VTE – Case Study

Dr Stephen Child, MD, FRACP, FRCP
General Physician
Respiratory Interest
Director of Clinical Training
Auckland District Health Board

(20 min)

Outline

Case for discussion

Issues
- Role of D-Dimer (Well's)
- Travel and VTE
- Dabigatran
- Other

68 year old female presents 4 days post-Fiji holiday with swollen, tender left calf

What is the differential diagnosis?

a) Should we order a D-Dimer?

b) When to do ultrasound?

c) Warfarin vs Dabigatran?

d) Duration of anticoagulation?

What is differential diagnosis

i) DVT

ii) Cellulitis

iii) Coral / toxin / jellyfish / insect

iv) Sunburn

v) Allergy

vi) Baker's cyst

vii) Fixed drug reaction

Travel and Risk for VTE

Meta-Analysis:

Chandra et al (Harvard)
Annals July 7, 2009

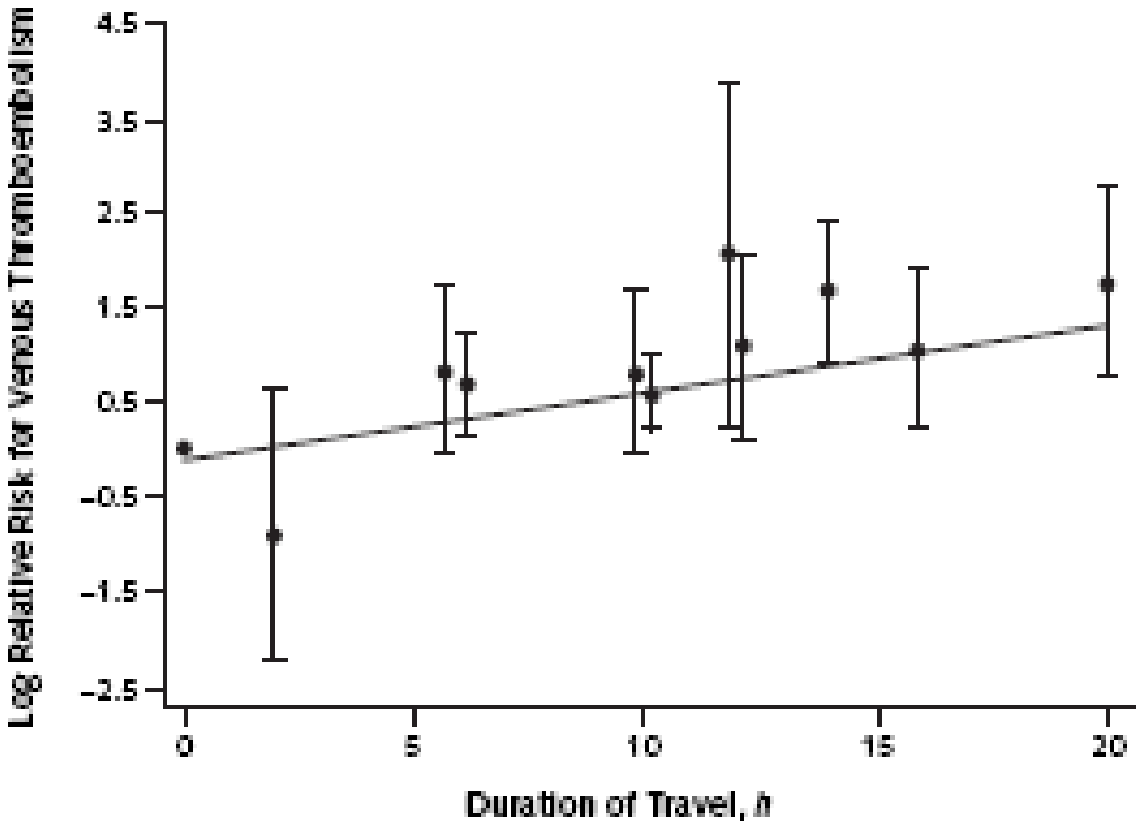
Background:

- 2.5 billion air travel passengers 2010
- 5 studies = no relationship VTE
- 8 studies = elevated risk

Conclusions:

- Overall RR 2.0
- Referred control excluded – RR – 2.8
- 18% risk per 2 hours travel
- 26% risk per 2 hours air travel

Figure 3. Relationship between duration of travel and relative risk for venous thromboembolism, as reported by 4 included studies.



1 VTE per 4600 flights = “healthy baseline”

Should we order a D-Dimer?

Active cancer? +1

Bedridden recently >3 days or major surgery within four weeks?

Calf swelling >3cm compared to the other leg?

Collateral (nonvaricose) superficial veins present?

Entire leg swollen?

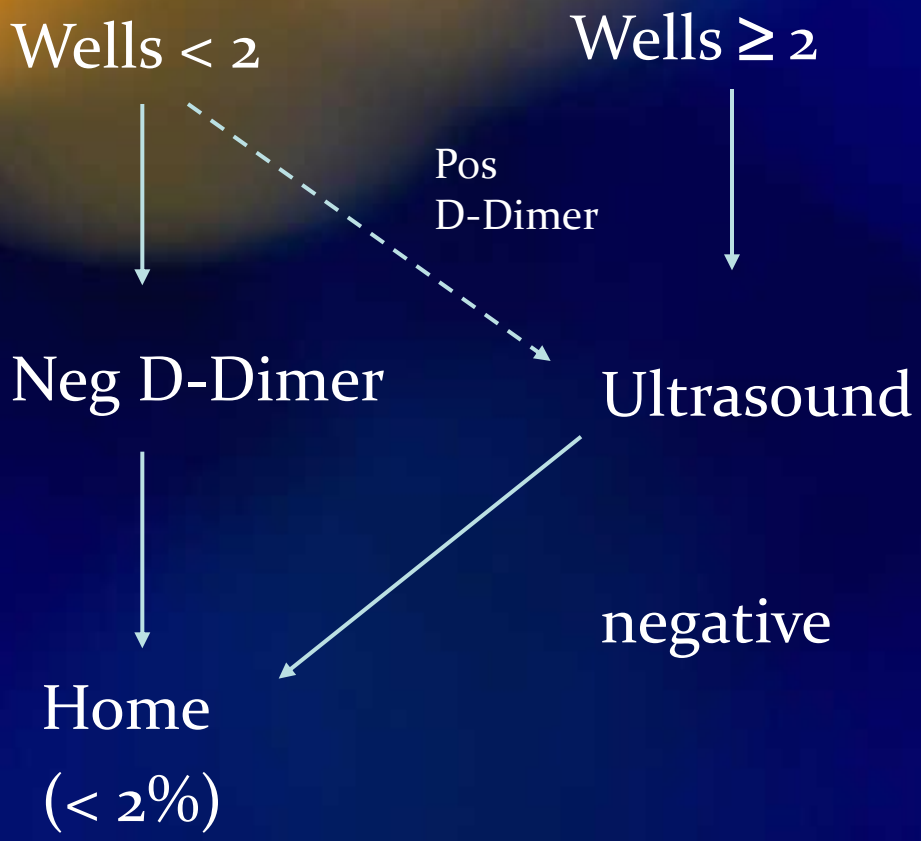
Localized tenderness along the deep venous system? Pitting edema, greater in the symptomatic leg?

Paralysis, paresis, or recent plaster immobilization of the lower extremity

Previously documented DVT?

Alternative diagnosis to DVT as likely or more likely?-2

Should we order a D-Dimer?

