Myocardial Infarction and Remodelling of the Heart

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NHS
National Institute for Health Research

Objectives

- To understand the pathogenesis of acute MI and LV remodelling and their natural history

- To use this knowledge to develop the rationale for the clinical assessment, diagnosis and treatment of acute MI and LV remodelling

Overview

- Basic science
  - Plaque
  - Myocardium
- Clinical
  - Classification
  - Diagnosis
  - Clinical Risk Stratification
  - Treatment

UK MI Statistics (2009-10)

- ~99,000 hospital admissions per year
- ~33,000 deaths per year (~6% of all deaths in UK)
- £3.6 billion per year

Definition

- Myocardial cell death arising from interrupted blood flow to the heart
  - Coronary plaque rupture
  - Coronary plaque erosion
  - Coronary dissection

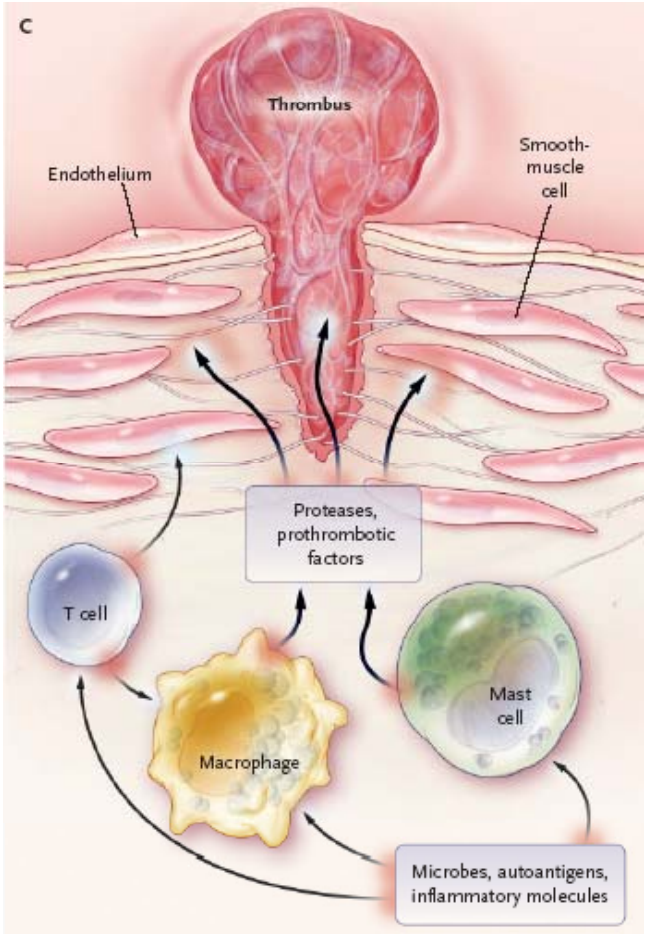
- Mechanisms of myocardial cell death
  - Oncosis
  - Apoptosis

