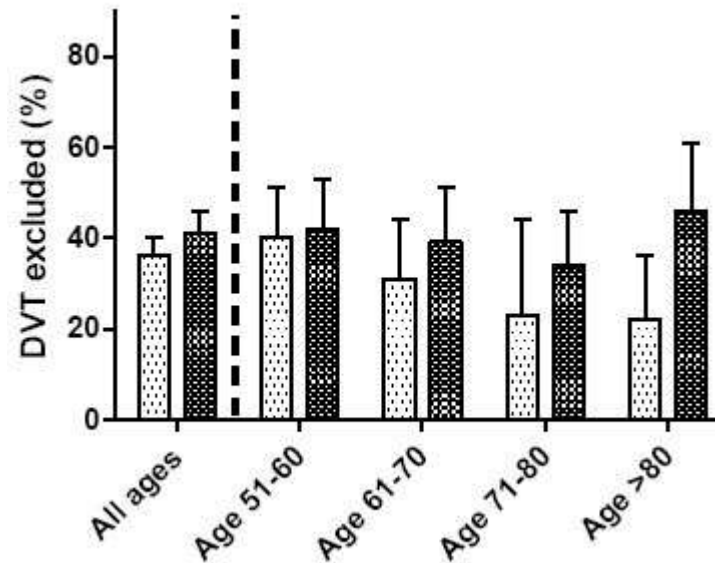Haas AJH 2009

Algorithm

Alternative approche (PE)

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%)

Cut-off = age x10 µg/L

Douma BMJ 2010

Retrospective: results of AIDA study (DVT)

Cut-off 500 µg/L – age adjusted cut-off

Douma Haematologica 2012

External validation of a D-dimer age-adjusted cut-off for the exclusion of pulmonary embolism
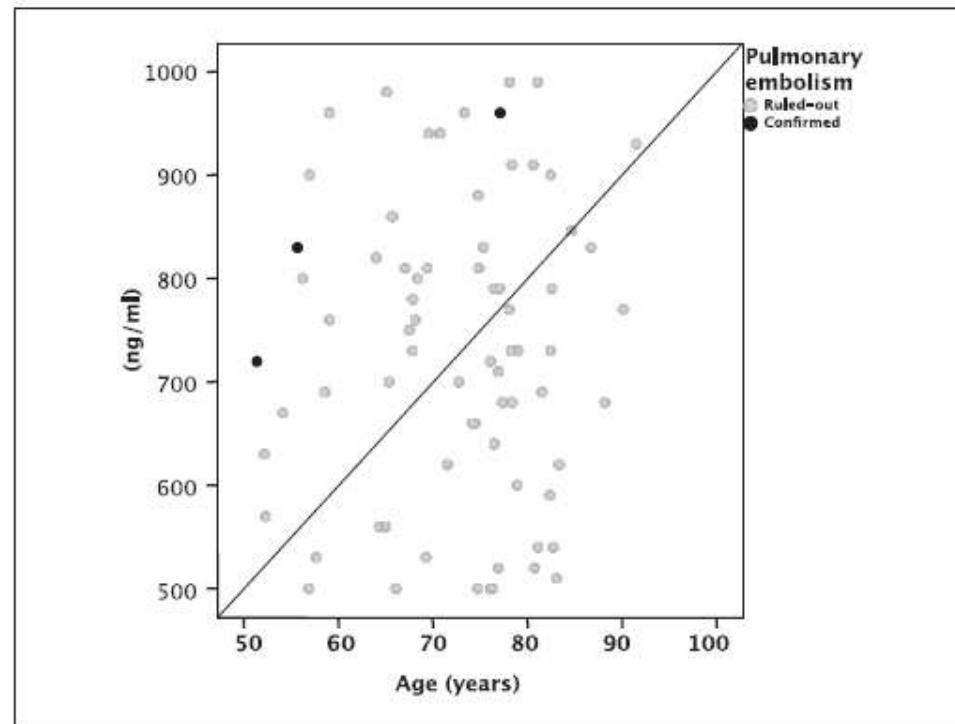

Figure 1: D-dimer levels of patients with and without PE according to patients' age, focusing on those with D-dimer values between 500 μg/l and 1,000 μg/l and with age between 50 and 100 years.

Jaffrelot TH 2012

Application of age-adjusted D-dimer treshold for exclusion thromboembolism in older patients: a retrospective study

- ➢ **423 patients > 50 years old**

- ➢ **22 (5.2%) D-dimer > 500 µg/L and < [age x 10] µg/L**

- ➢ **None with evidence of PE**

Leng Acute Med 2012

Validation of two age dependent D-dimer cut-off values for exclusion of deep vein thrombosis in suspected elderly patients in primary care: retrospective, cross sectional, diagnostic analysis

Schouten, BMJ 2012;344:e2985

Comparison dichotome (Haas) and continue (Douma) cut-off values (standard value of 500 µg/L): results are comparable: increase of exclusion 47.4% resp. 47.8% and false negative 0.3% resp. 0.5%.

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Conclusion

> **Adjusment of cut-off value with age: increase of specificity**

> Dichotome
> Continue or per decade
> Applicable for primary and secundary care

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Final conclusions

➢ **D-dimer combined with Wells score very useful in a safe exclusion of DVT (LE)**

➢ **Decrease false positives with age adjusted cut-off values**

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Thank you!

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