Update of VTE Guideline

2016-11-05

계명의대 내과
최원일

Grades of recommendation: methodological quality

- High(A): consistent results from RCTs or observational studies with very strong association and secure generalization
- Moderate(B): inconsistent results from RCTs or RCTs with methodological limitations
- Low(C): unbiased observational studies(e.g. well-executed cohort studies)
- Very low(D): other observational studies (e.g. case series)

Grades of recommendation: strength of recommendations

- Stronger recommendations(we recommend)
  -high-quality methods with large, precise effect
  -benefits much greater than downsides, or downsides much greater than benefits
  -do it or don`t do it- we recommend
  -Grade 1
- Weak recommendations(we suggest)
  -lower-quality methods with imprecise estimate
  -benefits not clearly greater or smaller than downsides
  -values and preferences very important
  -probably do it or probably don`t do it- we suggest
  -Grade 2

Incidence of VTE

- Estimated to affect 350,000 to 600,000 Americans annually
- Contributing to at least 100,000 deaths per year
- Will increase with ageing population

Healthcare Bigdata Hub
보건의료빅데이터개방시스템

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Home | 의료통계정보 | 질병/행위별 의료 통계 | 질병 소분류(3단 상병) 통계

질병 소분류(3단 상병) 통계

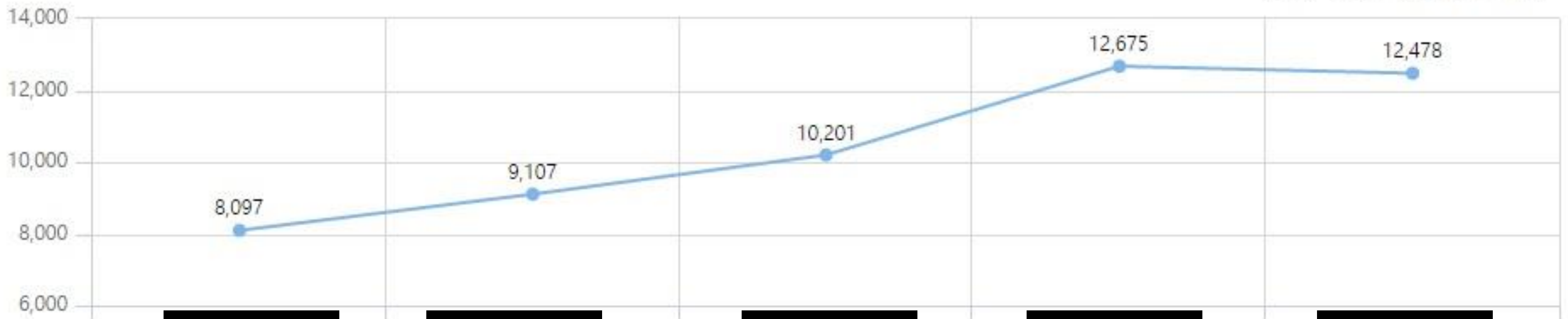
진료받은 모든 질병에 대한 통계를 2천여개의 한국표준질병・사인분류의 소분류로 조회하는 서비스입니다.

검색 폐색전증 I26 질병코드 조회

입원외래별 | 성별/연령5세구간별 | 성별/연령10세구간별 | 요양기관종별 | 요양기관소재지별

기간구분 ◉ 심사년도 ○ 진료년월 2011 ~ 2015 조회

연도별 환자수 추이 [단위:명]



질병 소분류(3단 상병) 통계

진료받은 모든 질병에 대한 통계를 2천여개의 한국표준질병・사인분류의 소분류로 조회하는 서비스입니다.

검색 기타 정맥의 색전증 및 혈전증 I82 질병코드 조회

입원외래별 | 성별/연령5세구간별 | 성별/연령10세구간별 | 요양기관종별 | 요양기관소재지별

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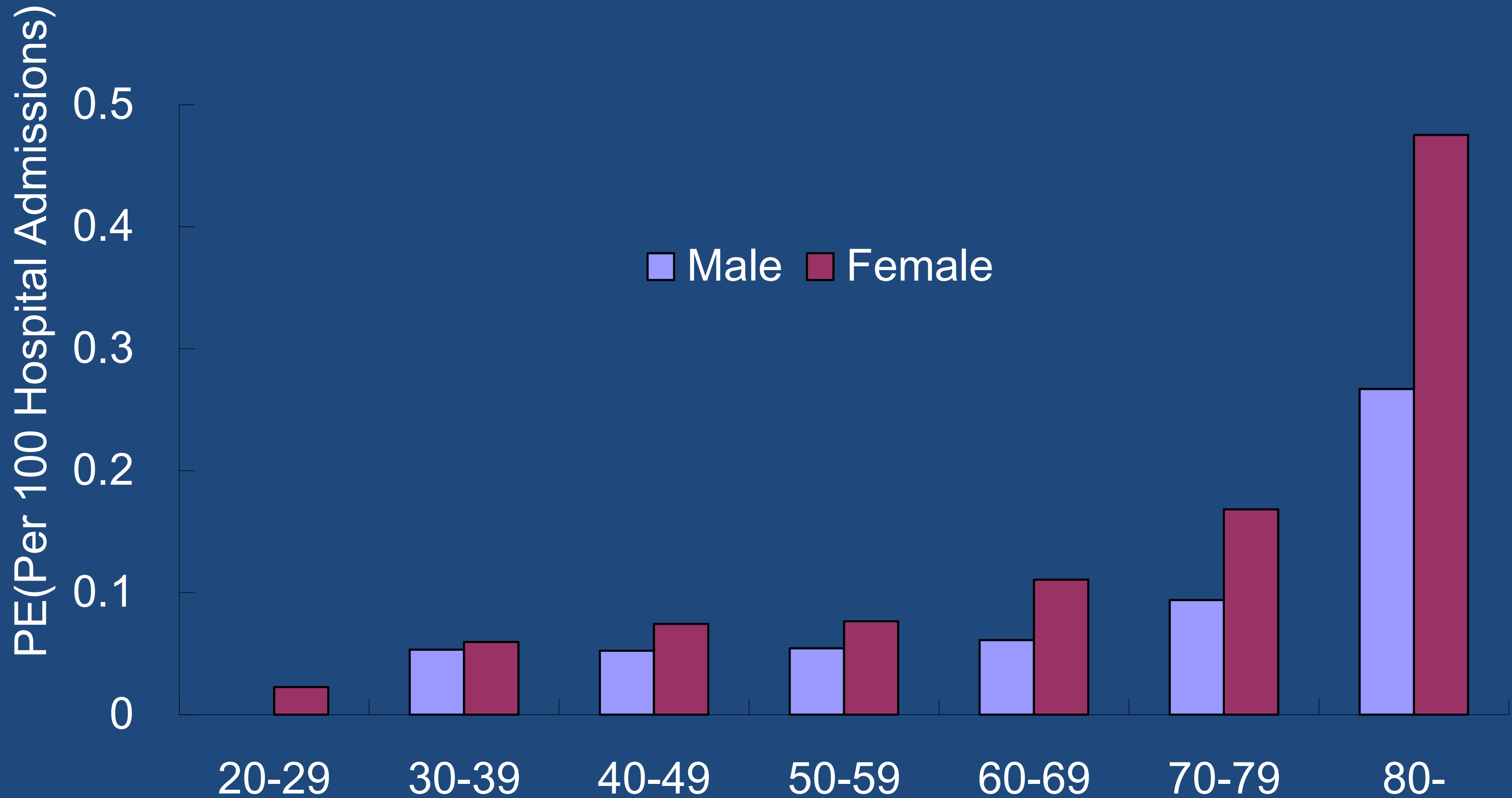
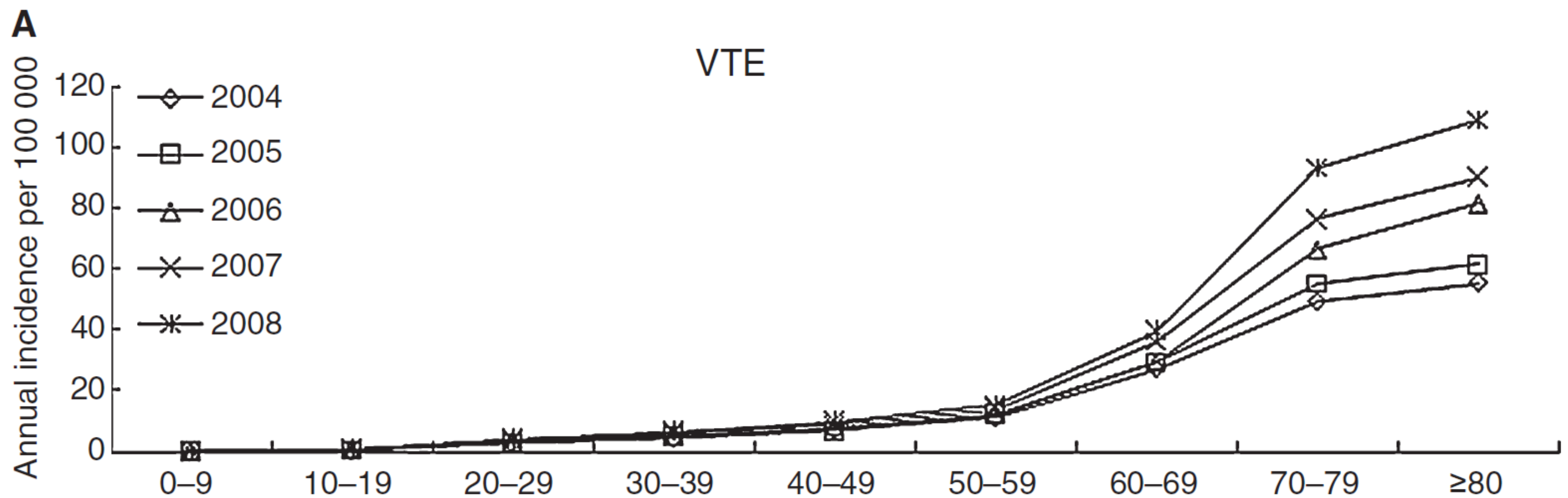
Incidence of PE