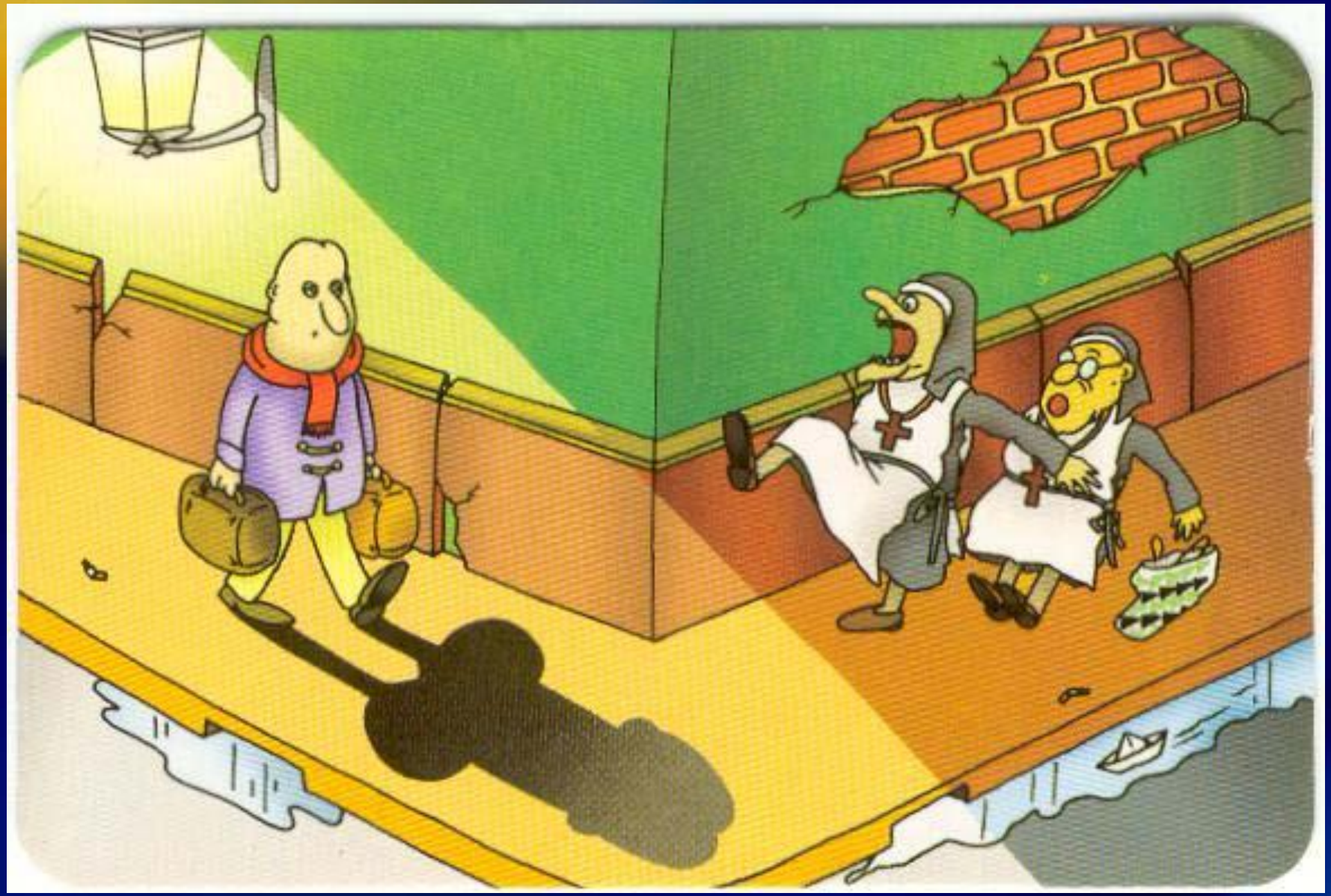


False '+' – Age !!!
- Surgery
- Infection
- Trauma
- etc

Dabigratran versus Warfarin?

No indication treatment VTE

SEEING THE SAME (information) DIFFERENTLY



The NEW ENGLAND JOURNAL of MEDICINE

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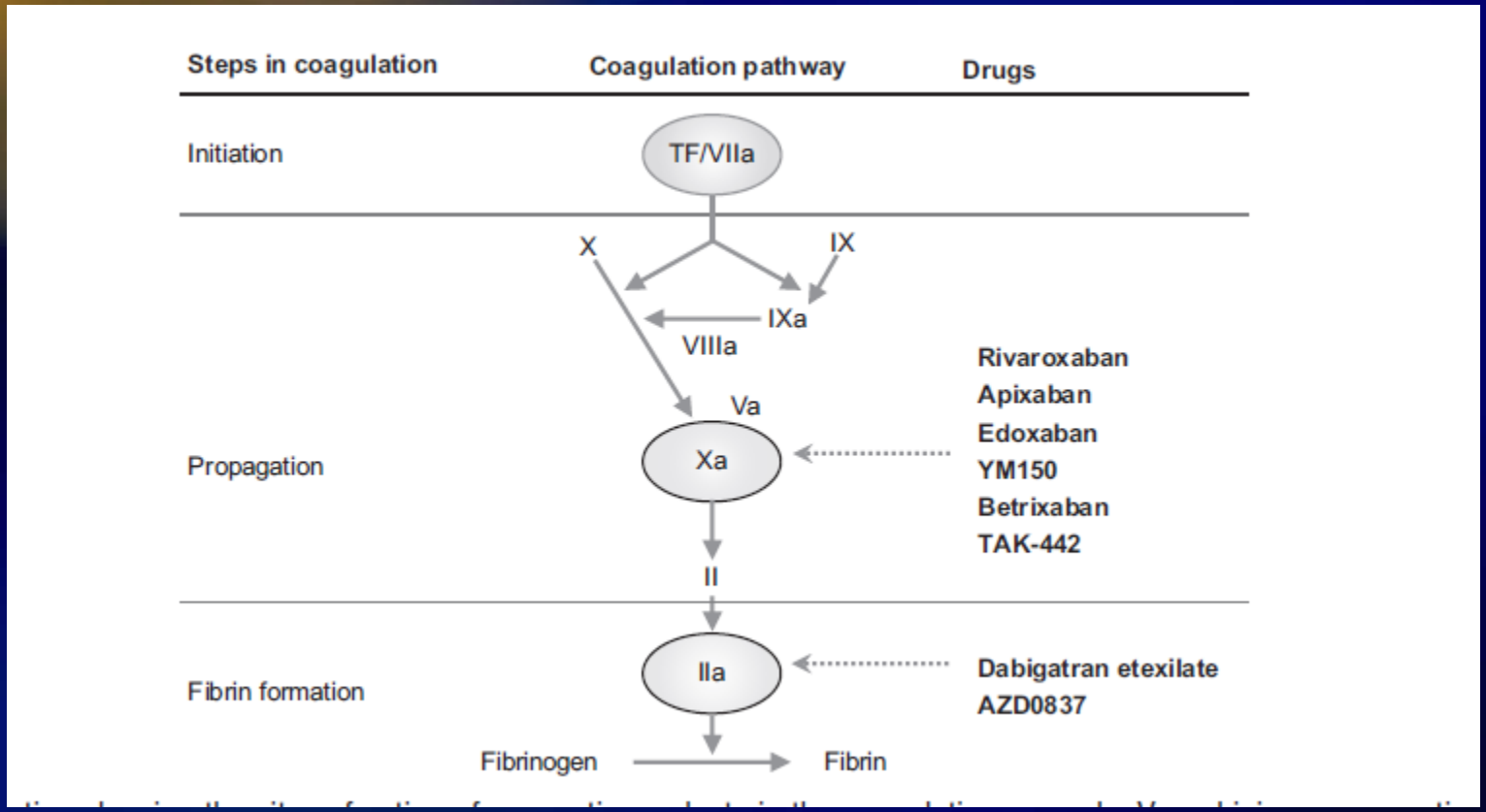
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

What is it?


Steps in coagulation
Coagulation pathway
Drugs
Initiation
TF/VIIa
X
IX
IXa
VIIIa
Va
Xa
Propagation
Rivaroxaban
Apixaban
Edoxaban
YM150
Betrixaban
TAK-442
II
IIa
Fibrin formation
Dabigatran etexilate
AZD0837
Fibrinogen
Fibrin

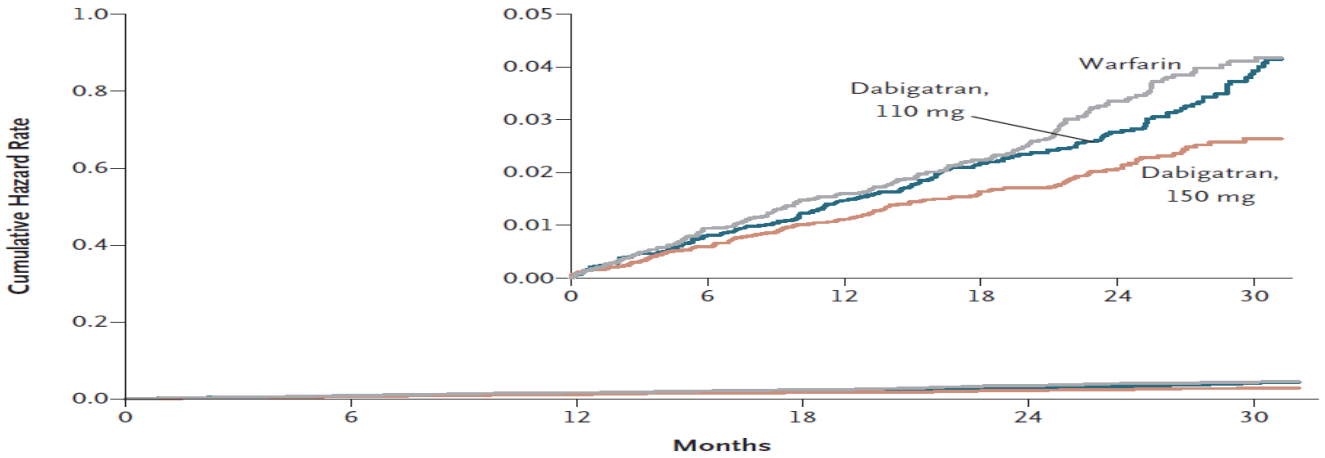
RE-LY design

- Randomised (18 113 patients)
- Non-inferiority
- AF patients (variety of forms)
  - Dabigatran 110mg bd blinded
  - Dabigatran 150mg bd blinded
  - Warfarin (INR 2-3) open label

