Managing Acute Coronary Syndromes

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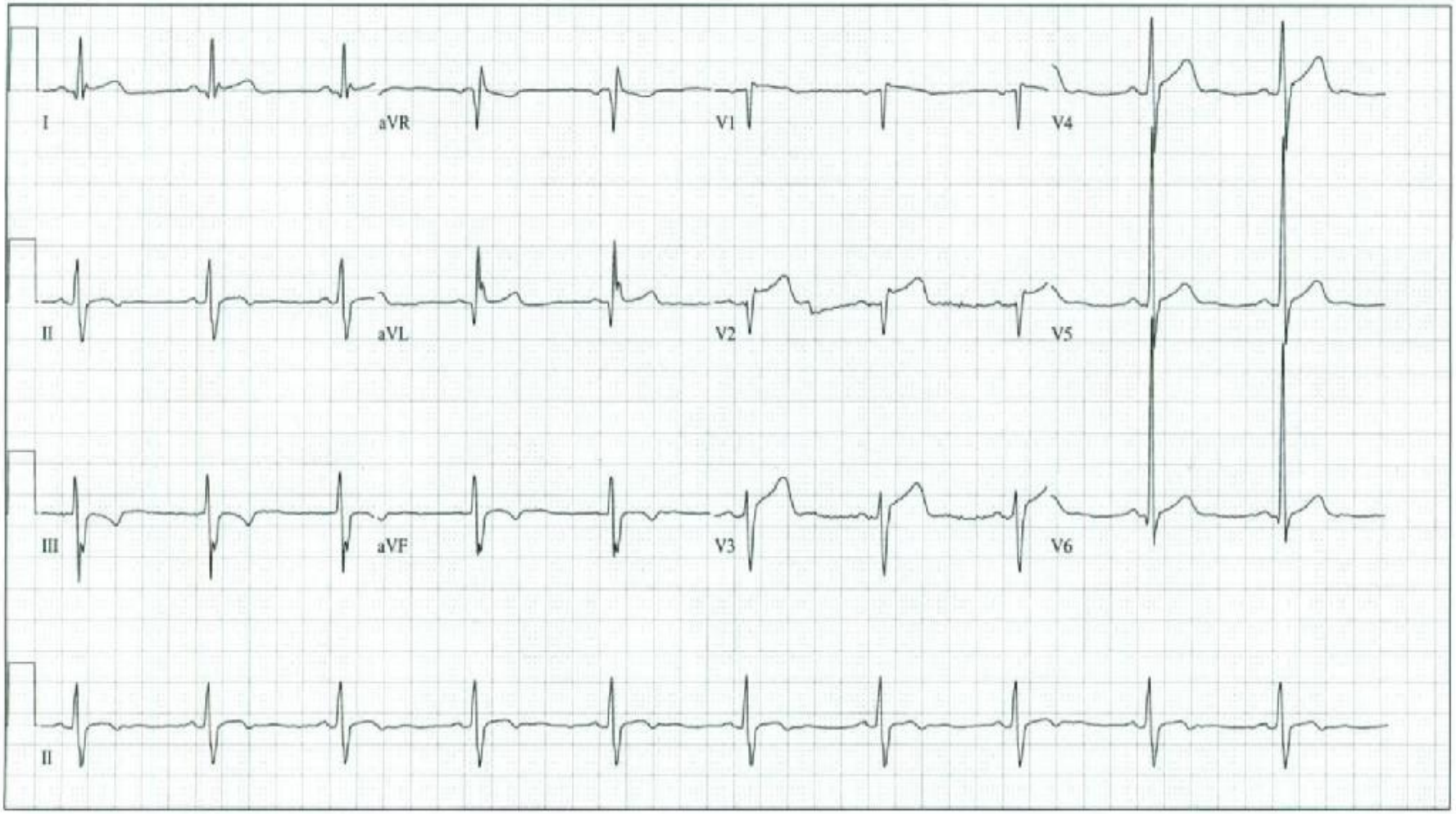
Managing Acute Coronary Syndromes

- Background
- What to do in General Practice
- Unmet need
- Current management with increasing role of invasive approach
- New therapies on the horizon
- Mechanisms causing troponin elevations
- Diagnosis of myocardial infarction
- Dealing with troponin elevations in clinical practice

67 year old male

- 67 year old male
- metastatic prostate adeno Ca
- Waiting for radiotherapy
- While in your waiting room has onset of sudden crushing central chest pain
- Unwell, sweating, pale, cold and clammy

Referred by: Unconfirmed



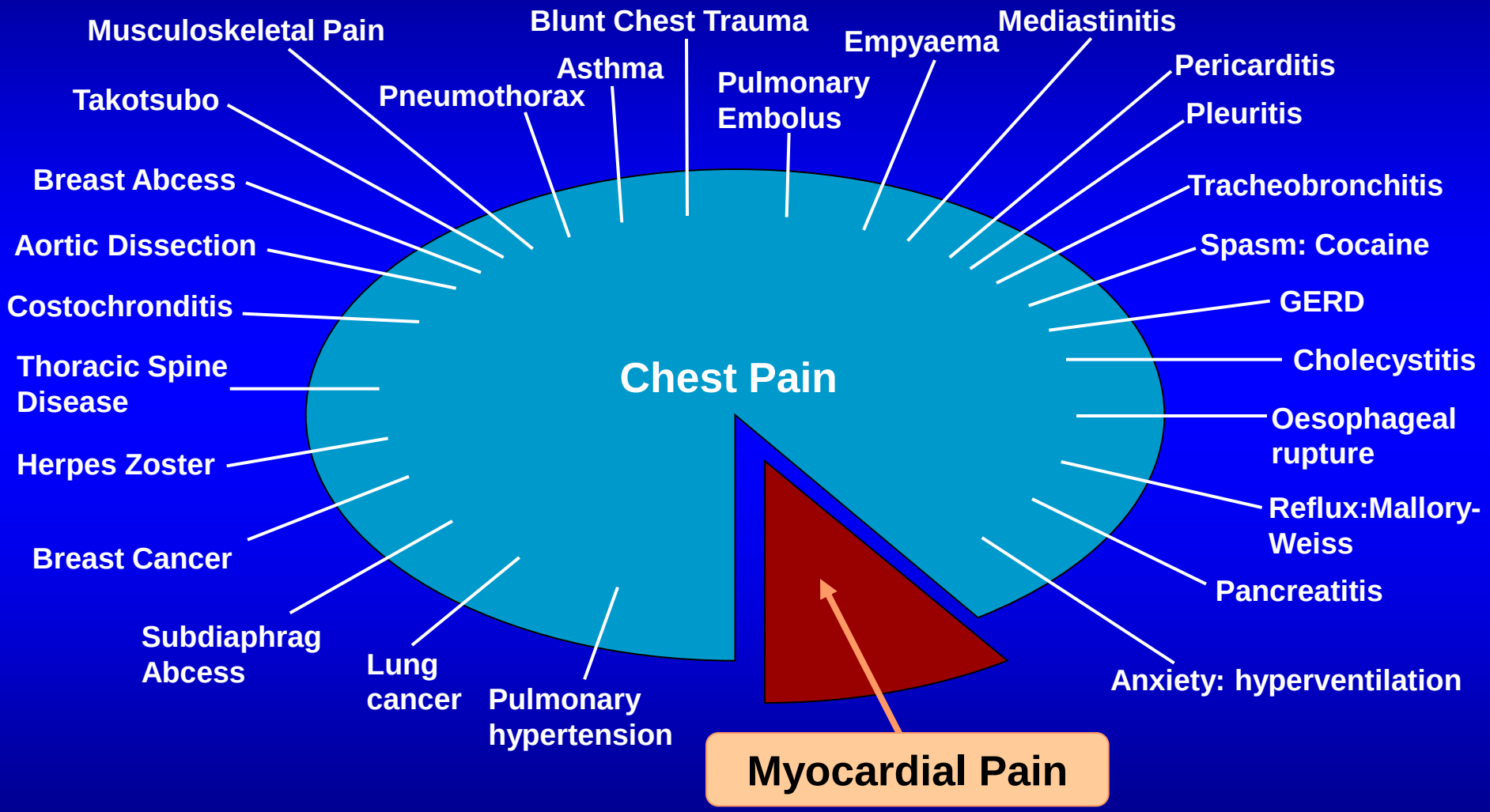
25mm/s 10mm/mV 100Hz 005C 12SL 86 CID: 1

EID:Unconfirmed EDT: ORDER:

What to do?