Choi WI et al. Thrombosis Research 2011

Age



Journal of Thrombosis and Haemostasis, 9: 85–91

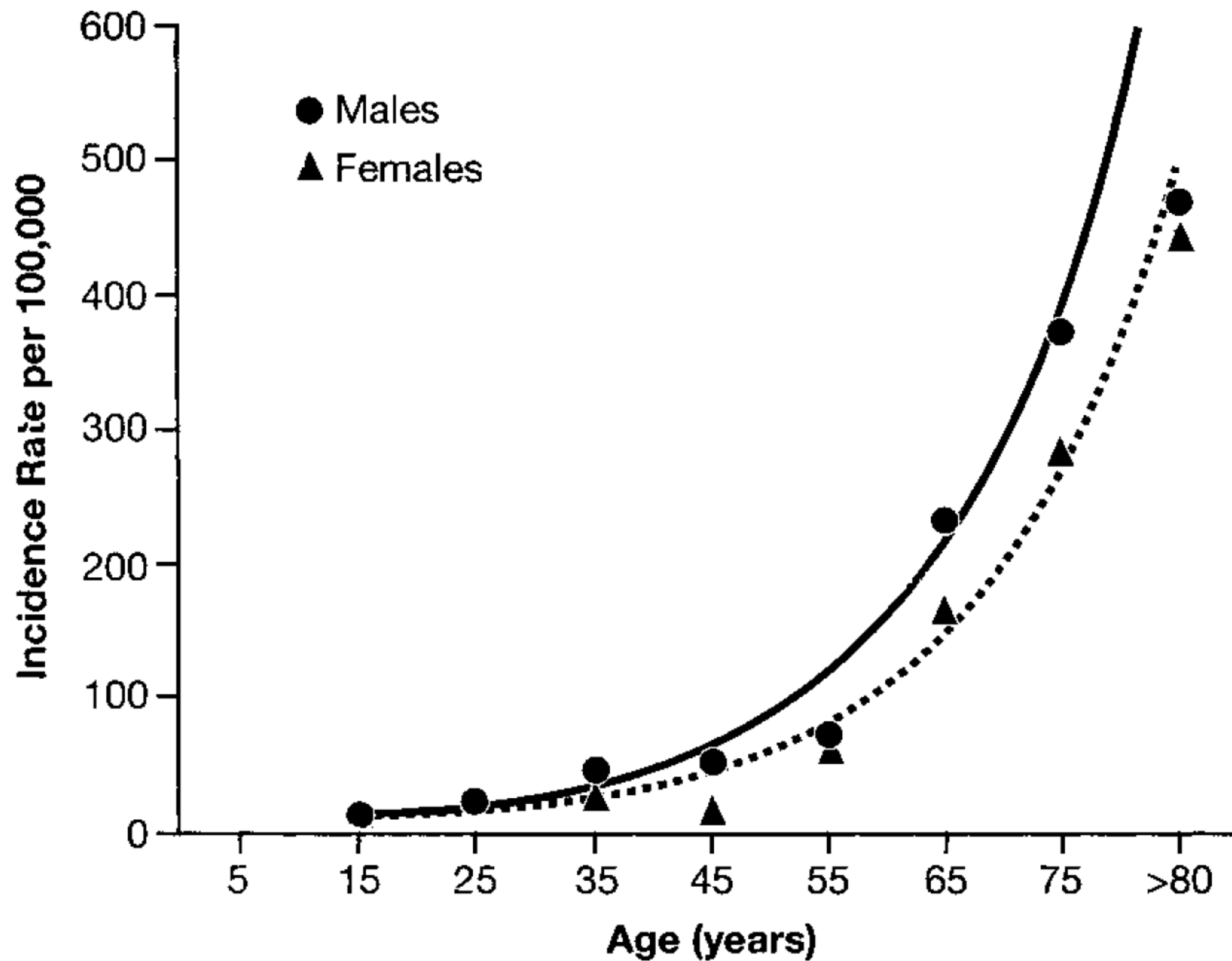
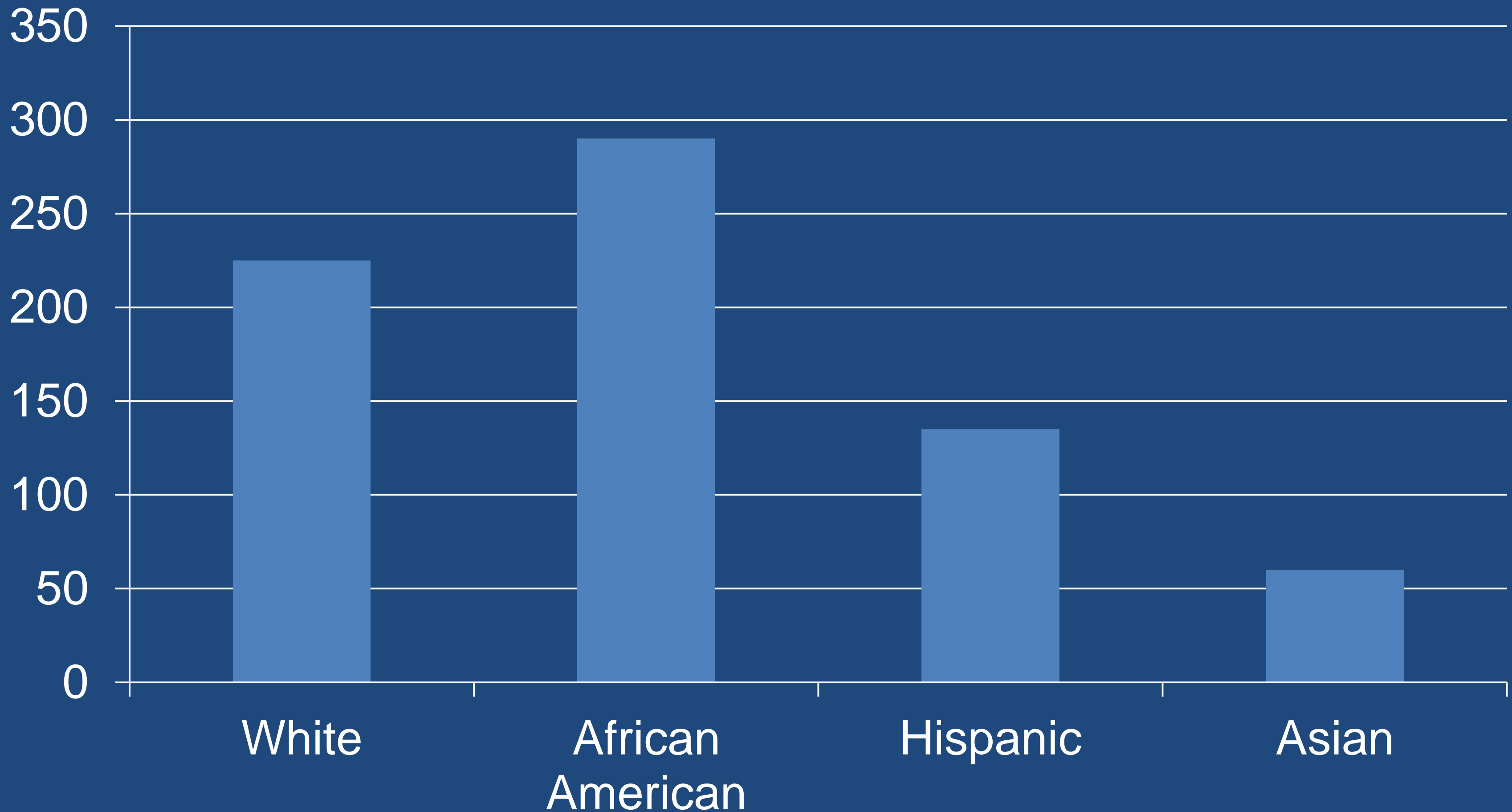