Outcomes

- Primary
  - stroke + systemic embolisation
- Primary net clinical benefit
  - S + SE + MI + PE + Death + Maj Haem

- 18 113 enrolled
- Mean age 71; 63% men
- Median follow up 2 years



No. at Risk

Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Primary outcome
D110 bd: S+SE = 1.53% pa
D150 bd: S+SE = 1.11% pa
Warfarin: S+SE = 1.69%pa

NNT = 172 pa

Warfarin efficacy

- Time during which INR 2 – 3
- 64%

RE-LY Safety

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

Dabigatran – MI/ACS risk

Meta analysis RCT x 7 = 30,514

Dabi	Placebo/Warf/Enox	
1.19%vz	0.79%	p0.03

Arch Intern Med 2012; 172(5):397-402

RE-LY results

- Both dabigatran regimens non-inferior
- Dabigatran 150mg bd “superior” to warfarin
- Major bleeding
  - D 110mg bd < warfarin
  - D 150mg bd = warfarin

Drug interactions

Table

DRUG INTERACTIONS WITH DABIGATRAN

Precipitant Drug	Dose; Time Relative to Dabigatran	Change in Dabigatran AUC
Amiodarone	600 mg; concurrent	↑ 58%
Clarithromycin	500 mg BID; 1 hr before	NC
Clopidogrel	300/600 mg LD; concurrent	↑ 30%-35%
Clopidogrel	75 mg/d; concurrent	NC
Ketoconazole	400 mg; concurrent	↑ 138%-153%
Pantoprazole	40 mg BID; 1 hr before	↓ 28%
Quinidine	200 mg Q2H x 5; concurrent	↑ 53%
Ranitidine	150 mg/d; 10 hr before	NC
Rifampin	600 mg; 12 hr before	↓ ~66%
Verapamil	120 mg BID IR; 1 hr before	↑ 243%
Verapamil	240 mg ER; concurrent	↑ 171%
Verapamil	120 mg BID IR; 2 hr after	NC

AUC = area under the concentration-time curve; BID = twice daily; ER = extended release; IR = immediate release; LD = loading dose; NC = no change; Q2H = every 2 hours.

Adapted from reference 3.

FDA

- Dabigatran approved October 2010

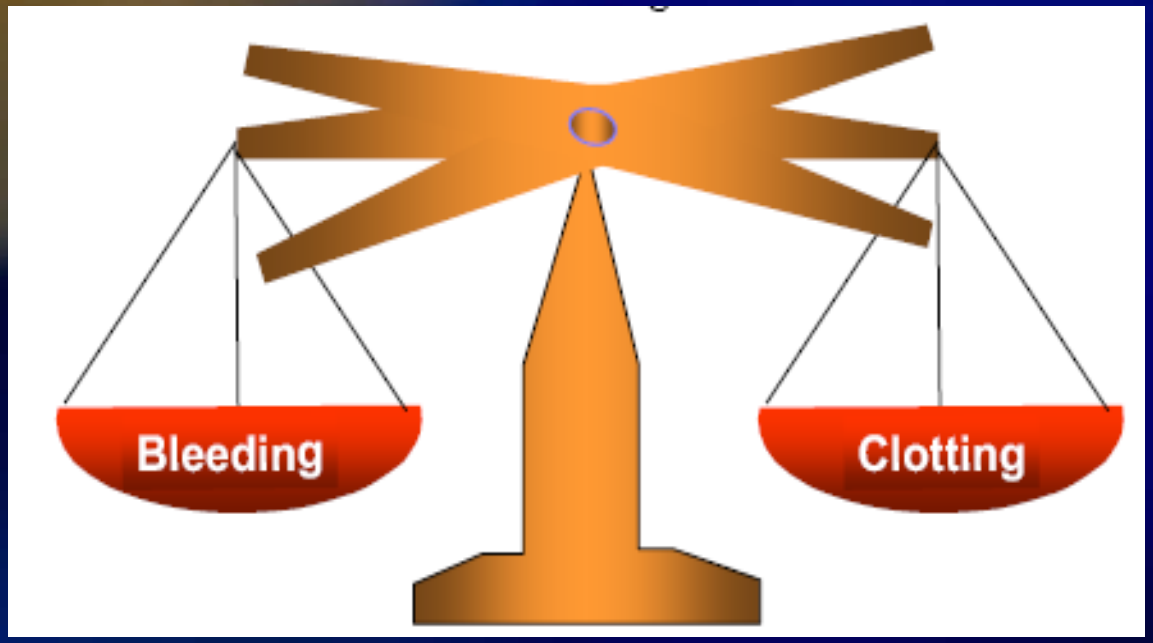
- Approved 150mg bd only
  - No specific population to benefit from 110mg bd
    - Older
    - ↓ GFR
    - Previous bleeds

NZ Indications

- AF (NNT 172 vs warfarin)
  - Not everyone with AF
  - Warfarin “intolerant” - maybe
  - Falls risk – no
  - Dementia – no
  - Poor compliance/alcohol - no
  - Inconvenience of blood tests – yes
  - Polypharmacy – maybe
  - EGFR < 30 - no