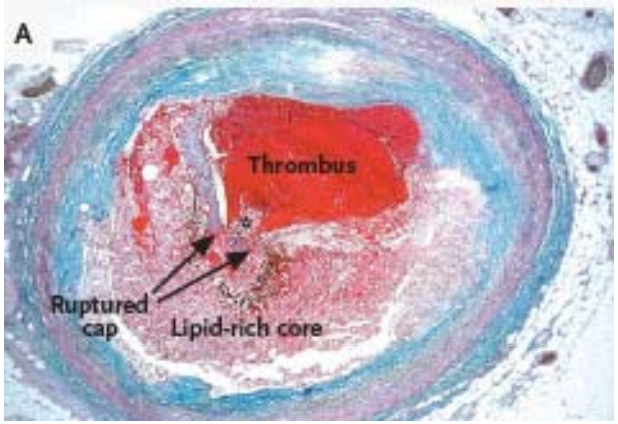
Acute MI

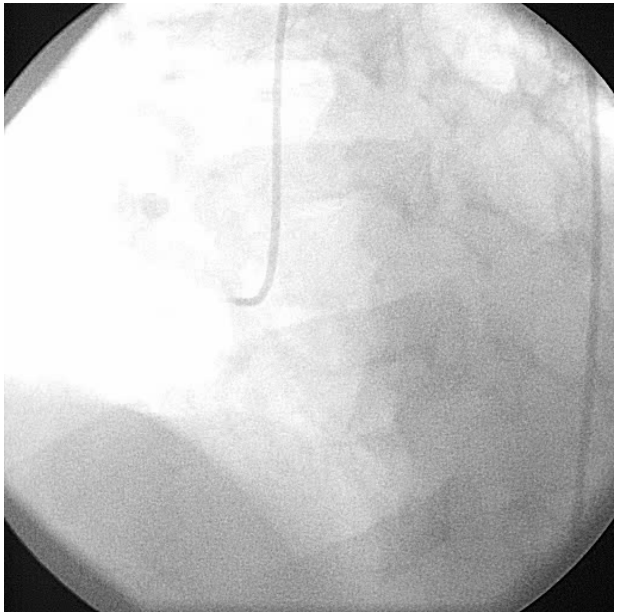
Key Elements for Acute MI

- Vulnerable plaque (inflammation)
- Trigger
- Thrombosis

Acute Coronary Syndromes







- **Inflammation**
  - Systemic
  - Local
- **Plaque**
  - Rupture
  - Erosion
- **Thrombosis**

Hansson N Engl J Med 2005

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When do MI's Happen?

Observation

- Morning, within 1st hour of waking
- Monday's
- Winter, cold weather
- Emotional stress
- Vigorous exercise

Potential mechanism

- Increased sympathetic activity → plaque disruption
  - ↑ BP, HR, CBF
- Thrombosis
  - ↑ platelet reactivity
  - hypercoagulability
  - ↓fibrinolysis
- Vasoconstriction

“Man lives with atherosclerosis but dies from thrombosis”