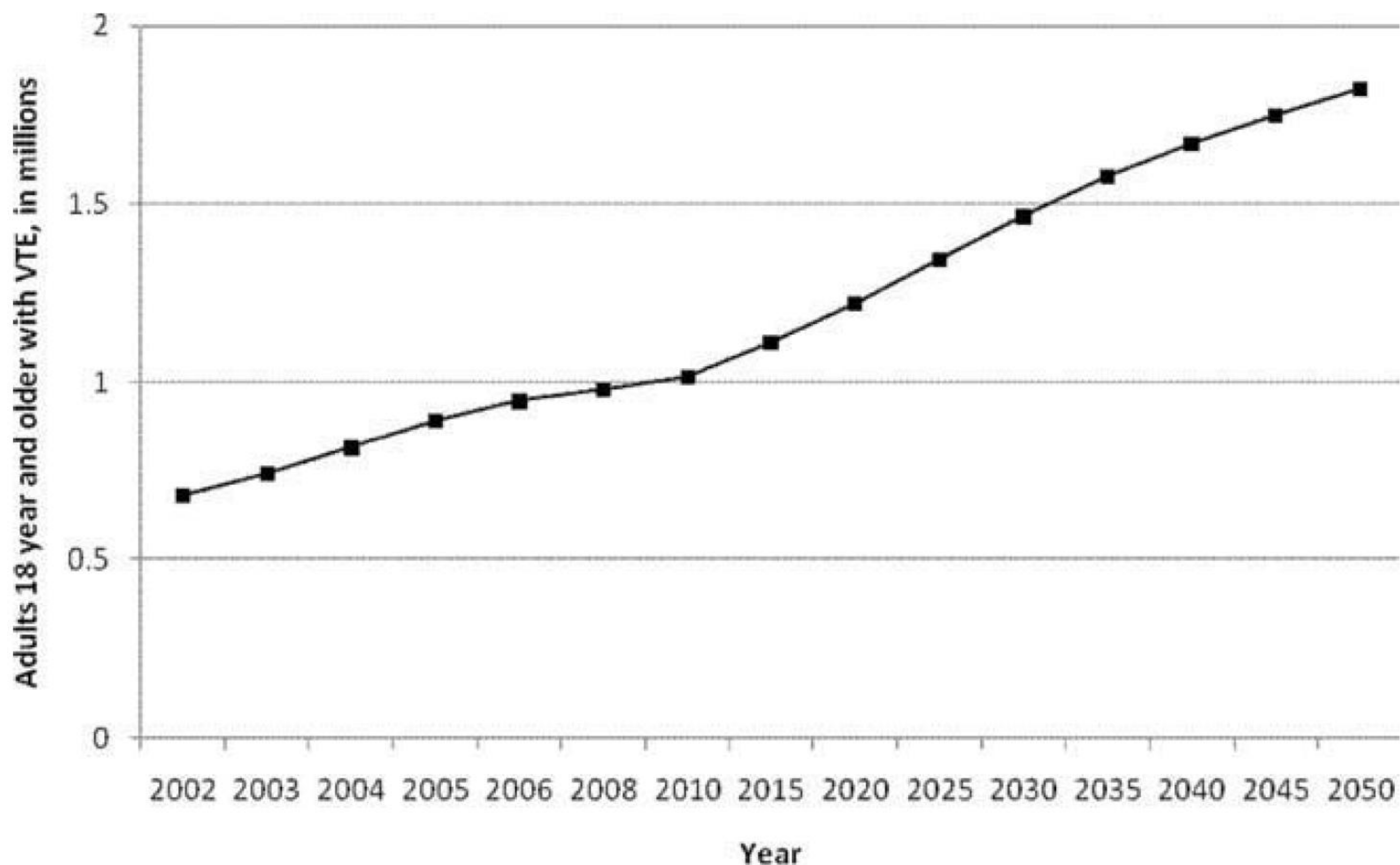
Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. *Arch Intern Med*. 1991;151:933–938.)