OPTIMAL DURATION:BENEFIT RISK

PATIENT CHOICE



BURDEN of THERAPY

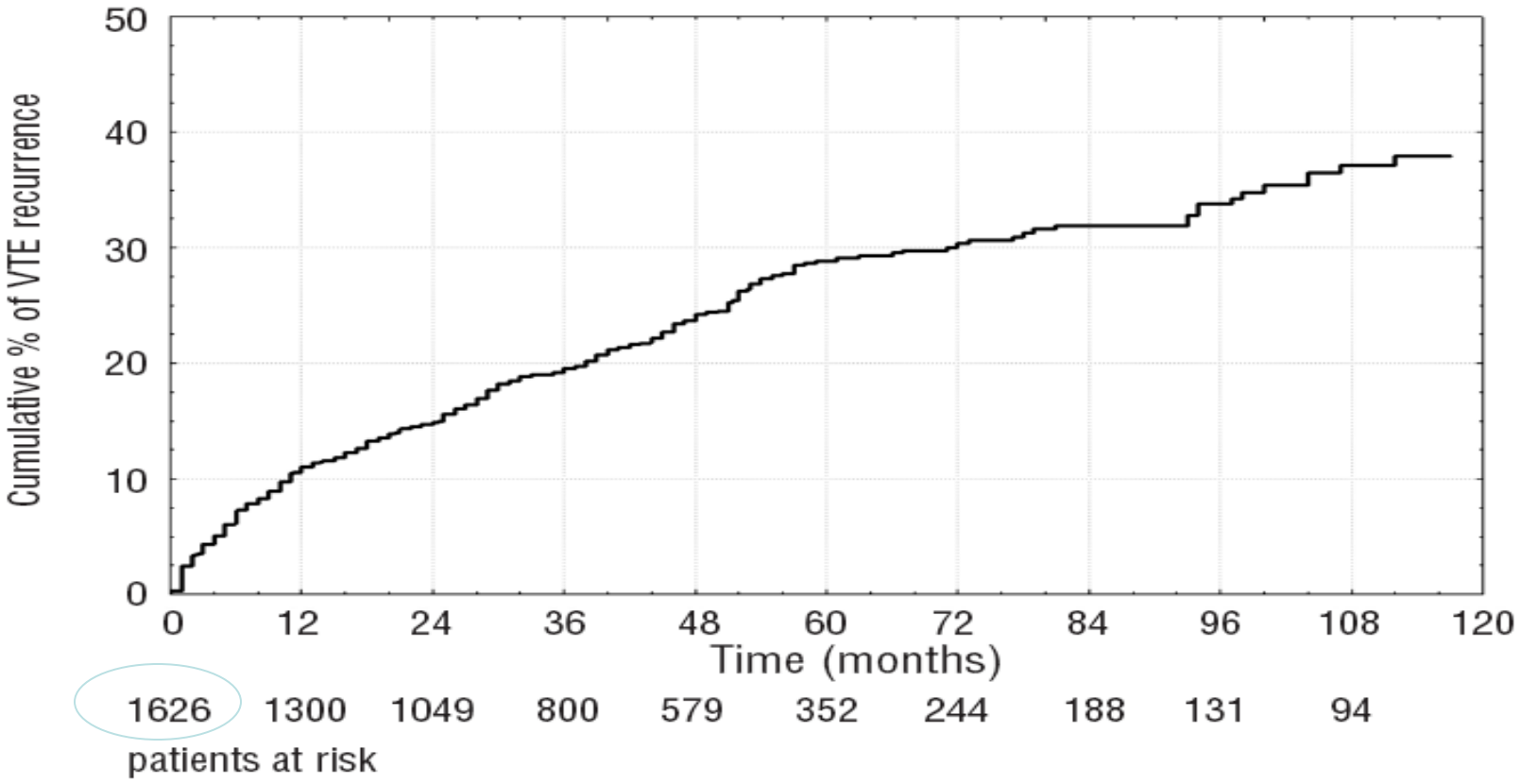
TREATMENT RELATED

Major 1-3% Cost
Death due bleeding

RECURRENCE

Post thrombotic syndrome 15-50%
Severe PTS 5%@10yrs
6x higher DVT recurrence rate
CPTEH 3-4%
Death due recurrence