Didischem 1957

ACS

THROMBOSIS

20-30 %
PLAQUE EROSION

70-80 %
PLAQUE RUPTURE

Acute MI – Thrombosis

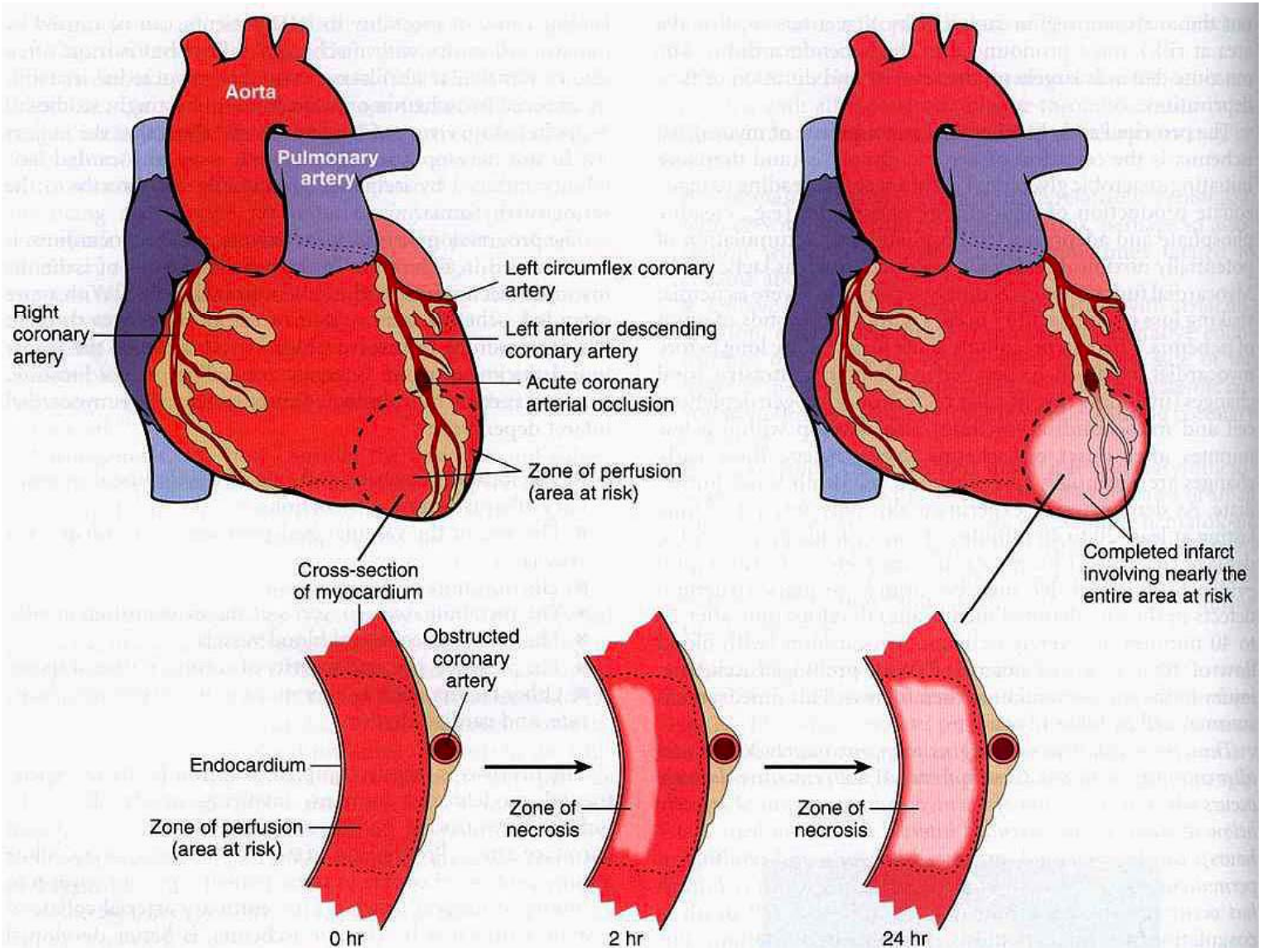
- Pro-coagulant state
  - Increased platelet reactivity
  - Increased circulating tissue factor
  - Reduced fibrinolysis
- Endothelial dysfunction
- Altered flow