Incidence by race



White RH. Ann Intern Med 1998

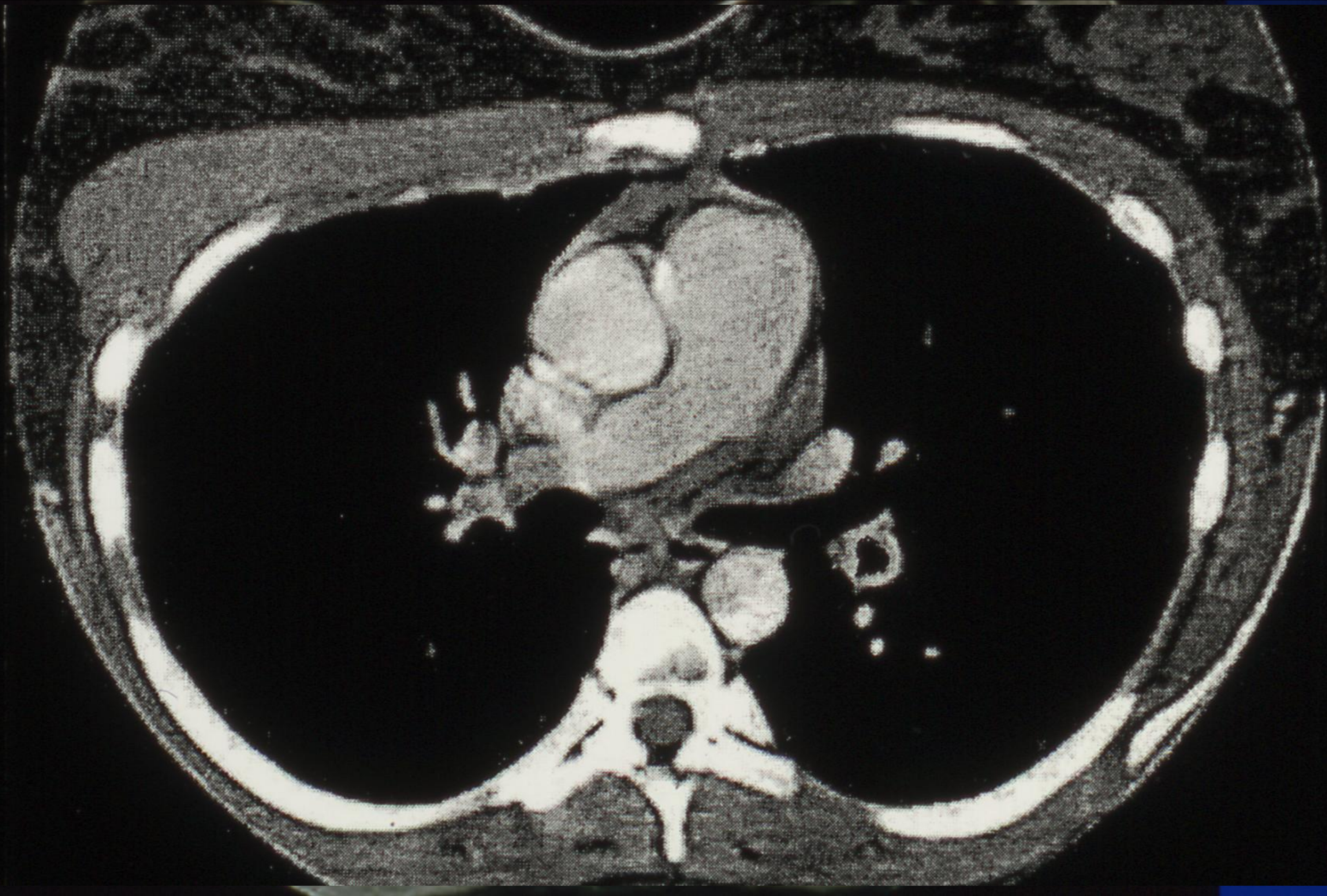
Prevalence of VTE is predicted to double by 2050



VTE cases per 100,000:

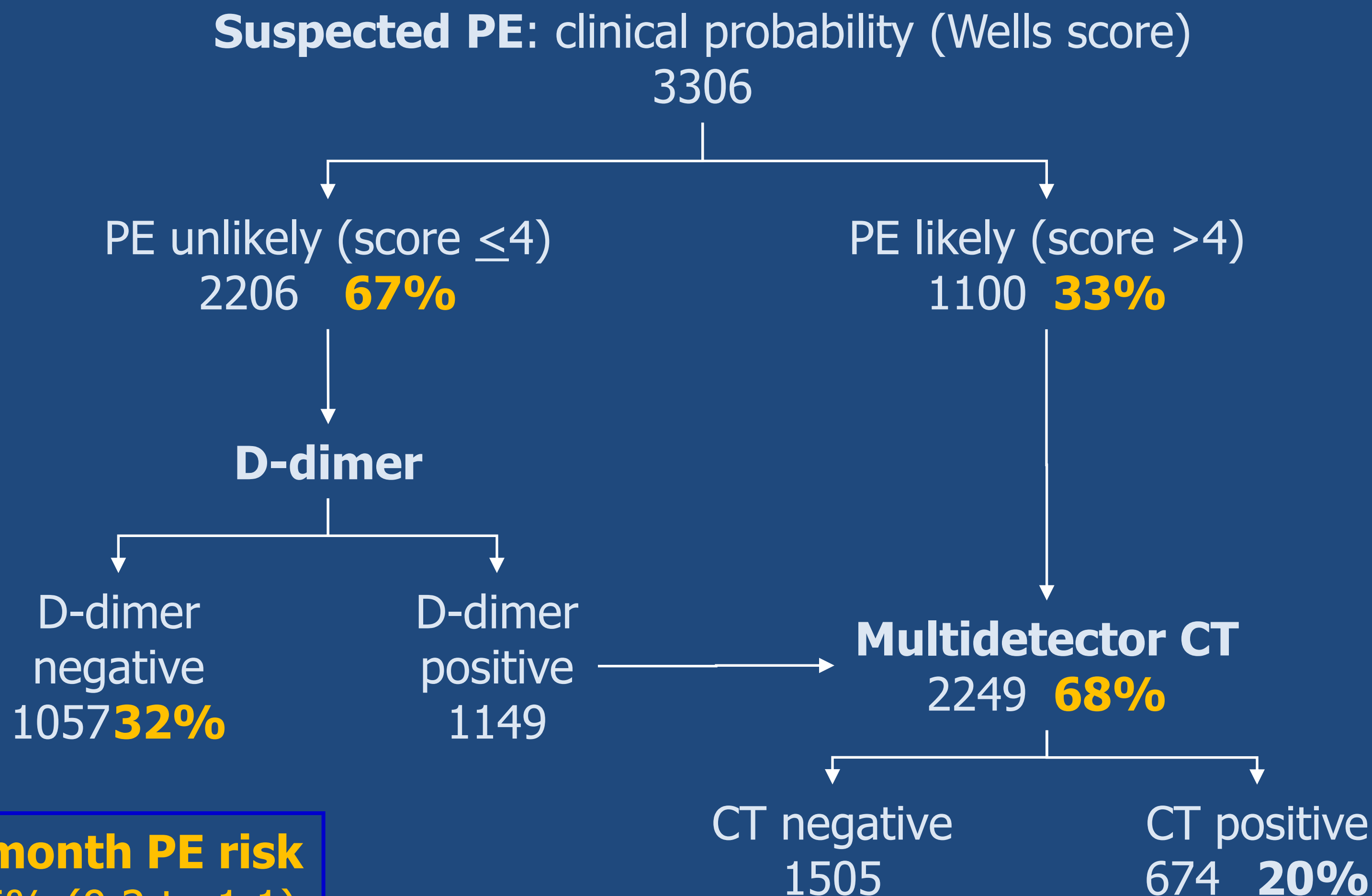
2002	2003	2004	2005	2006	2008	2010	2015	2020	2025	2030	2035	2040	2045	2050
317	341	371	401	422	426	432	453	478	505	527	544	556	563	567