- History and examination
- Relieve pain: morphine plus antiemetic plus NTG spray
- Half aspirin to chew
- Oxygen 2 L per minute (if saturation < 92)
- Call an ambulance
- Decisions on immediate management should not await hs-TnT results

Chest discomfort ... Is it from the Heart or Not?



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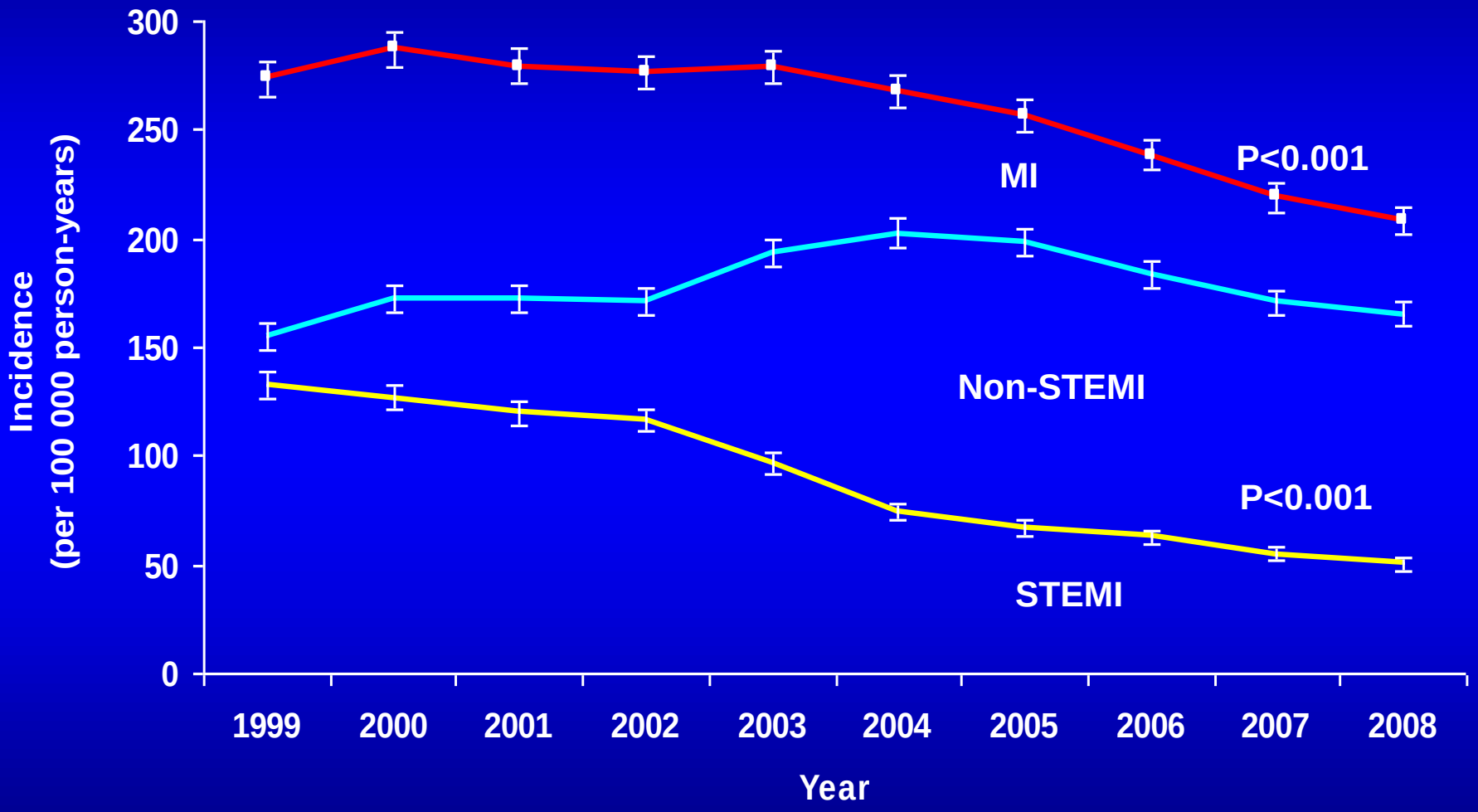
Age- and sex-adjusted incidence rates of acute myocardial infarction, 1999 to 2008



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Yeh RW et al. N Engl J Med 2010;362:2155-2165

Unmet need

Management of ACS

- Almost one-third of patients with UA/NSTEMI ACS will die, have a second event, or are rehospitalised within 1 year of their event
- Therapeutic approaches include:
  - Invasive procedures with pharmacotherapy
    - Diagnostic: cardiac catheterisation with coronary angiography
    - Therapeutic: percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG)
  - Management with medication only

Bill Gates, June 7, 2007
Harvard
Commencement
Address

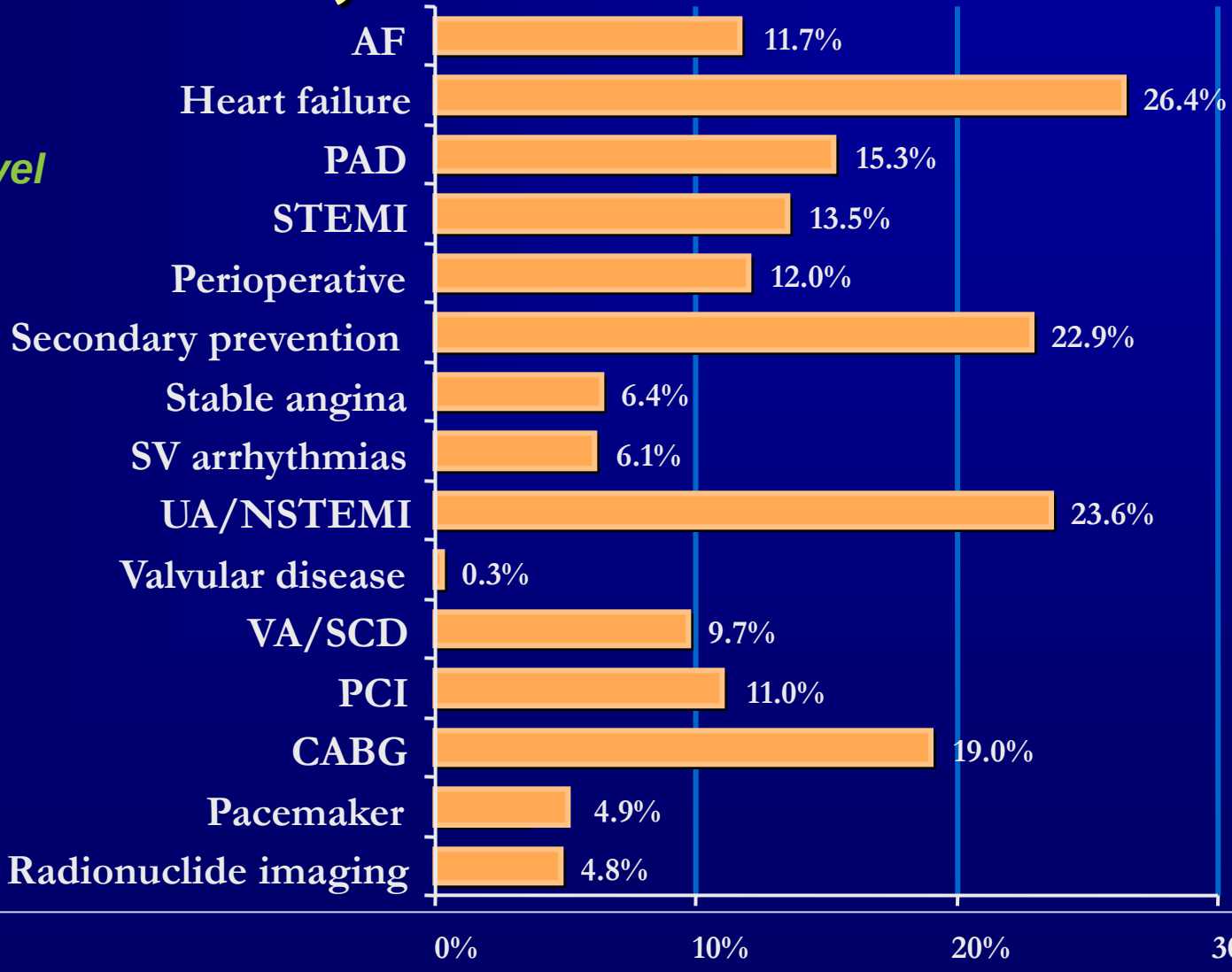
"Humanity's greatest advances are not in its discoveries – but in how those discoveries are applied ..."