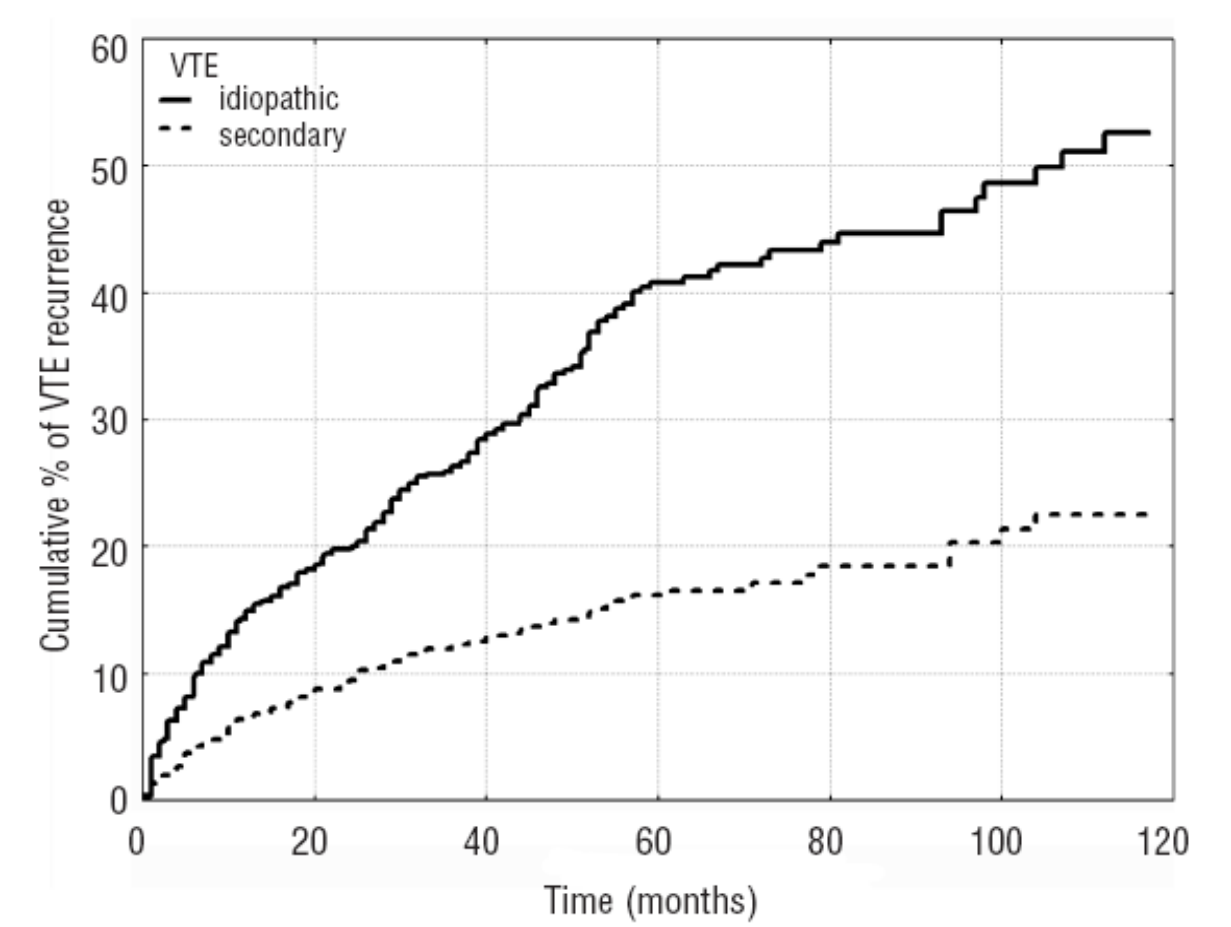
PROXIMAL DVT/PE: A CHRONIC DISEASE



PRANDONI; ANNALS INT MED 1996
HAEMATOLOGICA 2007;92:199

Mean 5yr followup

RECURRENCE RISK: UNPROVOKED v PROVOKED

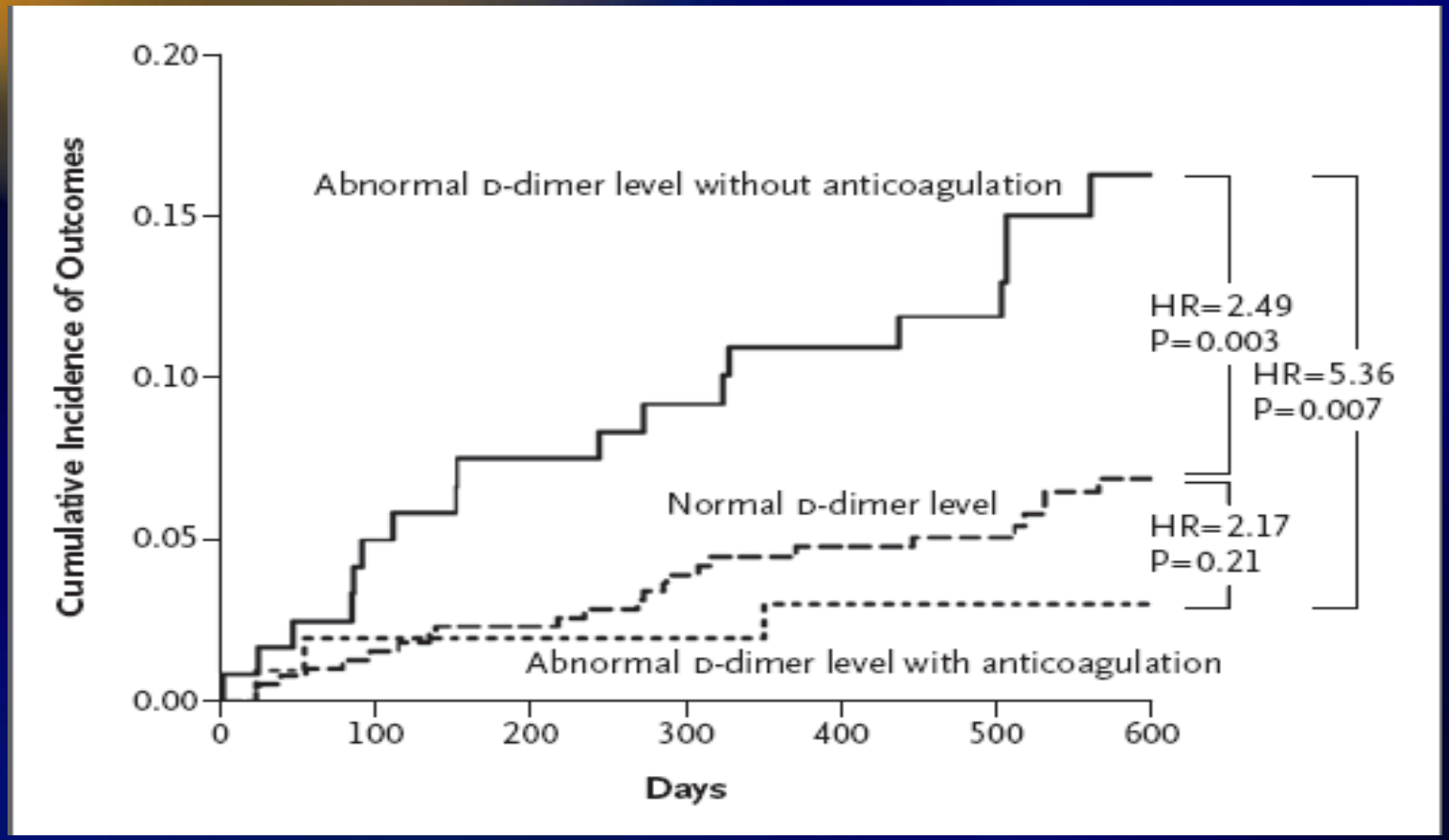


PRANDONI HAEMATOLOGICA 2007;92:199

POTENTIAL APPROACHES TO OPTIMAL DURATION UNPROVOKED VTE

- IDENTIFY THOSE AT HIGHEST RECURRENCE RISK
  - DEFAULT POSITION ?? CONTINUE 'lifelong' (ACCP 2008).
- IDENTIFY THOSE AT LOWEST RECURRENCE RISK (?<1-3%)
  - DISCONTINUE TREATMENT
- IDENTIFY THOSE AT LOWEST BLEEDING RISK
- DO SOMETHING DIFFERENT
  - NEW DRUGS WITH DIFFERENT RISK PROFILE
  - USE OLD DRUGS DIFFERENTLY (ASPIRIN??)

POTENTIAL CANDIDATE PARAMETERS RECURRENCE RISK PREDICTION:DDIMER



15.5%

2.9%

6.2% RECURRENCES with NORMAL DDIMER(~4.4%/YR)

PALARETI NEJM 2006;355:1780

PROLONG STUDY

Summary:

- Consider Differential'
- Always Wells > D Dimer
- False Pos D Dimer
- Dabigatran for who ?
- Duration ?

20 min

Chest Pain

Case Study

41 year old man with family hx of CAD and epilepsy, presents with 2 day history of chest pain (March)

November – Florida

Jan – Half marathon

Feb – Stress !

“Squeezing, 2 – 3 hours, intermittent, no association, worse at night”

Which associated feature is most "reassuring"?

a) Associated SOB with pain
b) Worse lying flat
c) Radiation to right shoulder
d) Localised (<2 FB) at left breast
e) No history of leg swelling

Would you do an ECG?

a) Yes
b) No

Would you do a CXR?

a) Yes
b) No

Would you request urgent cardiac enzymes ?

a) Yes
b) No

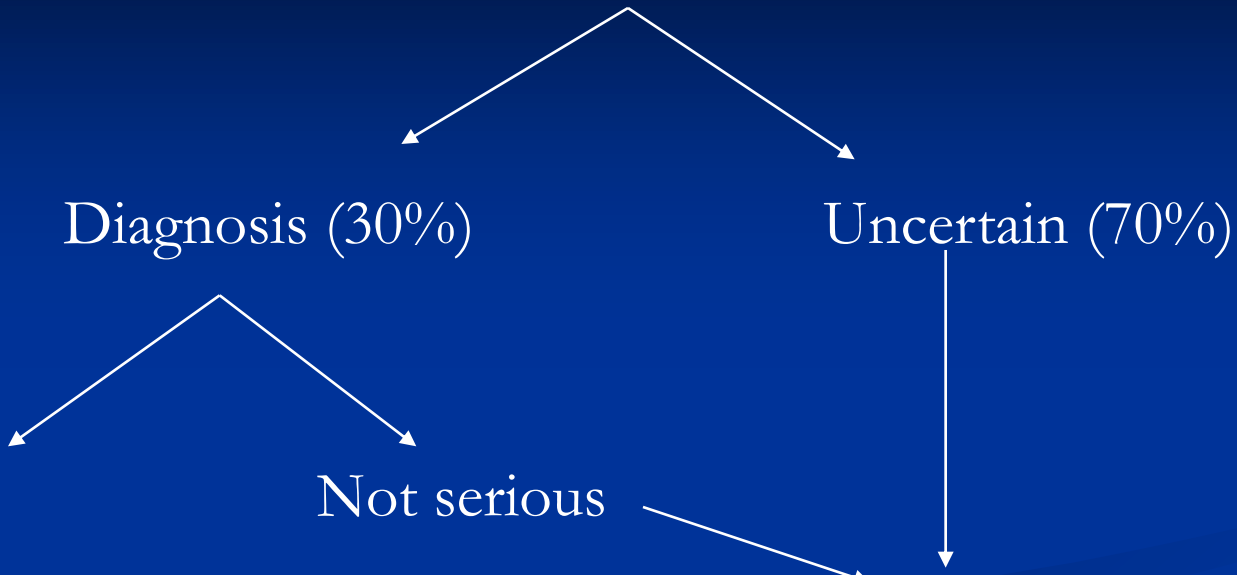
Which is the least useful exam finding ?

a) Presence of heart murmur
b) Abdominojugular reflex positive
c) Symmetrical air entry at apices
d) BP in both arms
e) Presence of S4

Would you do an acute referral to hospital ?

a) Yes
b) No

Chest Pain



T ension pneumo

E mbolus

P ericarditis

I schemia

D issection

MSK

HVS

GI → 50% PPI response

Shingles

Pleurisy

Other

Odds :

- 6/400 or 1.5% had Unstable Angina or MI

and 1.9 – 4.0% of patients discharged from ED had acute coronary syndrome

GP = "Best Guess"

Chest Pain

Serious

Hospital

Not serious

- Document Clearly!
- Pain > 5 days
- One finger localized
- Movement or palpation
- Fleeting Pain

Pre-test probability	+		Tests	=	Post-test probability	
Non-cardiac Atypical Cardiac pain	+	Risks	+	ECG Troponin CXR	=	Post-test probability

"Low risk" - History

- Sharp
- Localised < 2 FB
- Pleuritic or positional
- Reproducible

* Note * 48/51 Rt arm radiation = MI !