Am J Haematol 2011;86:217-20



The CHRISTOPHER study

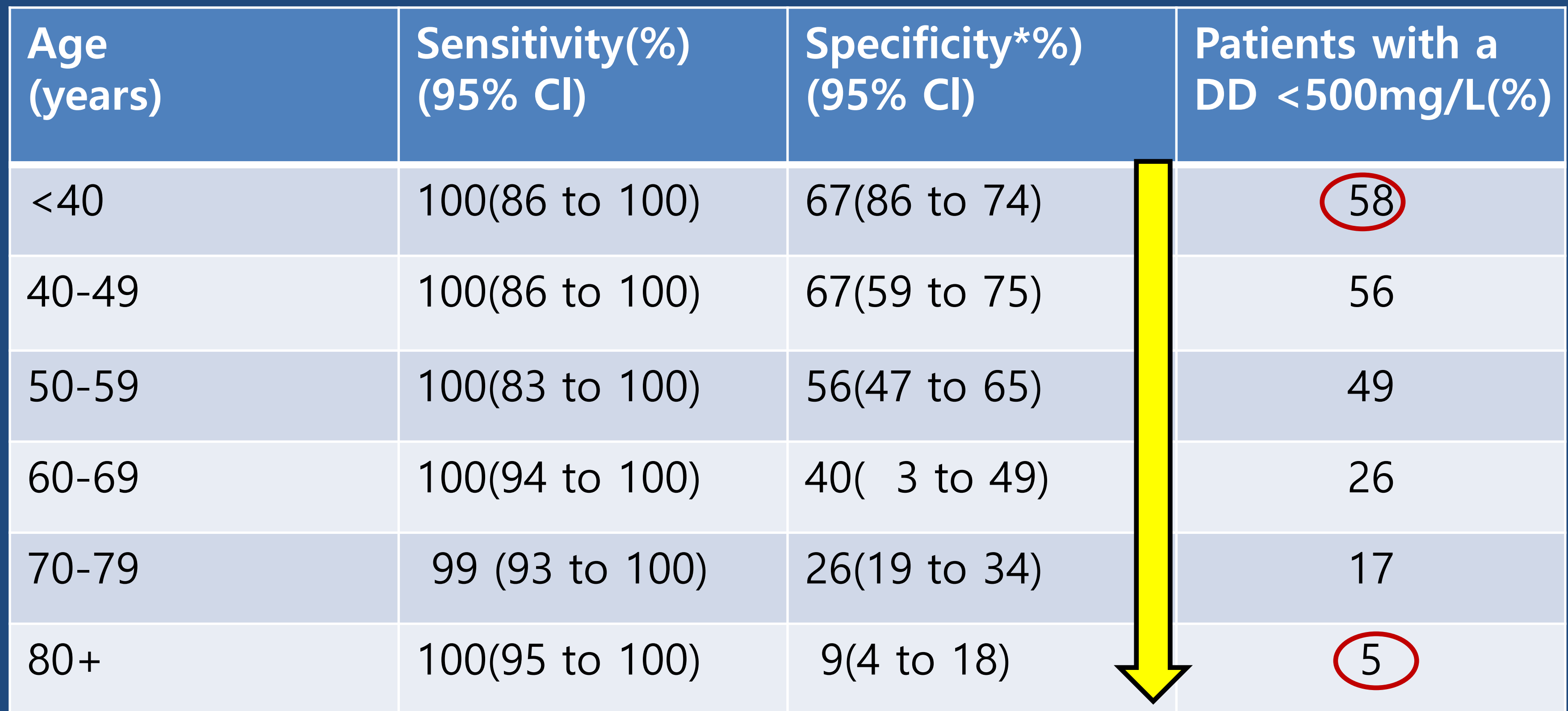
JAMA 2006;295:172-9



Can CT be avoided?

- Systematic review: : Low probability in Well`s score& D-dimer neg: 28% avoided
- Well`s score& age adjusted D-dimer(age x 10mg/L) for pt> 50 y.o. : 33% avoided
- Well`s score& and probability adjusted D-dimer currently studied

Influence of Age on Diagnostic Characteristics and Clinical Usefulness of D-dimer



Age (years)	Sensitivity(%) (95% CI)	Specificity*%) (95% CI)	Patients with a DD <500mg/L(%)
<40	100(86 to 100)	67(86 to 74)	58
40-49	100(86 to 100)	67(59 to 75)	56
50-59	100(83 to 100)	56(47 to 65)	49
60-69	100(94 to 100)	40(3 to 49)	26
70-79	99 (93 to 100)	26(19 to 34)	17
80+	100(95 to 100)	9(4 to 18)	5

Am J Med 2000;109:357

Age-adjusted Cut-off for D-dimer

Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts

Renée A Douma, physician,[1] Grégoire le Gal, physician,[2] Maaike Söhne, physician,[1] Marc Righini, physician,[3] Pieter W Kamphuisen, physician,[1] Arnaud Perrier, professor,[4] Marieke J H A Kruip, physician,[5] Henri Bounameaux, professor,[3] Harry R Büller, professor,[1] Pierre-Marie Roy, professor[6]

BMJ 2010; 340: c1475

Age-adjusted DD cut-off in suspected PE

Derivation set

N=1721
Prevalence of PE:24%

Age-adjusted
Cut-off value:
Agex 20(㎍/L FEU)
Above 50 years

(1 FEU=2 x DDU)