Ischaemic Cell Death

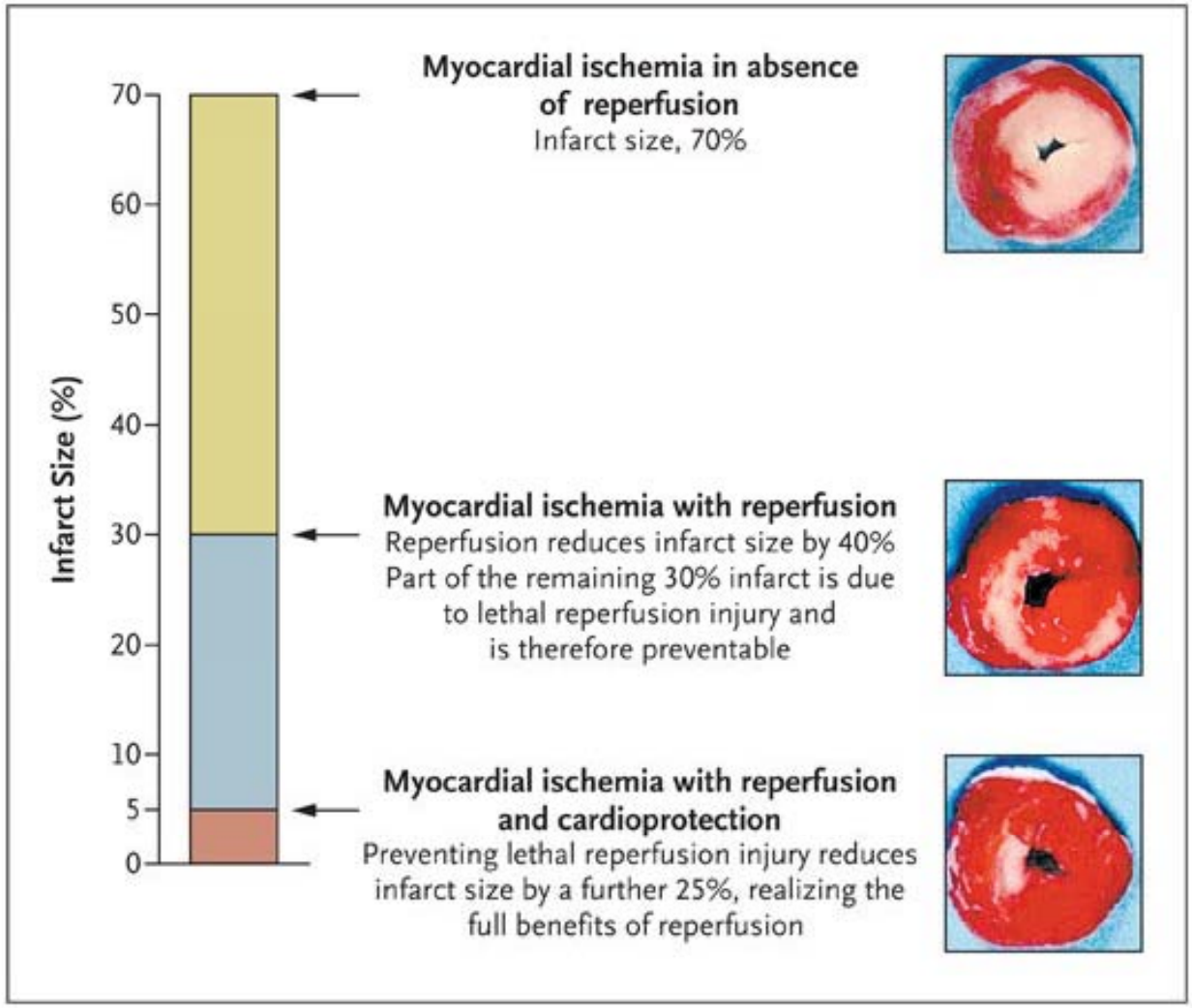
Oncosis	Apoptosis
o Cell swelling + death o Depletion of high energy phosphates o Accumulation of intracellular water, Na^+ ($\rightarrow \uparrow Ca^{++}$), H^+, Cl^-, o Cytoplasmic, organellar, cellular swelling o Plasma membrane blebbing o Cell rupture	o Cell shrinkage + death o Depletion of high energy phosphates o Run down of mitochondrial electron transport chain o Cytochrome c release o Caspase activation o Cell shrinkage and fragmentation