Bill Gates – only Harvard College drop-out who has received an honorary degree at Harvard !

We need better evidence

*Current Guidelines: 53 guidelines on 22 topics with 7196 recommendations; Level of Evidence A: 11%

*Guidelines expressing Level of Evidence



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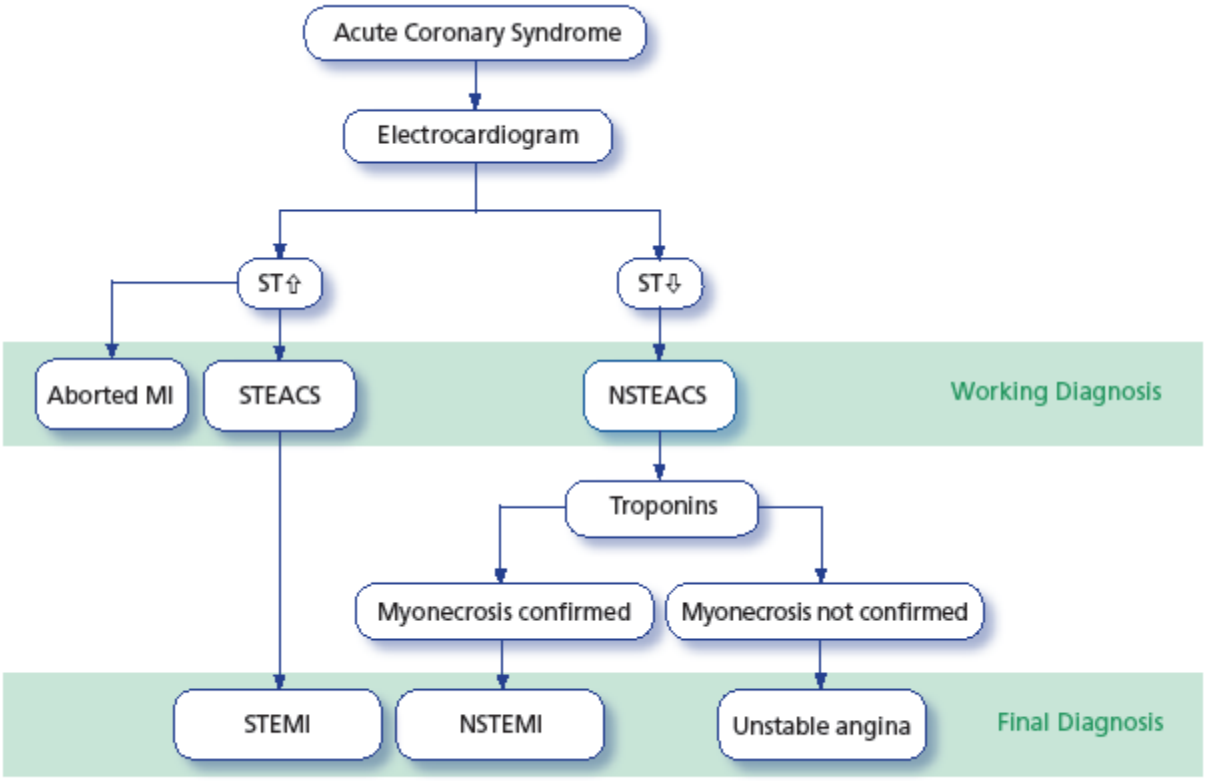
-Tricoci P, et al. JAMA 2009

Classification of acute coronary syndromes

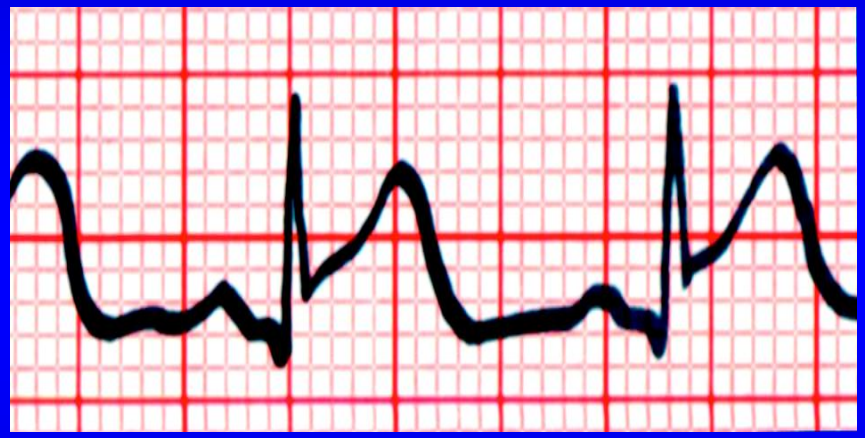


White, Lancet, 2008

ECG manifestations of acute myocardial ischemia

New ST elevation at the J point ≥0.2 mV in men or ≥0.15 mV in women in V_2-V_3; and/or ≥0.1 mV in other leads in both genders.

ST elevation greater than this should be criteria for reperfusion therapy (White, Lancet 2008).



ESC-ACCF-AHA-WHF Universal Definition of Myocardial Infarction

A Guidelines-based approach to the management of STEMI

- Risk stratification: both for ischaemia and bleeding
- Antiplatelet agents: ASA, Clopidogrel, Prasugrel, Ticagrelor, GP IIb/IIIa antagonists
- Anticoagulant agents: UFH, Enoxaparin, Fondaparinux, Bivalirudin
- Fibrinolytic therapy or PCI
- Pharmacoinvasive approach
- Ace inhibitors, beta blockers
- Nicotine patches on day 1
- Rehabilitation
- Improved systems of health care

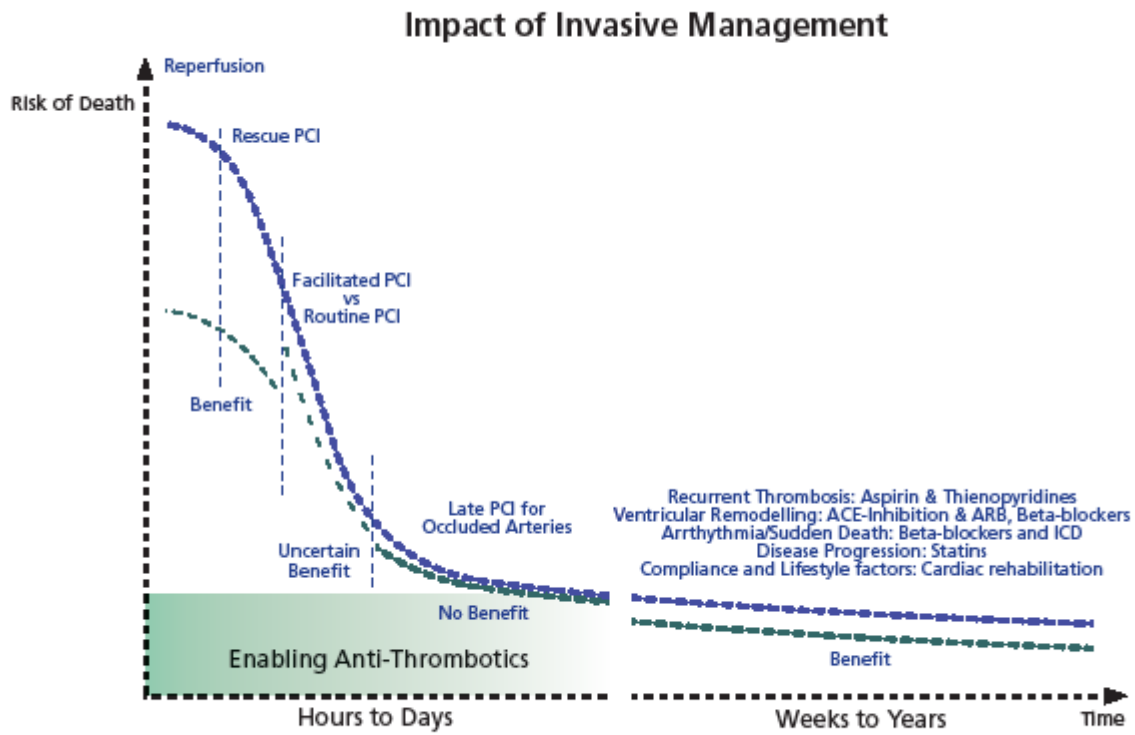
Fibrinolytic Therapy

- Systems to ensure shortened door to needle time: transmission of ECG, prehospital; < 30 minutes
- Aspirin 300mg
- Clopidogrel 600mg if ≤75 years, 75mg if >75 years
- Enoxaparin: 30mg IV bolus if <75 years, 1m/kg sc bid, >75 years, no IV bolus, 0.75mg/kg sc bid, Fondaparinox
- Rescue PCI if < 50% ST resolution at 90 minutes
- Systematic PCI at 3 – 24 hours (pharmacoinvasive)
- Ace inhibitors, beta blockers, statins, stop smoking (nicotine patches), spironolactone (heart failure or decreased EF), rehabilitation