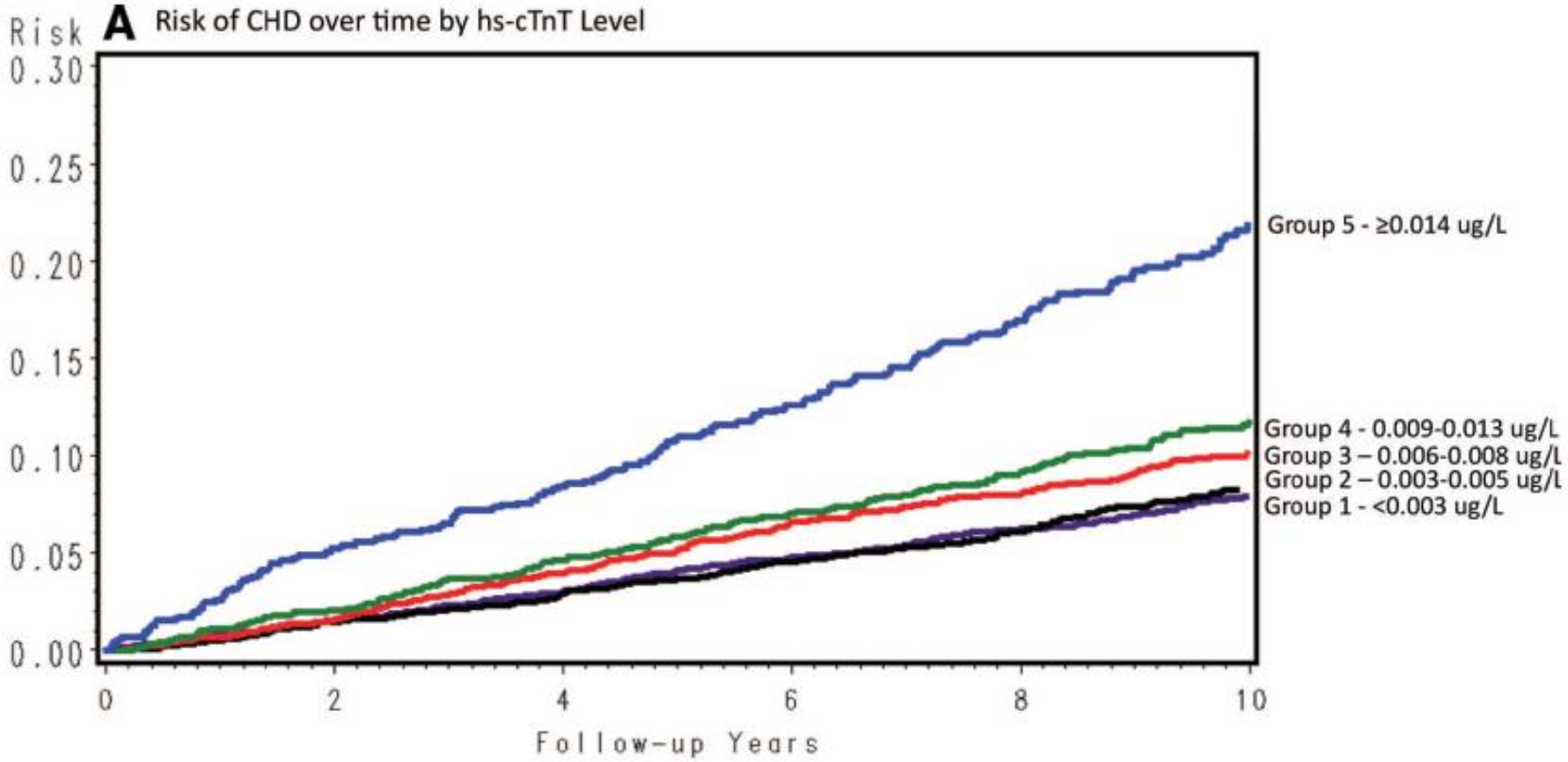
Pearls

- Clinical exam (Hx + Dx) – 88% accurate for non-organic
- 13% suspected cardiac with histrionic actress vs 50%
- NTG relief does not distinguish (35 vs 41%)
- 4 – 40% of ECG's are "false negative"
- 20% of CXR can be "useful"

Elevated Troponins

Any elevation, in no matter what setting, denotes a worse prognosis

Risk of CHD over time by hs-cTnt level



Saunders et al. *Circulation* 2011;123:1367-76

Classification of potential types of mechanisms causing troponin elevations

Type 1	Myocyte necrosis
Type 2	Apoptosis
Type 3	Normal myocyte turnover
Type 4	Cellular release of proteolytic troponin degradation products
Type 5	Increased cellular wall permeability
Type 6	Formation and release of membranous blebs

White, HD. JACC 2011 in press

Elevations of Troponin in the absence of an Acute Coronary Syndrome

- Congestive heart failure - acute and chronic
- Renal Failure
- Tachy or bradyarrhythmias, or heart block
- Acute neurological disease, including stroke, or subarachnoid haemorrhage
- Pulmonary embolism, severe pulmonary hypertension
- Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
- Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
- Inflammatory diseases, e.g., myocarditis, myocardial extension of endocarditis

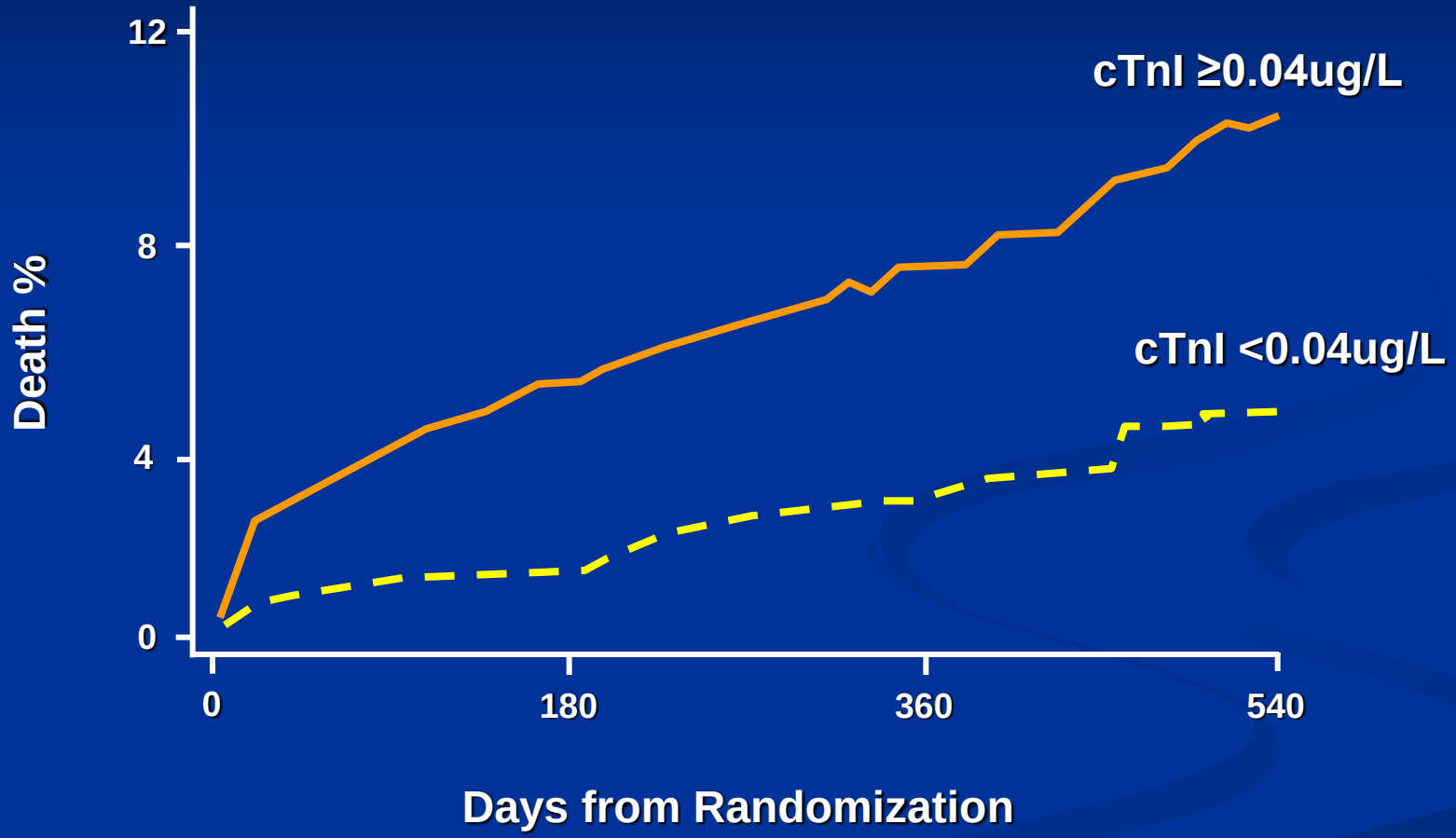
White HD Lancet 2008

Elevations of Troponin in the absence of an Acute Coronary Syndrome

- Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, capecitabine
- Aortic dissection, aortic valve disease, hypertrophic cardiomyopathy
- Hypothyroidism
- Phaeochromocytoma
- Takosubo cardiomyopathy
- Burns affecting >30% of body surface area
- Rhabdomyolysis with cardiac injury
- Critically ill patients with respiratory failure, or sepsis
- Electroconvulsive therapy
- Snake bites