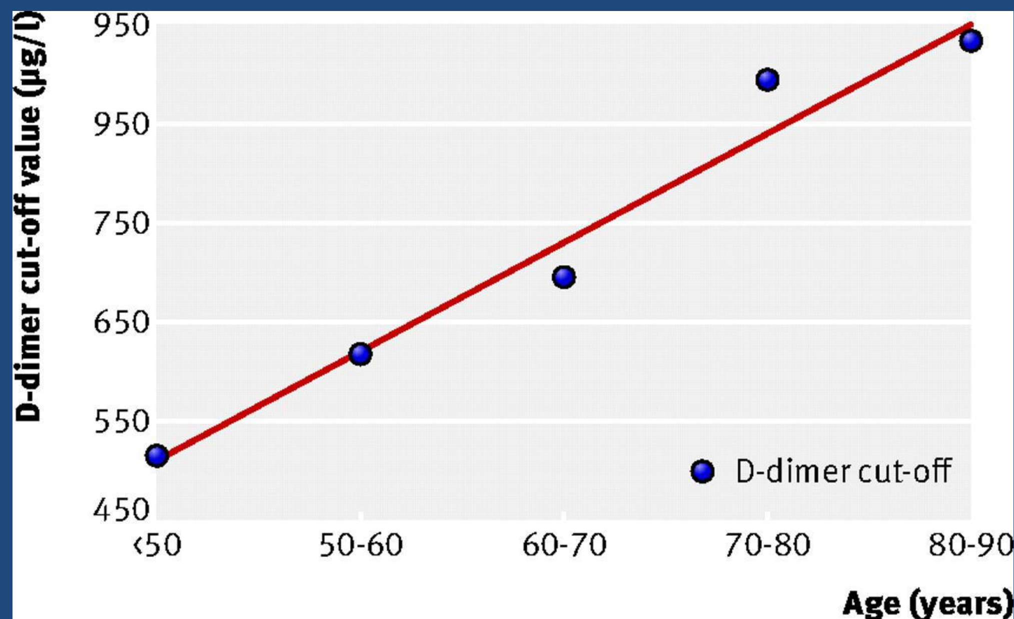
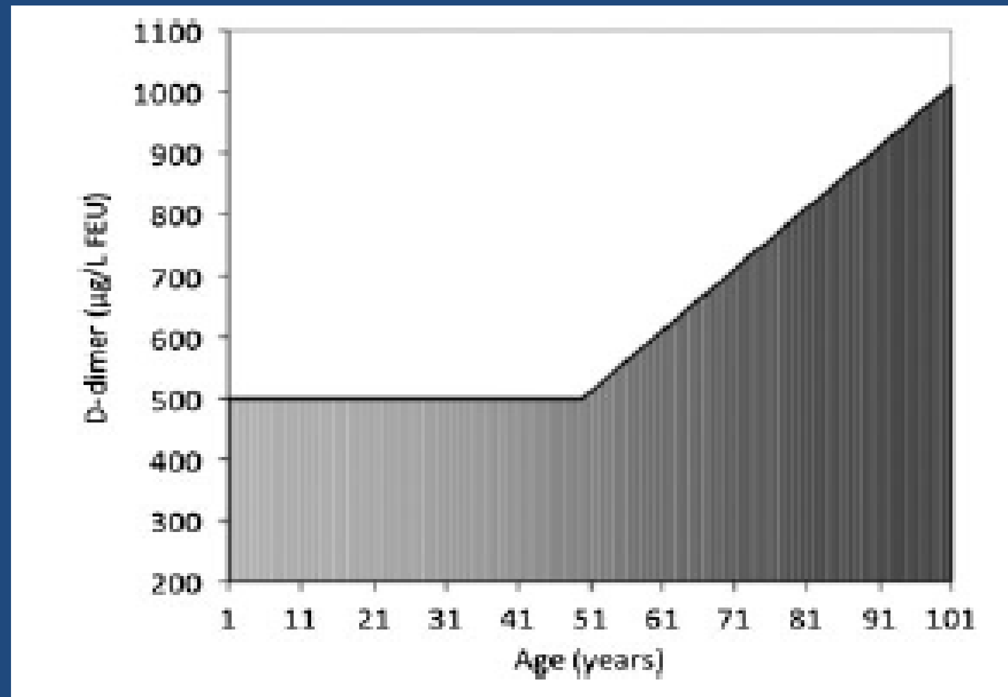


Fig1) Optimal cut-off values for D-dimer test for pulmonary embolism by age in patients with an unlikely clinical probability of pulmonary embolism(sensitivity set at 100%)

BMJ 2010; 340: c1475

Age-adjusted Diagnostic Thresholds for D-dimer



- This allows increasing specificity(~40%)while retaining a sensitivity>97%
- Such a strategy deserves to be prospectively evaluated in management studies of patients suspected of VTE

Original Investigation

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism

The ADJUST-PE Study

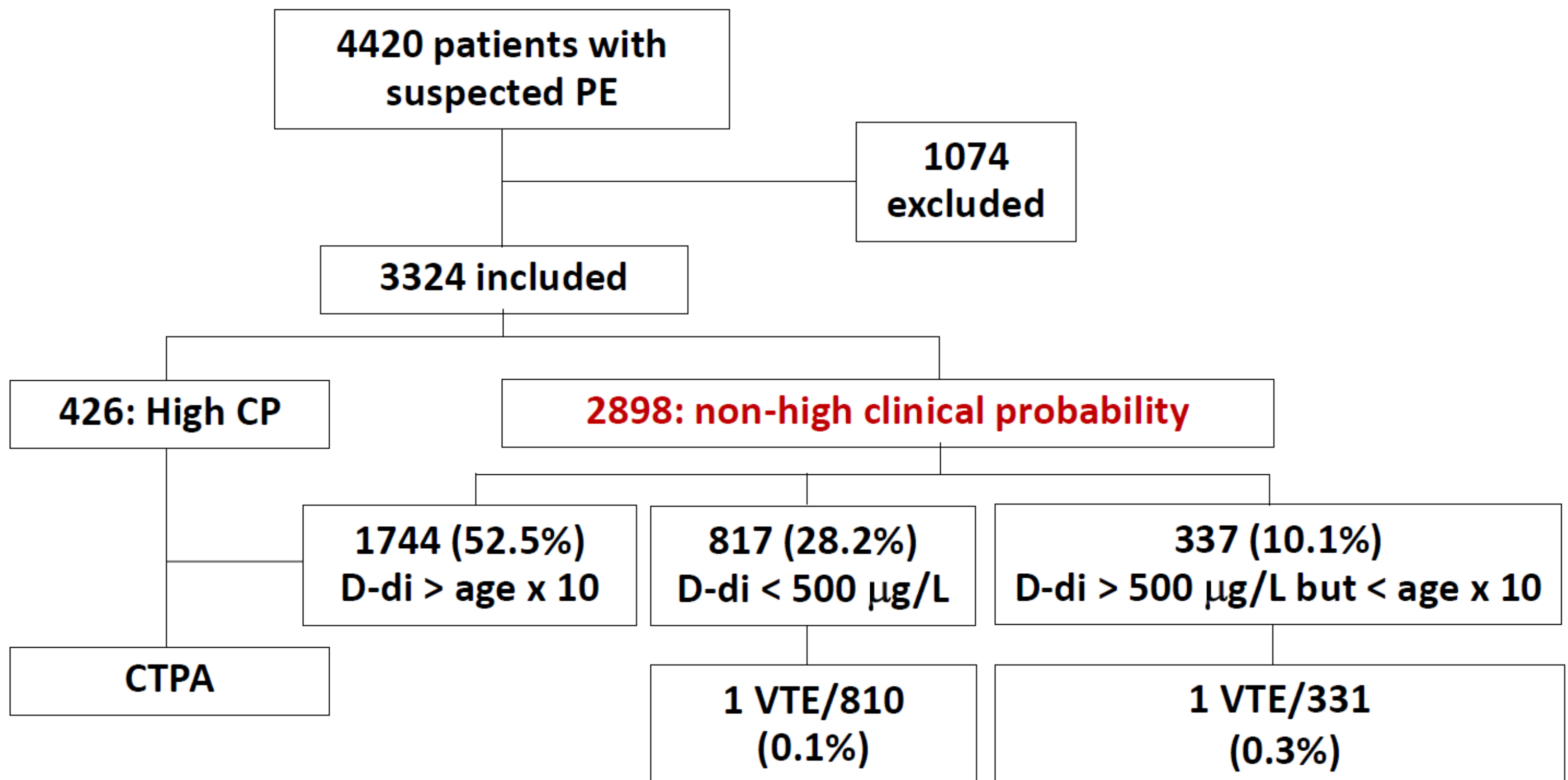
Marc Righini, MD; Josien Van Es, MD, PhD; Paul L. Den Exter, MD; Pierre-Marie Roy, MD, PhD; Franck Verschuren, MD; Alexandre Ghuysen, MD; Olivier T. Rutschmann, MD; Olivier Sanchez, MD; Morgan Jaffrelot, MD; Albert Trinh-Duc, MD; Catherine Le Gall, MD; Farès Moustafa, MD; Alessandra Principe, MD; Anja A. Van Houten, MD; Marije Ten Wolde, MD, PhD; Renée A. Douma, MD, PhD; Germa Hazelaar, MD; Petra M. G. Erkens, PhD; Klaas W. Van Kralingen, MD; Marco J. J. H. Grootenboers, MD, PhD; Marc F. Durian, MD; Y. Whitney Cheung, MD; Guy Meyer, MD; Henri Bounameaux, MD; Menno V. Huisman, MD, PhD; Pieter W. Kamphuisen, MD, PhD; Grégoire Le Gal, MD, PhD

- A multicenter, prospective management study evaluating the age adjusted cut-off in a cohort of 3346 patients with suspected PE.