Primary PCI

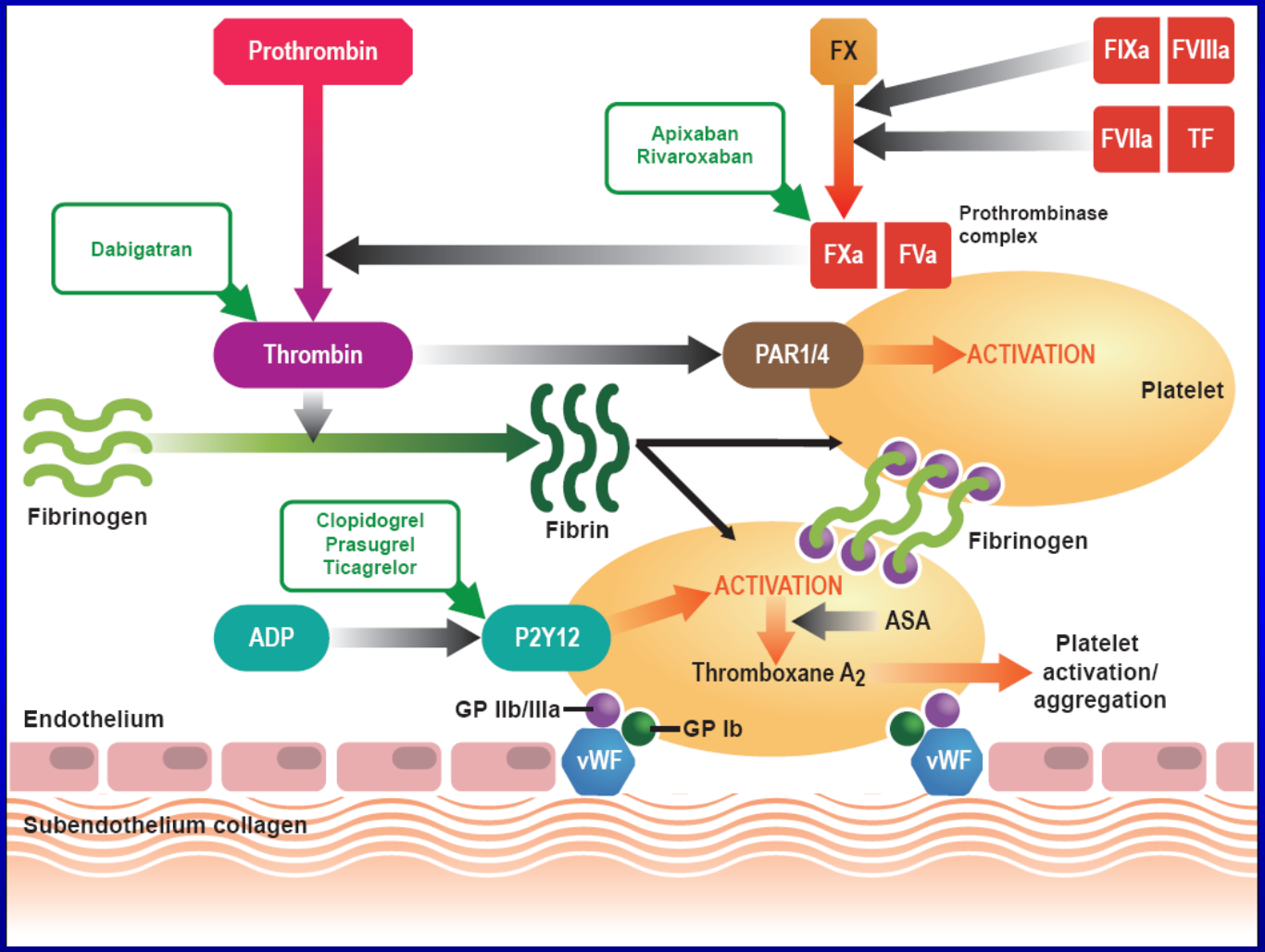
- Systems to ensure shortened door to balloon time: transmission of ECG; one call to activate team, bypassing ED, straight to cath lab
- Aspirin 300mg (In the ambulance or GP)
- Clopidogrel 600mg, 150mg for 1 week
  Prasugrel/Ticagrelor (? In the ambulance or GP)
- Bivalirudin /Enoxaparin/UFH + IIB/IIIa antagonists/UFH
- IIb//IIIa antagonists (? In the ambulance)
- Aspiration catheter, IC IIb//IIIa antagonists, stenting drug eluting or bare metal

Integration of therapies and invasive management to impact on mortality in STEMI



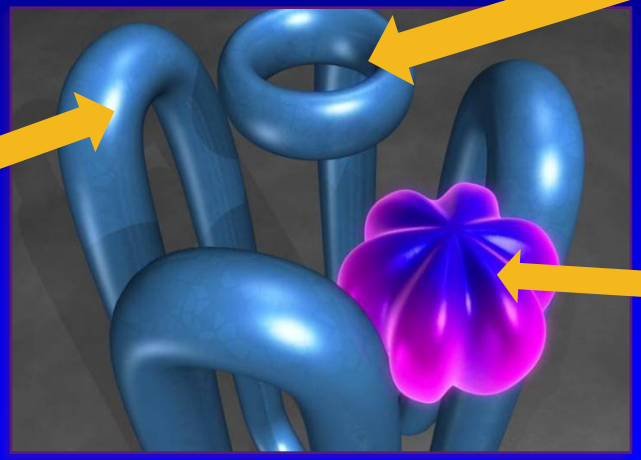
White, Lancet, 2008

Simplified view of primary and secondary haemostatic responses to vascular injury and commonly used or trialled antithrombotic agents in patients with ACS

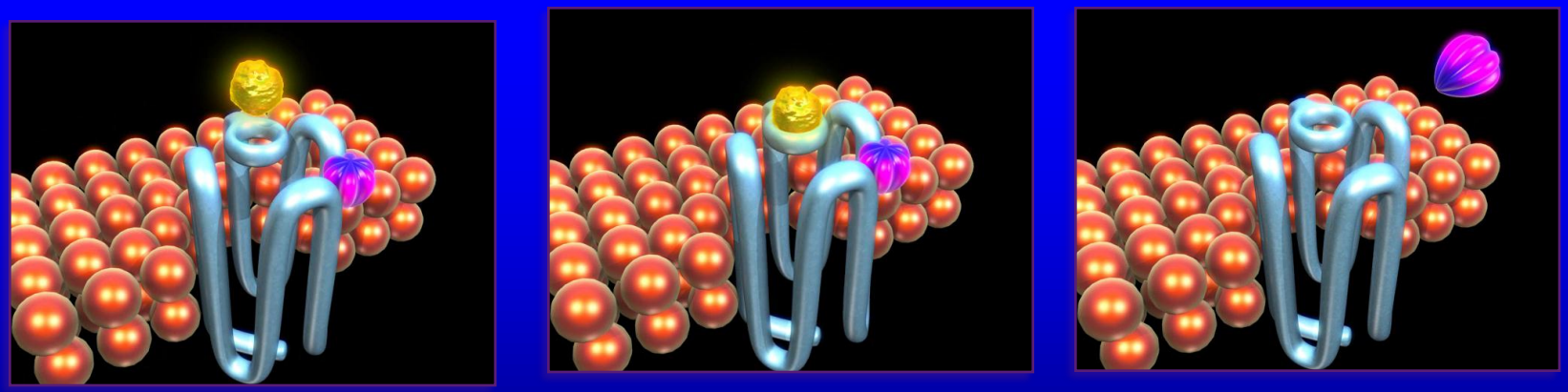


White HD American Heart journal 2012

Ticagrelor mechanism of action



Ticagrelor does not interact with the ADP receptor binding site



Ticagrelor binds directly to $P2Y_{12}$ receptor to reversibly inhibit platelet activation and aggregation