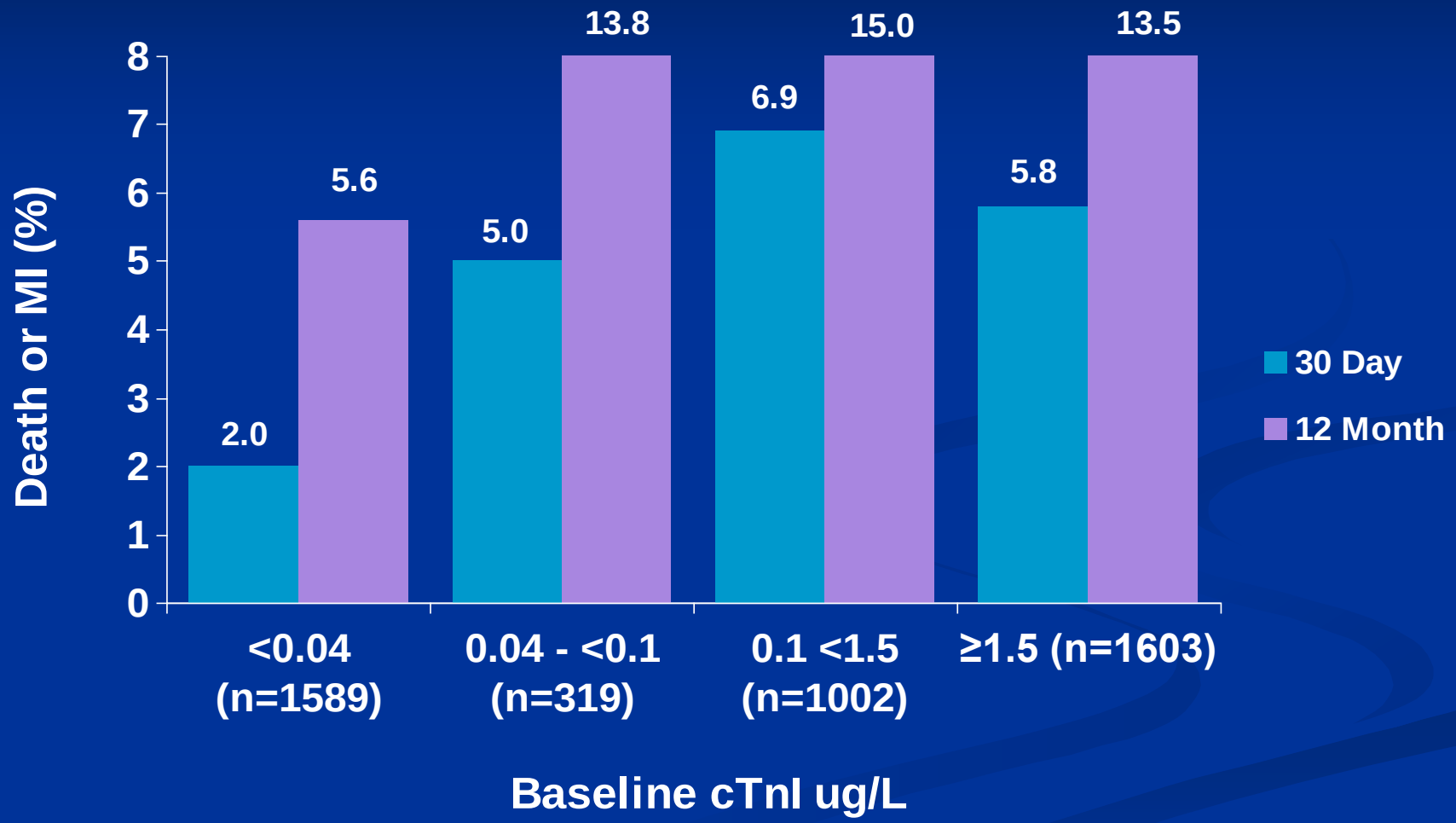
White HD Lancet 2008

Risk of death by baseline TnI result



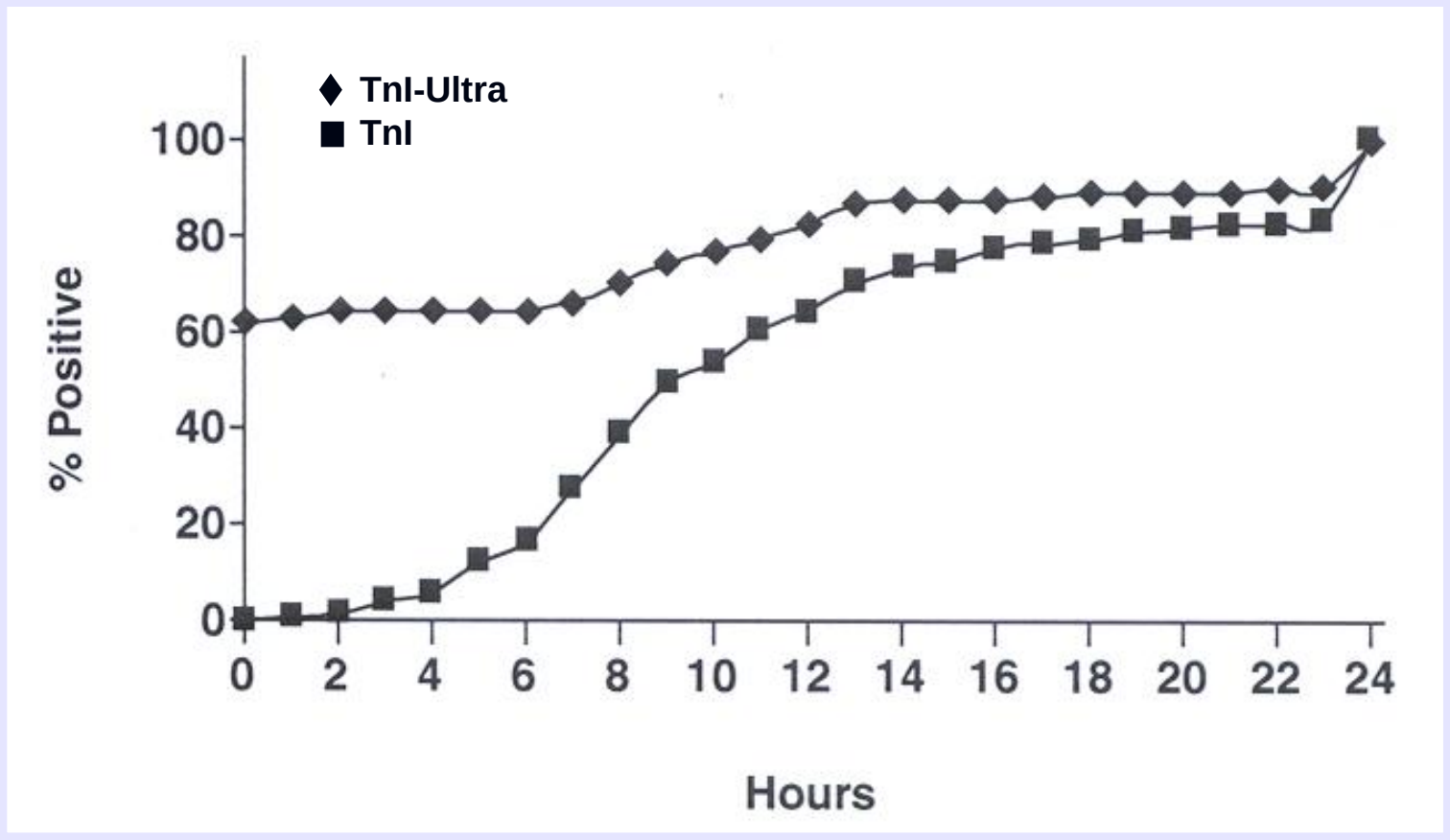
Bonaca et al. JACC 2010

Death or MI with lower levels of TnI



Bonaca et al. JACC 2010

Timing of conversion to positive Troponin in patients with myocardial injury



Melanson Am J Clin Pathol 2007; 128: 282

Classification of Myocardial Infarction

Type 1	Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion or rupture, fissuring or dissection
Type 2	Myocardial infarction secondary to ischemia due to imbalance between oxygen demand and supply e.g. coronary spasm, anemia, or hypotension
Type 3	Sudden cardiac death with symptoms of ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography or autopsy, but death occurring before blood samples could be obtained
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with verified stent thrombosis
Type 5	Myocardial infarction associated with CABG

The Universal Definition of Myocardial Infarction

Criteria for Myocardial Infarction:

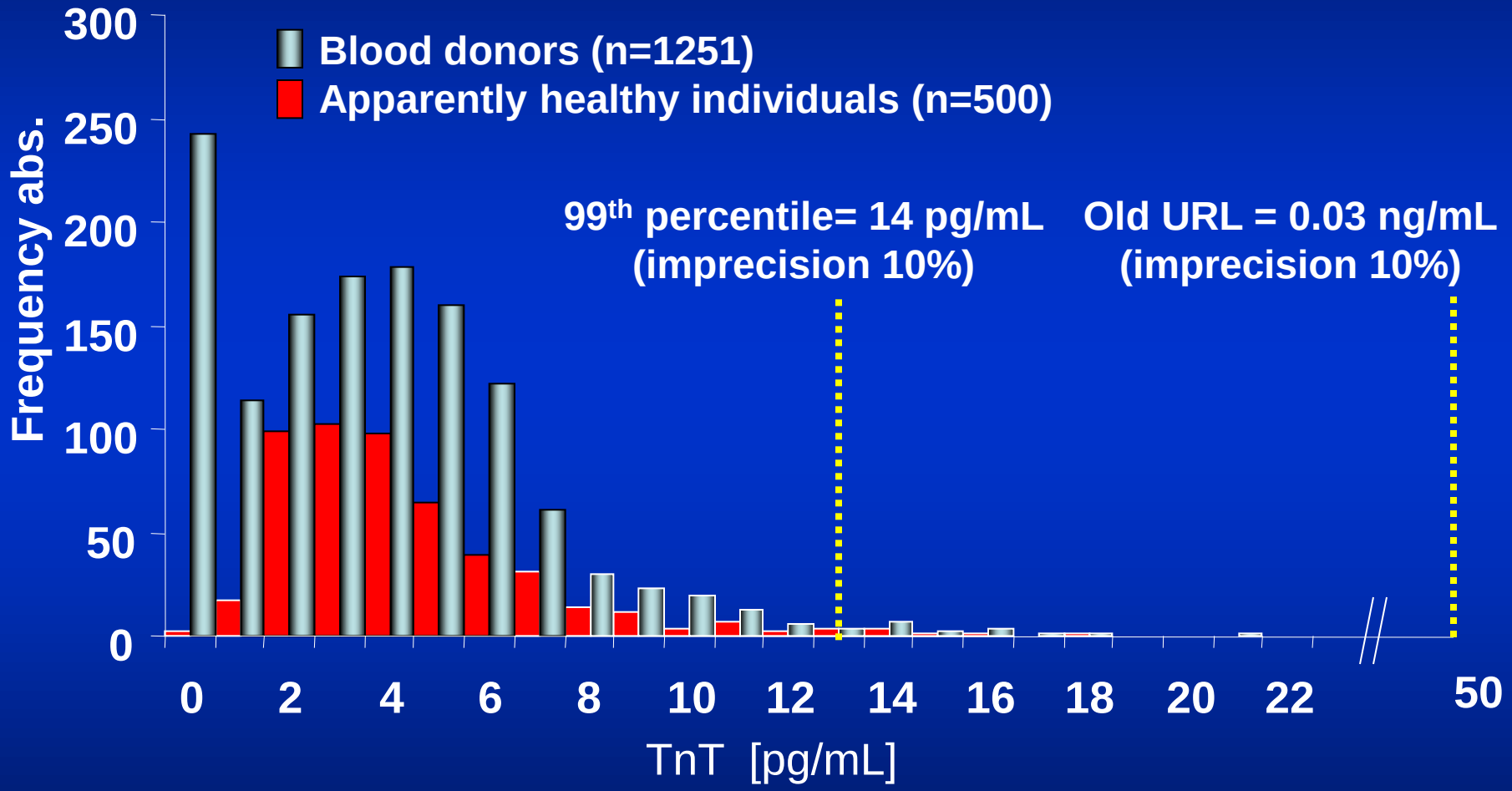
'Detection of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia...'

Requirements for assays:

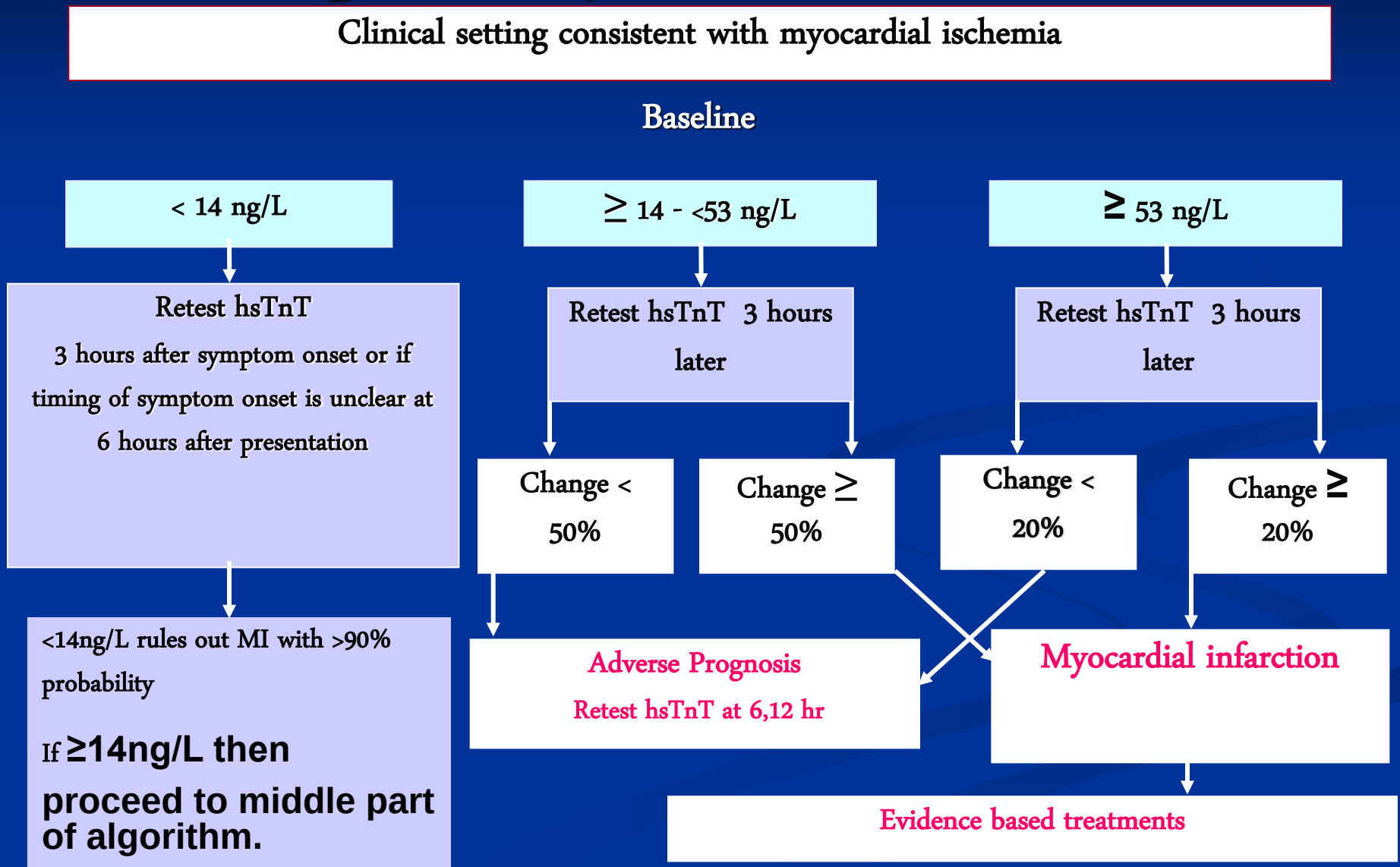
"Optimal precision [coefficient of variation (CV)] at the 99th percentile URL for each assay should be defined as ≤10%"

Thygesen, Alpert, White. Universal Definition of Myocardial Infarction 2007 EHJ, JACC, CIRC

99th Percentile for hs Troponin T



Use of high sensitivity troponin T to diagnose myocardial infarction



White HD; AHJ 2010

Dealing with Troponin elevations in clinical practice

- Elevations always mean poor prognosis
- Changing levels are indicative of acute processes
- Non changing levels are indicative of chronic processes

Which of the following treatments improves survival in acute coronary symptoms?

a) Aspirin
b) Nitrates
c) Diltiazem
d) Oxygen
e) Morphine
f) More than 1 above

"Serious"

→ O2, Aspirin

→ IV + Monitor

→ Nitrates (beware Viagra/AS)

“Not Serious”

- Trial PPI
- Open mind
- Review

20 min

Case Study
Fatigue

History

20 year old female

- “sudden” onset “fatigue” in November 2011
    - ? Preceding URTI
    - University exams

DDx		Questions
1. Apathetic	……	Good/Bad; Post-exertional; Progression
2. Hypersomnolence	……	24 hour cycle; sleep; syncope; catatonia
3. Cardiovascular/ Resp/Muscle	……	Exertional ? myopathy

History

…. still going to gym

…. “bad every day”

…. Sleep 01^{00} – 10^{00} - unrefreshed

DDx	Questions
…. Infectious	….. fever, night sweats, weight loss
…. Allergy	….. atopy, sneezing, itch
…. Inflammatory	….. Raynaud's, Sicca, iritis, rash, LBP
…. Malignancy	….. "common" for age group
…. Deficiency	….. nutrition, bowels, periods, syncope
…. Hormone	….. periods, thyroid

Physical

- Left nasal polyp
- Right post cervical LN

Lab

Ferritin - 17

Plan

1. Fe-def “work-up”
2. ?Sinusitis vs allergy vs OSA
3. Exercise, nutrition
4. Trial antidepressant

Discussion