- Patients with a normal age-adjusted D-dimer value did not undergo CT pulmonary angiography and were left untreated and followed up three month period.

JAMA 2014;311:117

ADJUST PE: Study Design and Results



JAMA 2014;311:117

ADJUST PE: Patient≥75years

- 766 patients ≥ 75 years
- 673 with low or intermediate clinical probability
- D-dimer <500㎍/L: 43(6.4%)
- D-dimer<age x 10: 200(29.7%)
- 3-month VTE: 0/195

JAMA 2014;311:117

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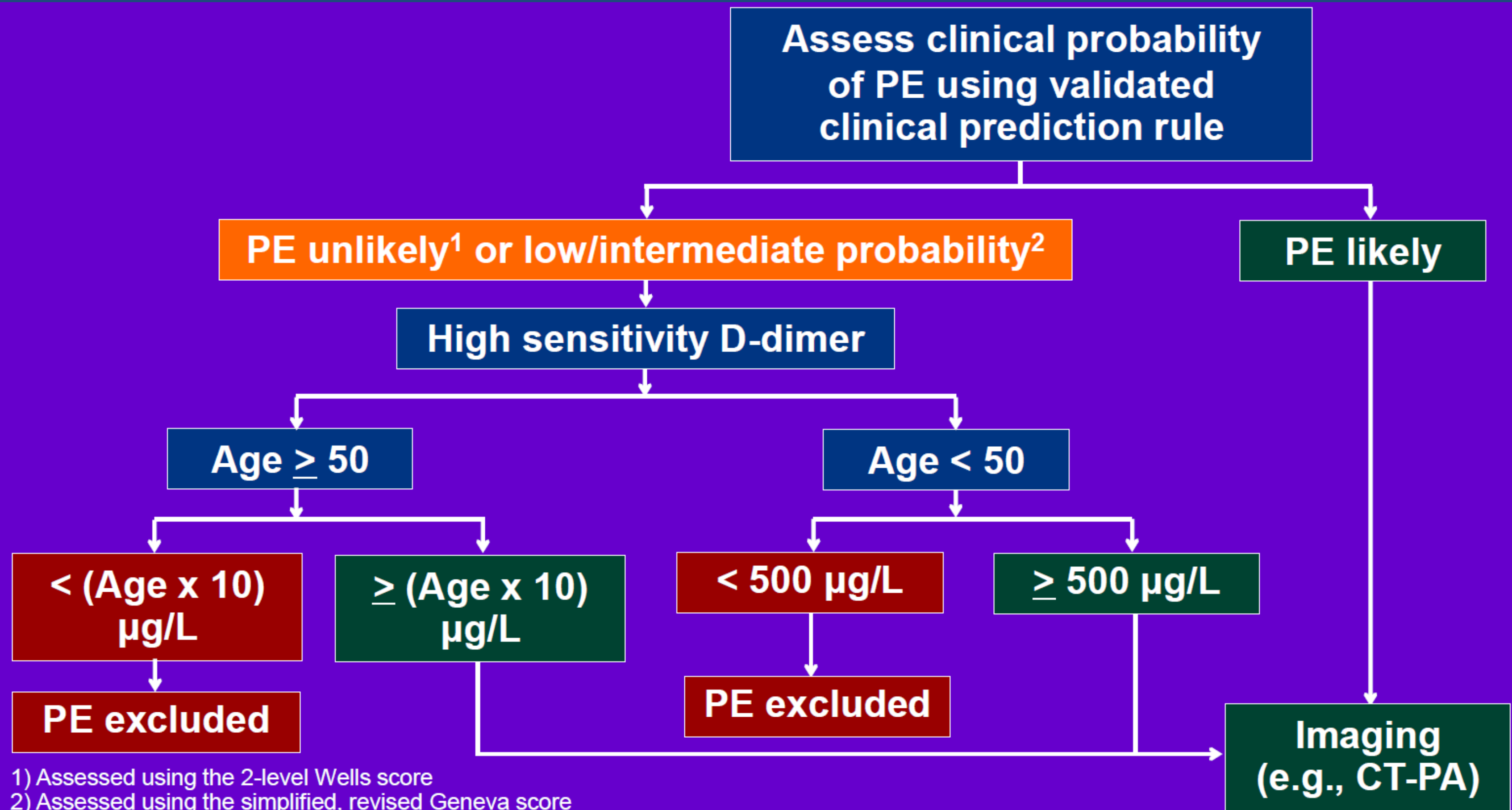
CONCLUSIONS:

- Compared with a fixed D-dimer cutoff of 500 μg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical VTE.

JAMA 2014;311:117

Diagnostic Evaluation of Patients with Suspected Pulmonary Embolism



Can my PE-patient in ER go home?

- Pulmonary Embolism Severity Index(PESI)

-Age	1p/yr	SBP<100	30p
-Male sex	10p	Pulse>110	20p
-Cancer	30p	RR>30	20p
-CHF	10p	Temp<36	20p
-Chron lung dis.	10p	SaO2<90%	20p
-△ mental status	60p		