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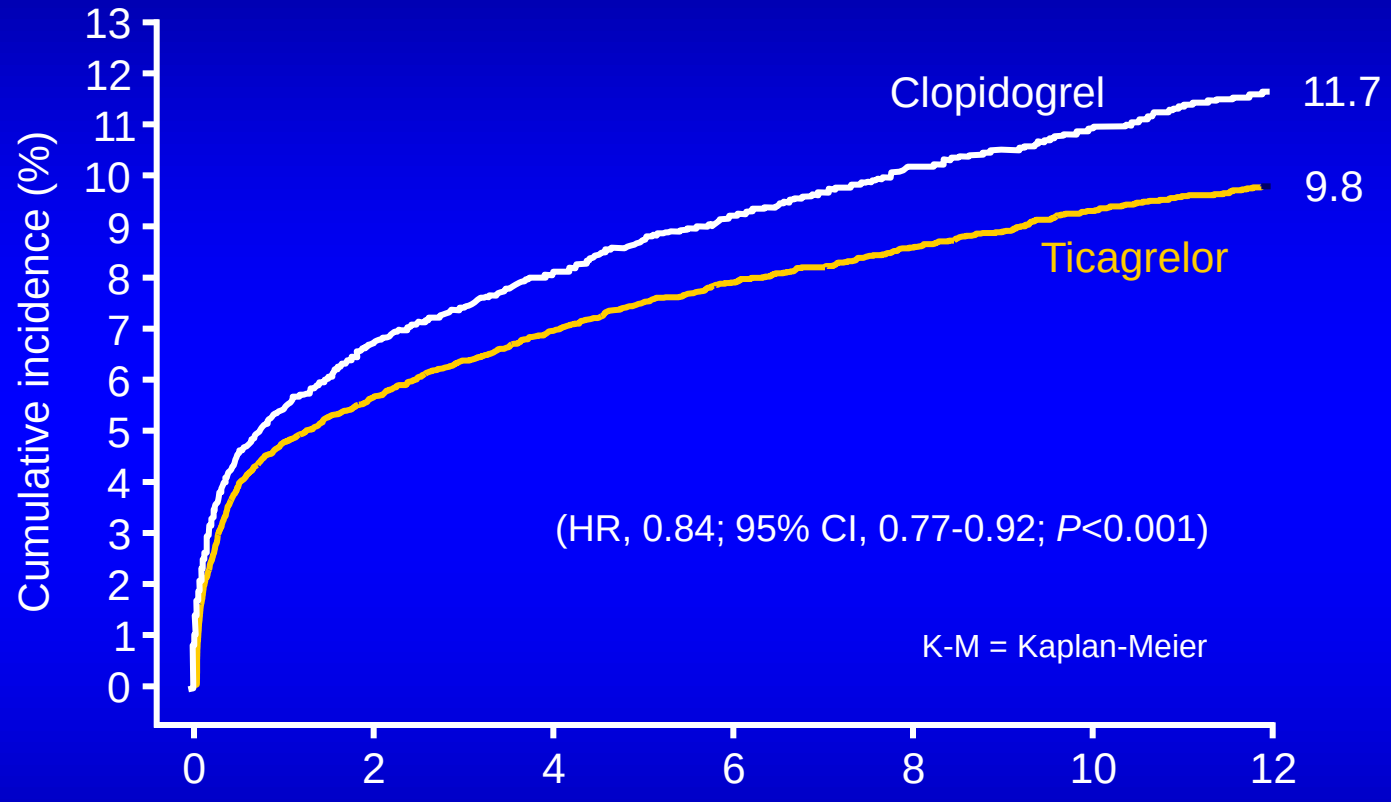
Husted S, et al. *EHJ.* 2006; 27: 1038; Gurbel PA, et al. *Expert Opin Drug Metab Toxicol.* 2009; 5(8): 989; Van Giezen JJ, et al. *J Thromb Haemost.* 2009; 7:1556

PLATO: primary efficacy endpoint:

K-M estimate of time to major CV event (composite of CV death, MI or stroke)



No. at risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

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Wallentin L, et al. *N Engl J Med*. 2009;361:1045

PLATO: hierarchical testing of major efficacy endpoints

All Patients**	Ticagrelor (n=9333)	Clopidogrel (n=9291)	HR for ticagrelor (95% CI)	*P* value†
Primary endpoint, n (%)				
CV death + MI + stroke	864 (9.8)	1014 (11.7)	0.84 (0.77-0.92)	<0.001
Secondary endpoints, n (%)				
Total death + MI + stroke	901 (10.2)	1065 (12.3)	0.84 (0.77-0.92)	<0.001
CV death + MI + stroke + severe recurrent ischaemia + recurrent ischaemia + TIA + arterial thrombus	1290 (14.6)	1456 (16.7)	0.88 (0.81-0.95)	<0.001
MI	504 (5.8)	593 (6.9)	0.84 (0.75-0-95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69-0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91-1.52)	0.22*
Death from any cause	399 (4.5)	506 (5.9)	0.78 (0.69-0.89)	<0.001

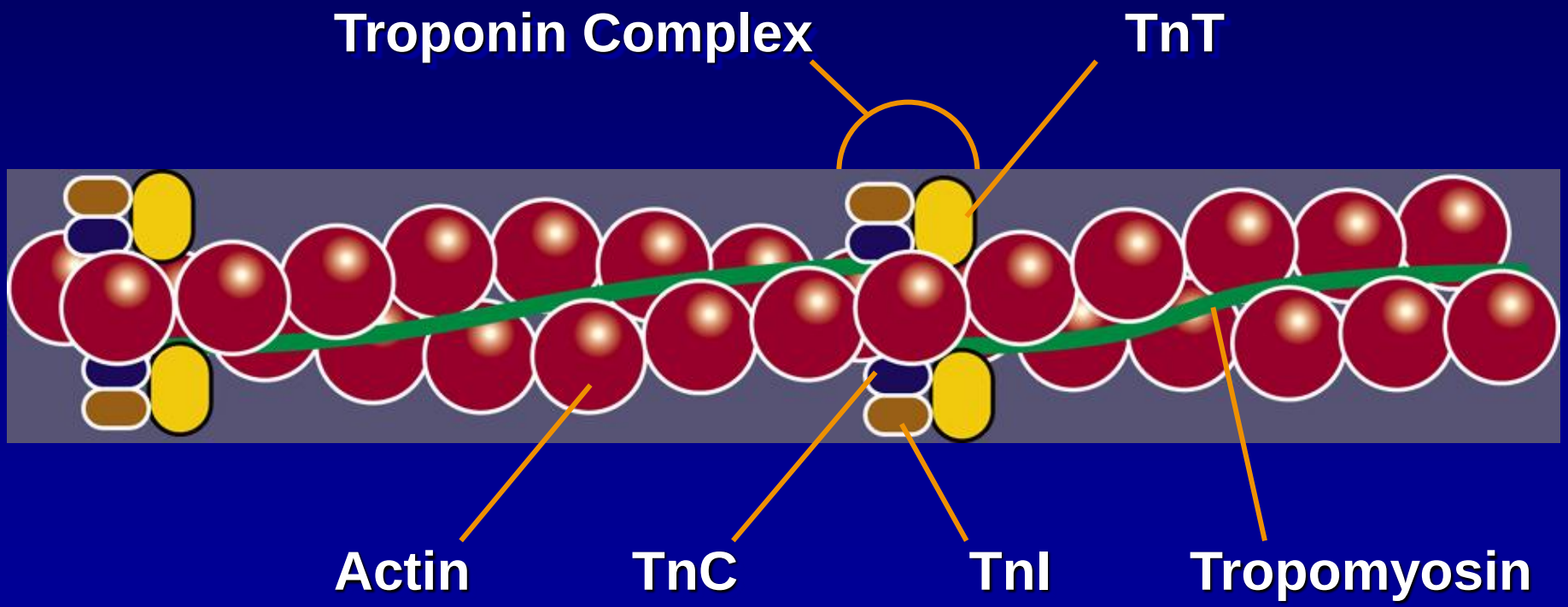
*non-significant

**The percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than one type of endpoint. Death from CV causes and fatal bleeding, as only traumatic fatal bleeds were excluded from the CV death category. Death from any cause was tested after stroke, which was non-significant, so the results should be considered nominally significant; †By Cox regression analysis using treatment as factor.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045

Cardiac Markers

The Troponins



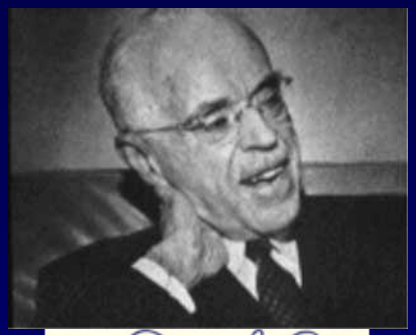
Utility of troponins in ACS

White HD., Ed. White, HD. *Future Medicine.* 2012.

High sensitivity troponins

- With better tests will be found in all individuals
- Even small concentrations of troponin in the context of ACS or in community populations predict a higher risk for CHD events
- Consensus statements recommend use of "the 99th percentile" for a normal population as the upper reference limit for troponin assays with a coefficient of variation (CV) of 10%
- In the absence of ACS, very low cardiac troponin values are expected and therefore it is critical that we evaluate changes in levels to distinguish acute from chronic conditions: biological variability is ~ 50%

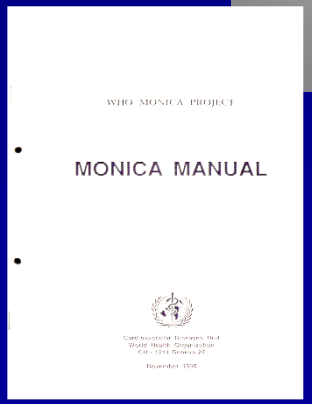
Changing definitions of Myocardial Infarction since 1950s



Dr. Paul D. White

”Small heart attacks are so common

that they are within the normal range”



Consensus Document

Myocardial infarction redefined - A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial infarction

The Joint European Society of Cardiology/ American College of Cardiology Committee**

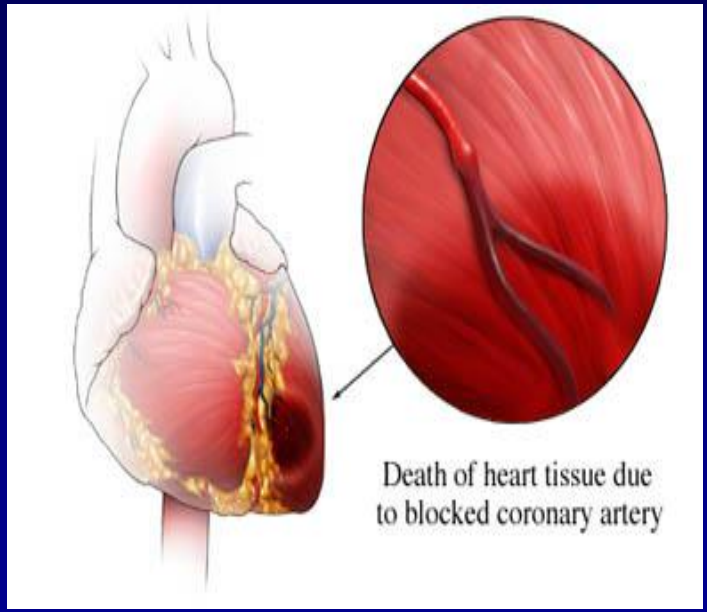
The Joint ESC/ACC Committee Eur Heart J 2000; 21:1502-13, JACC 2000;36:959-69

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

Thygesen, Alpert, Jaffe, Simoons and White. Universal Definition of Myocardial Infarction 2012 EHJ, JACC, CIRC

Pathological Definition of Acute Myocardial Infarction

Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischemia



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

The Universal Definition of Myocardial Infarction: 2012

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:

- *Symptoms*
- *ECG changes*
- *New Q waves*
- *New loss of viability*
- *Identification of intracoronary thrombus by angiography*

Thygesen, Alpert, White. Universal Definition of Myocardial Infarction 2012

Clinical Classification of different Types of Myocardial Infarction: 2012

Type 1 Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion or rupture

Type 2 Myocardial infarction secondary to ischemia due to imbalance between oxygen demand and supply

Type 3 Sudden cardiac death with symptoms of myocardial ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography, but death occurring before blood samples could be obtained

Type 4a Myocardial infarction associated with PCI associated with ischaemic chest discomfort, ECG changes, or angiographic decreased flow, embolism or loss of a side branch, and elevation of biomarkers 5X 99th percentile. Troponin preferred

Type 4b Myocardial infarction associated with stent thrombosis

Type 5 Myocardial infarction associated with CABG associated with Q waves or new graft or native artery occlusion and elevation of biomarkers 10 X 99th percentile

Thygesen, Alpert, White. Universal Definition of Myocardial Infarction 2012

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
- Chronic obstructive pulmonary disease
- Pulmonary embolism, severe pulmonary hypertension
- Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
- Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, and scleroderma

White HD Lancet 2008

Elevations of Troponin in the absence of an Acute Coronary Syndrome

- Inflammatory diseases, e.g., myocarditis, myocardial extension of endocarditis
- Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, capecitabine
- Aortic dissection, aortic valve disease, hypertrophic cardiomyopathy
- Hypothyroidism
- Phaeochromocytoma
- Takostubo (stress) cardiomyopathy
- Burns affecting >30% of body surface area
- Rhabdomyolysis with cardiac injury
- Critically ill patients with respiratory failure, or sepsis
- Electroconvulsive therapy
- Snake and spider bites

White HD Lancet 2008

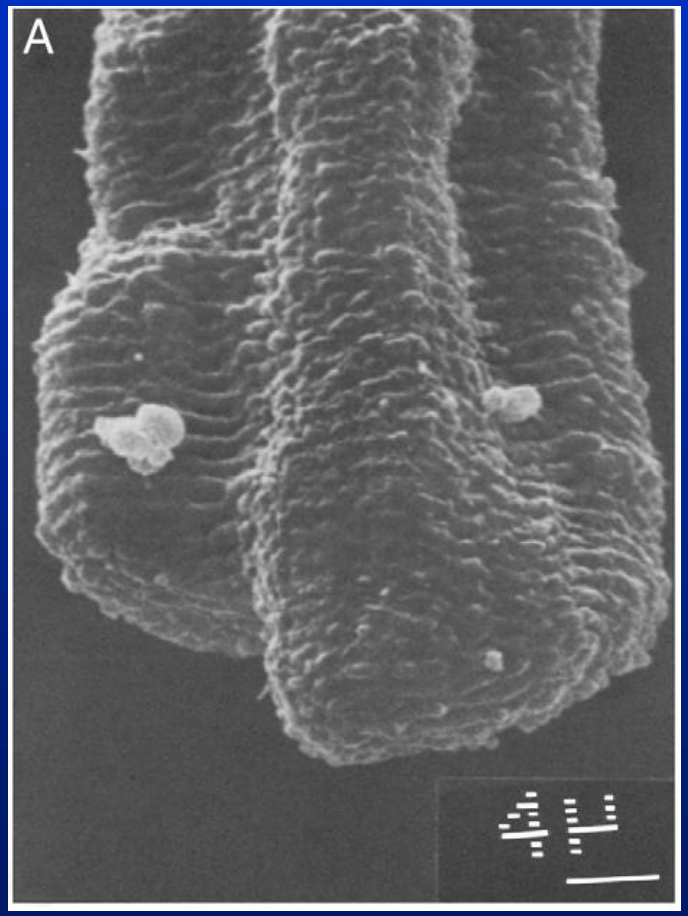
Classification of potential types of mechanisms causing troponin elevations