85 p or less= low risk of fatal PE-NPV=99%

Aujeusky D et al. Am J Resp Crit Care Med 2005;172:1041-6

External validation in : J Intern Med 2007;261:597-604

Simplified PESI

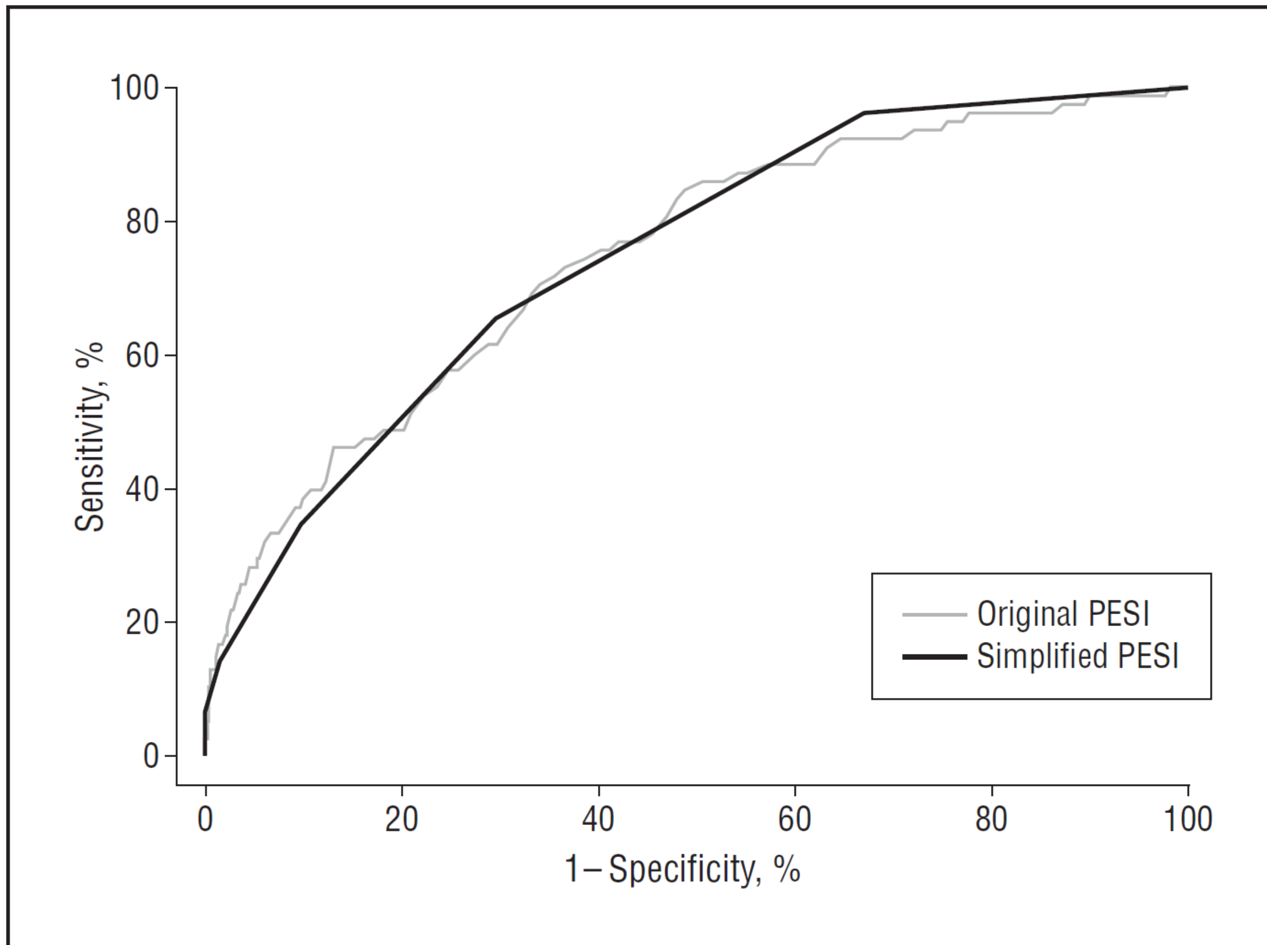
- Retrospective analysis of RIETE registry

Age>80	1P
History of Cancer	1P
Chronic cardiopulmonary dis.	1P
Pulse>110	1P
SBP<100	1P
SaO2<90%	1P

0=low risk, 1 or more= high risk

Jiménez D et al. Arch Intern Med. 2010;170:1383-9

Simplified PESI result



Arch Intern Med 2010;170:1383-9

High-risk PE

- Hemodynamically unstable-systolic BP<90mmHg-mortality is 58%. Grade 2B
- Thrombolysis-preferred route is I.V. Grade 2C
- Reduces mortality by =42% and recurrence by 50%
- But increases major hemorrhage 2.8-fold and intracranial hemorrhage 3.6-6.8-fold

Eur Heart J. 2015;35:605-14.
Blood 2015;125:2191-9.

Hemodynamically stable with RV-strain

Outcome	Tenecteplase (N=506)	Placebo (N=498)	Odds ratio (95% CI)	P-value
All cause Mortality	6(1.2%)	9(1.8%)	0.65(0.23-1.85)	0.42
Hemodynamic Decompensation	8(1.6%)	25(5.0%)	0.30(0.14-0.68)	0.002
Major Extracranial Bleeding	32(6.3%)	6(1.2%)	5.55(2.3-13.4)	<0.001
Stroke [a]	12(2.4%)	1(0.2%)	12.1(1.6-93.4)	0.001

Thrombolysis for large DVT

Meta-analysis of trial with catheter directed thrombolysis

Outcome	Odds ratio	95% CI
Complete lysis within 30days	91	19.3-429
Patency at 6months	5.77	1.99-16-7
Reduced post-thrombotic syndrome	0.4	0.19-0.96
Venous obstruction	0.20	0.09-0.44
Major bleeding	2.0	1.62-2.62

NOACs for treatment of VTE

- Cochrane meta-analysis of 11 randomized trials-major bleeds are fewer in DVT:

  -Thrombin inhibitors: odds ratio 0.68; 95% CI, 0.47-0.98

  -Xa inhibitors: adds ratio 0.57;95% CI,0.43-0.76
- No difference in PE for recurrence, mortality or major bleeds
- ACCP 2016 suggests NOACs rather than VKA

Grade 2B

Treatment for special patient group

Grade 2C

- VTE and Cancer: LMWH first 3 months
- Elderly patients(>75): meta-analysis shows

  NOACs more effective than VKA,

  odds ratio 0.45;95%CI,0.27-0.77

  NO increase in bleeding,

  odds ratio 1.02;95% CI, 0.73-1.43

  or lower : relative risk 0.49;95% CI,0.25-0.96
- Renal failure(CrCl 30-49)-NOACs vs. VKA

  -Efficacy: relative risk 0.70;95% CI, 0.43-1.15

  -Major bleeds: relative risk 0.51; 95% CI, 0.26-0.99

Duration of anticoagulation
ACCP 2016

- Extended duration for
  -Second event or Cancer — Grade 1B
  -1st unprovoked VTE & low-moderate risk of bleeding — Grade 2B
- Most other patients-3 months

Additional risk factors for recurrence

- Male sex
- Elevated D-dimer 1 month after stopping
- Residual thrombosis

Clinical prediction rules

Name, ref	Components	Interpretation
Vienna	Male sex Proximal DVT and/ or PE Elevated D-dimer	Nomogram with continuous Model
DASH	D-dimer Age Sex Hormonal therapy	Score ≤ 1→annual risk 3.1%
Men continue And HER DOO2	Post- thrombotic signs D-dimer≥250mg/L Body mass index≥30 Age≥65	(only for females) 0 or 1 of the criteria →annual Risk<3%

Perhaps no anticoagulation?

- Distal DVT without risk factors

  -In that case, consider serial ultrasound for 2w

  Grade 2C

- Subsegmental PE without risk factors

  -Do bilateral CUS of the legs.

  -In case of risk factors- anticoagulate

  Grade 2C

Risk factors supporting Rx

Distal deep vein thrombosis	Subsegmental pulmonary embolism
External thrombus(>5cm) or present in several veins	Marked symptoms, not attributable to other cause
Location close to proximal veins	Low cardiopulmonary reserve
Permanent provoking risk factor or unprovoked thrombosis	Permanent provoking risk factor or unprovoked thrombosis
Active cancer	Active cancer
Hospitalized patient	Hospitalized patient
Previous venous thromboembolism	Previous venous thromboembolism
High D-dimer level without another apparent cause	

Compression stockings?

- Compression stockings for 2years did not reduce post-thrombotic syndrome or pain
- Stockings are not recommended for routinely use in DVT

Grade 2B

- Patients with symptoms may benefit

IVC Filter?

- VTE treated with anticoagulants, we recommend against an IVC filter (Grade 1B).
- The PREPIC 2 randomized trial found that placement of an IVC filter for 3 months did not reduce recurrent PE, including fatal PE, in anticoagulated patients with PE and DVT who had additional risk factors for recurrent VTE

JAMA 2015;313(16):1627-35.

For recurrent VTE

- For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C),
- For recurrent VTE on LMWH we suggest increasing the LMWH dose (Grade 2C).

Conclusions

- VTE is an increasing problem
- Several risk scores and risk stratification tools are available and should be used
- Diagnostic algorithm for DVT/PE is helpful
- Many options for treatment of VTE exist
- Decide at 3-6months regarding stopping or indefinite anticoagulation