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

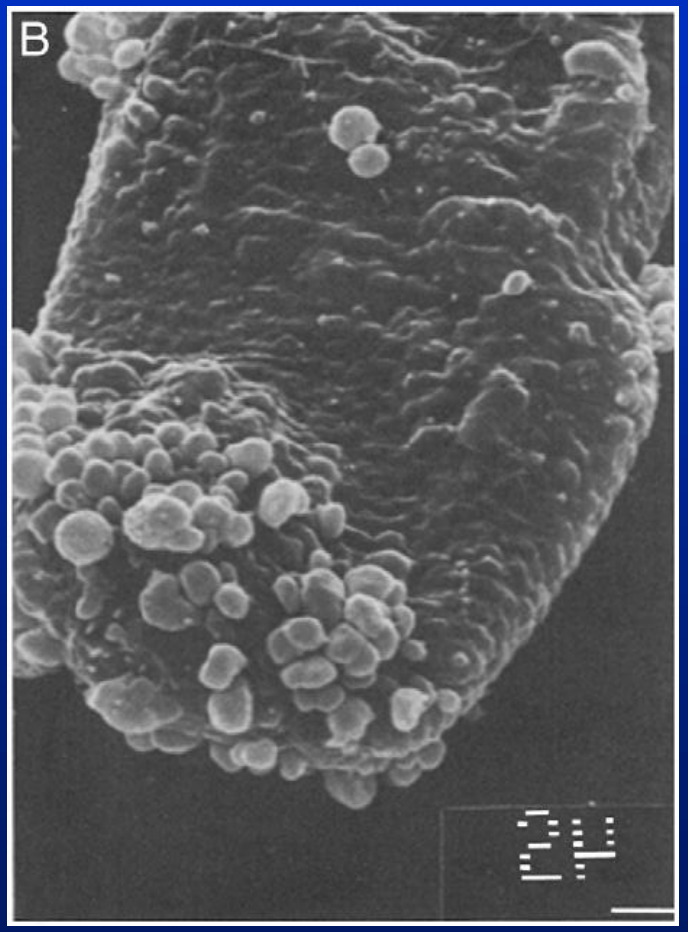
White, HD. JACC 2011

Microbleb formation of adult cultured cardiac myocytes

Baseline



30 min of anoxia



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Schwartz et al. *Am J Pathol* 1984 in *Hickman* et al. *Clin Chem* 2010;411:318-23

Dealing with Troponin elevations in clinical practice

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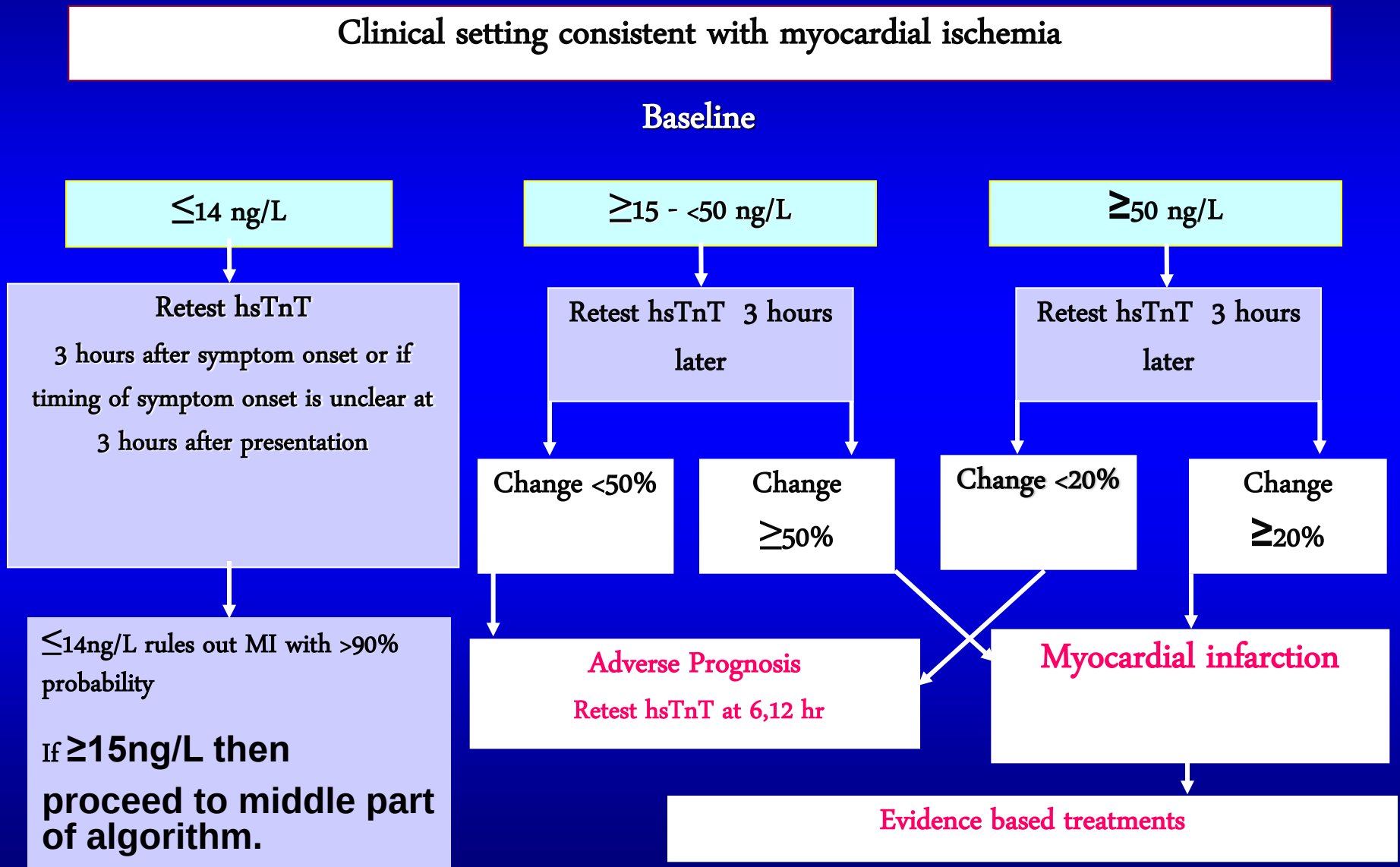
Elevated Troponins

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

What does an elevated Troponin mean?

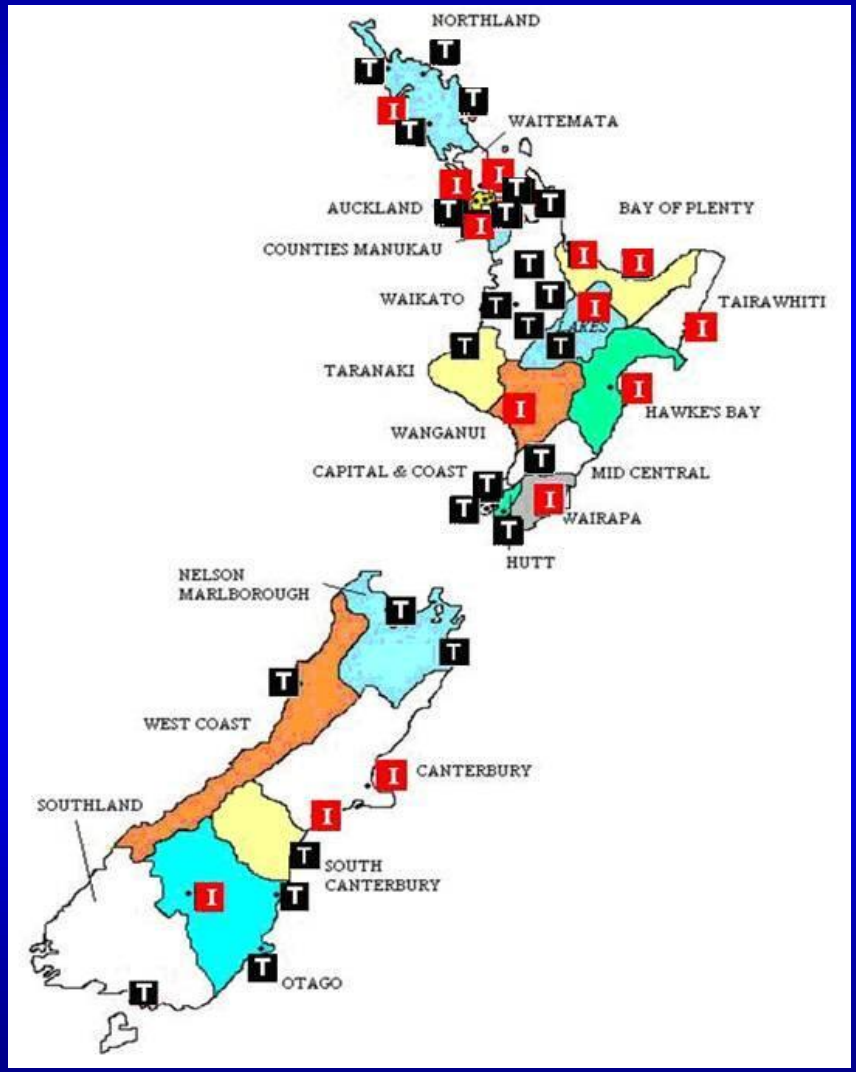
- In an ischaemic setting with a rise and fall: myocardial infarction
- In a non-ischaemic setting: search for a cause, not necessarily a need for cardiology consultation

Use of high sensitivity troponin T to diagnose myocardial infarction

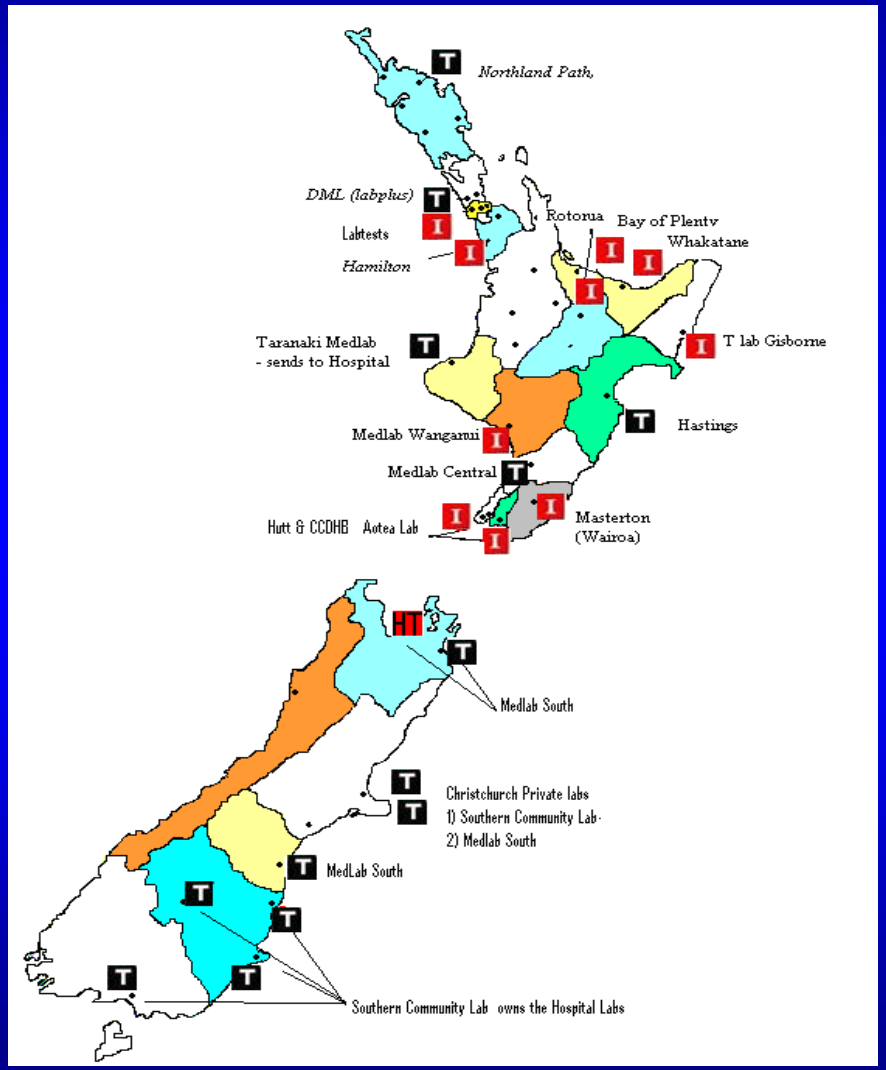


White HD; American Heart Journal 2010

Distribution of troponin T, troponin I and mixed assays by District Health Board Hospital laboratories in 2011 (Chatham Islands [troponin T] not shown)



Distribution of troponin T and troponin I assays used by community laboratories in 2011



Troponins and silliness

- Use of term “troponin leaks”
- Description “only a small elevation”
- A low level is checked against CKMB (which should be abandoned) to see if it is a ‘real MI’
- Troponin is elevated in an ischaemic setting but coronary arteries are normal : “false positive” troponin
- Not doing a troponin on Monday morning after chest discomfort on Saturday

‘Things ain’t what they used to be’

White HD. Things ain’t what they used to be: impact of a new definition of myocardial infarction. Am Heart J. 2002;144:933-7.

‘Things ain’t what they used to be’

A heart attack isn’t what it used to be

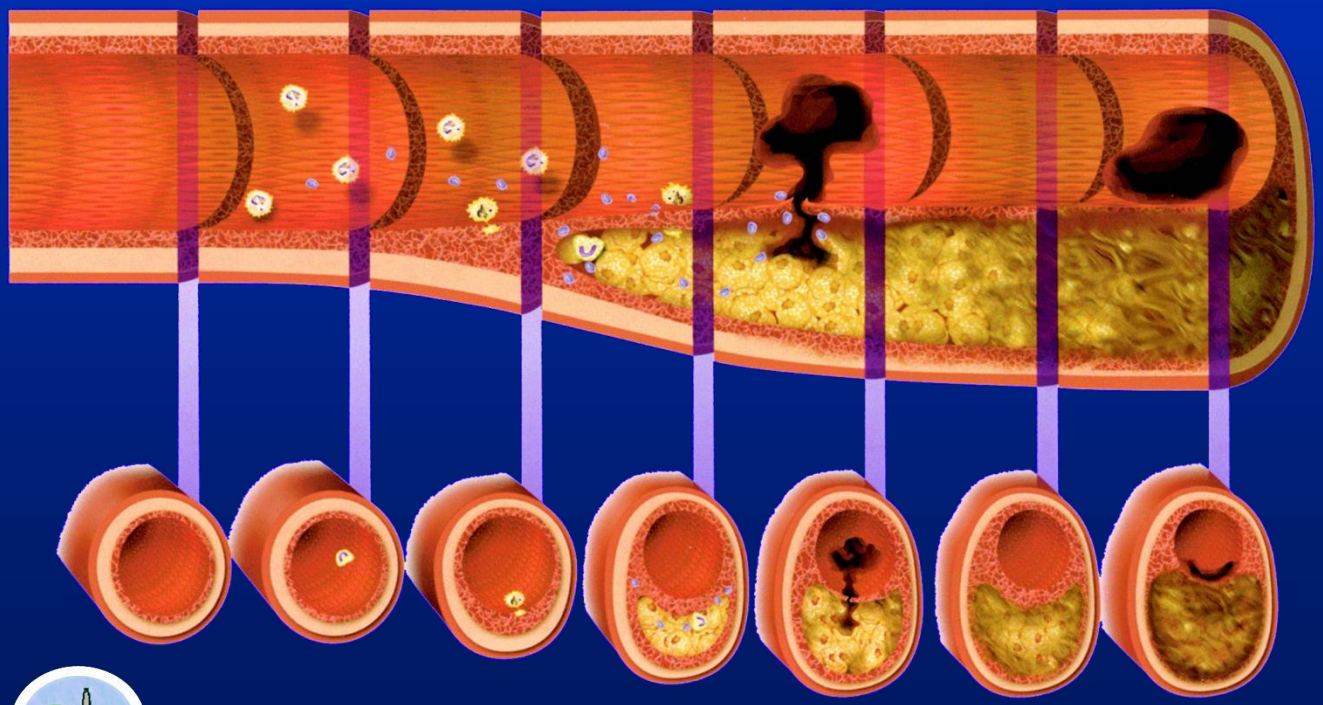
White HD. Things ain’t what they used to be: impact of a new definition of myocardial infarction. Am Heart J. 2002;144:933-7.

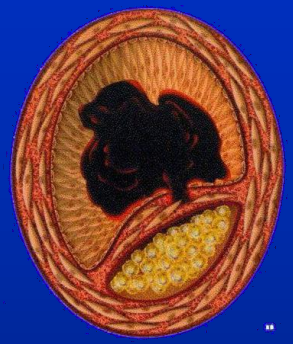
Progression of Atherosclerosis and Troponin values

Minimal or no disease: troponin detectable with hsTroponins

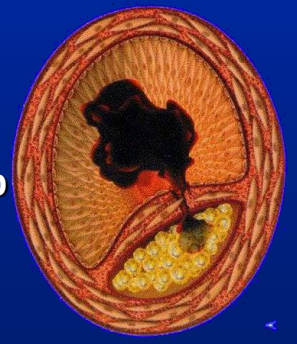
Significant structural disease troponin higher than 99th %

ACS and other acute situations - rising troponin values





Superficial Erosion



Ruptured Fibrous Cap

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Modified from Libby P Circ 104:365,2001

What will high sensitivity troponins result in?

What will high sensitivity troponins result in?