Coagulative necrosis
Neutrophil then monocyte/macrophage influx

Development of Infarction



Reperfusion Injury

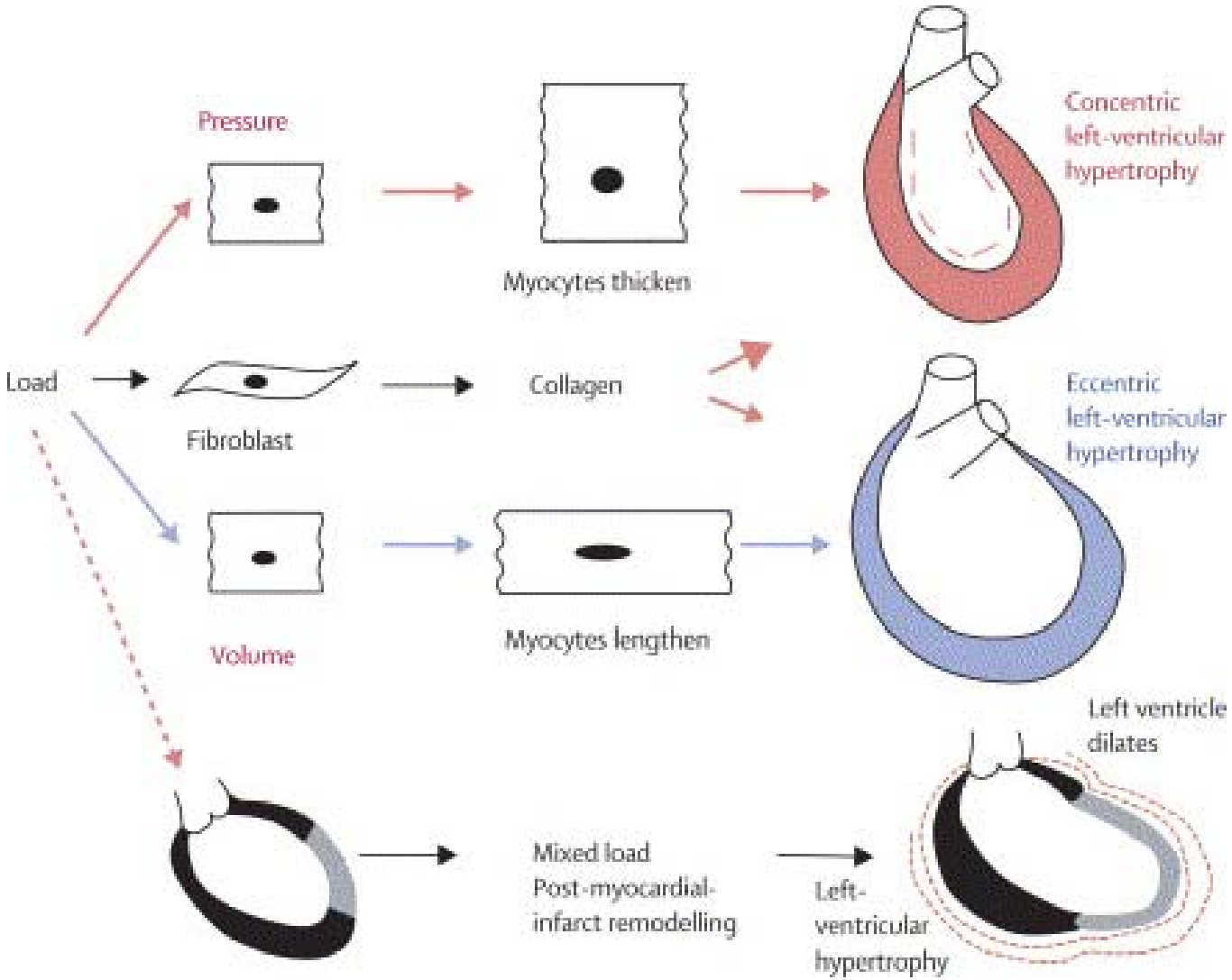


Yellon & Hausenloy NEJM 2007

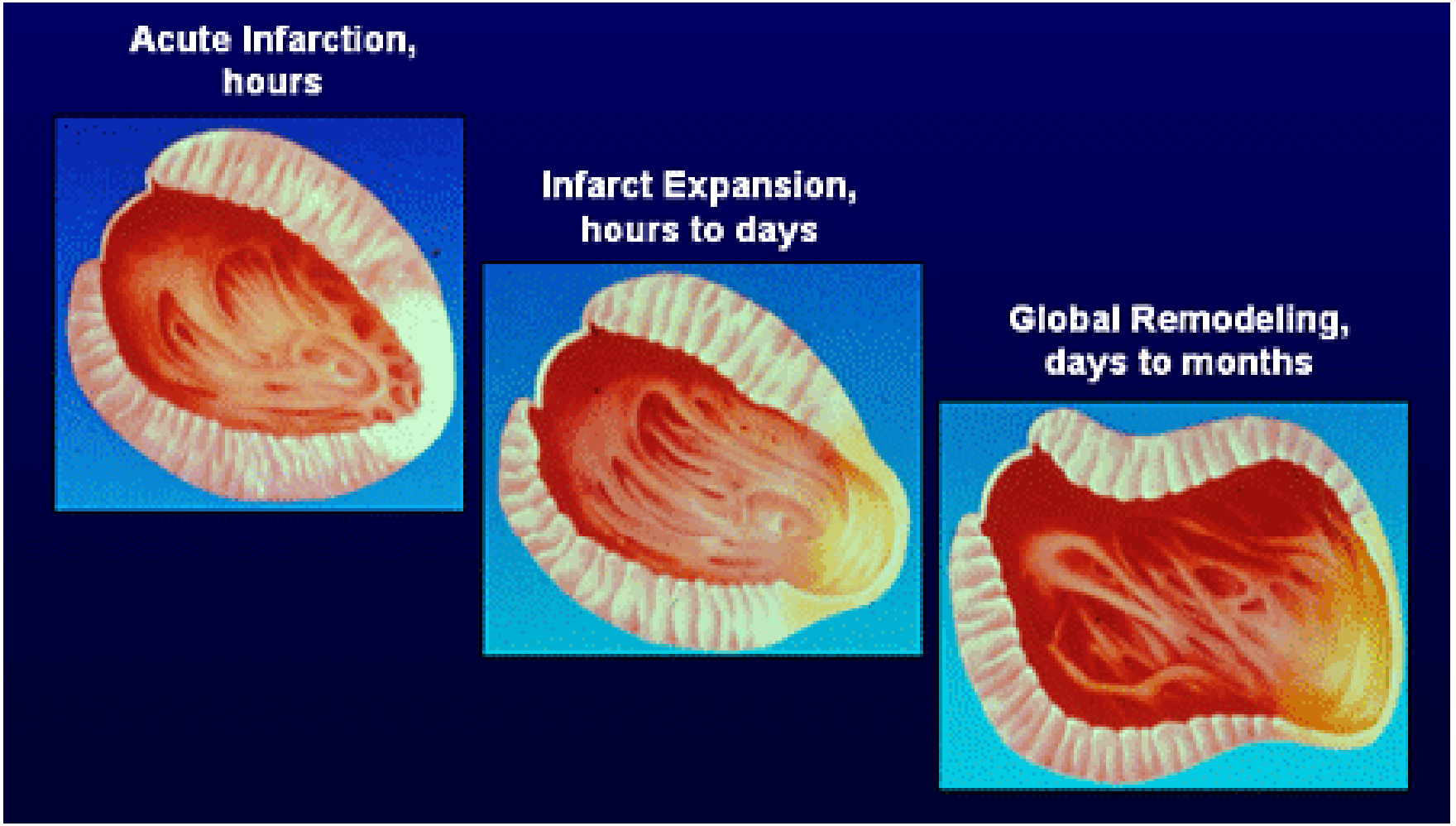
Reperfusion Injury - Mechanisms

- Oxygen paradox: free radicals
- Calcium paradox
- pH paradox
- Inflammation: “no-reflow” (neutrophils)
- mPTP opening: uncouples oxidative phophorylation

LV Remodelling



Post-MI LV Remodelling



Mechanisms Underlying LV Remodelling

- Infarct thinning, elongation, expansion
- LV dilatation
  - reduce wall tension
  - maintains cardiac output
- Non-infarcted myocardium
  - LVH + myofilament dysfunction
  - Altered electromechanical coupling
  - Myocardial fibrosis
  - Apoptosis
  - Inflammation

Consequences of Adverse LV Remodelling

- Increased systolic wall tension/stress
- Increased MVO2
- Reduced myocyte shortening
- Increased diastolic wall tension/stress
- Reduced subendocardial perfusion
- Dysynchronous depolarization/contraction
- Mitral regurgitation
- Ventricular arrhythmias
- Ventricular fibrillation

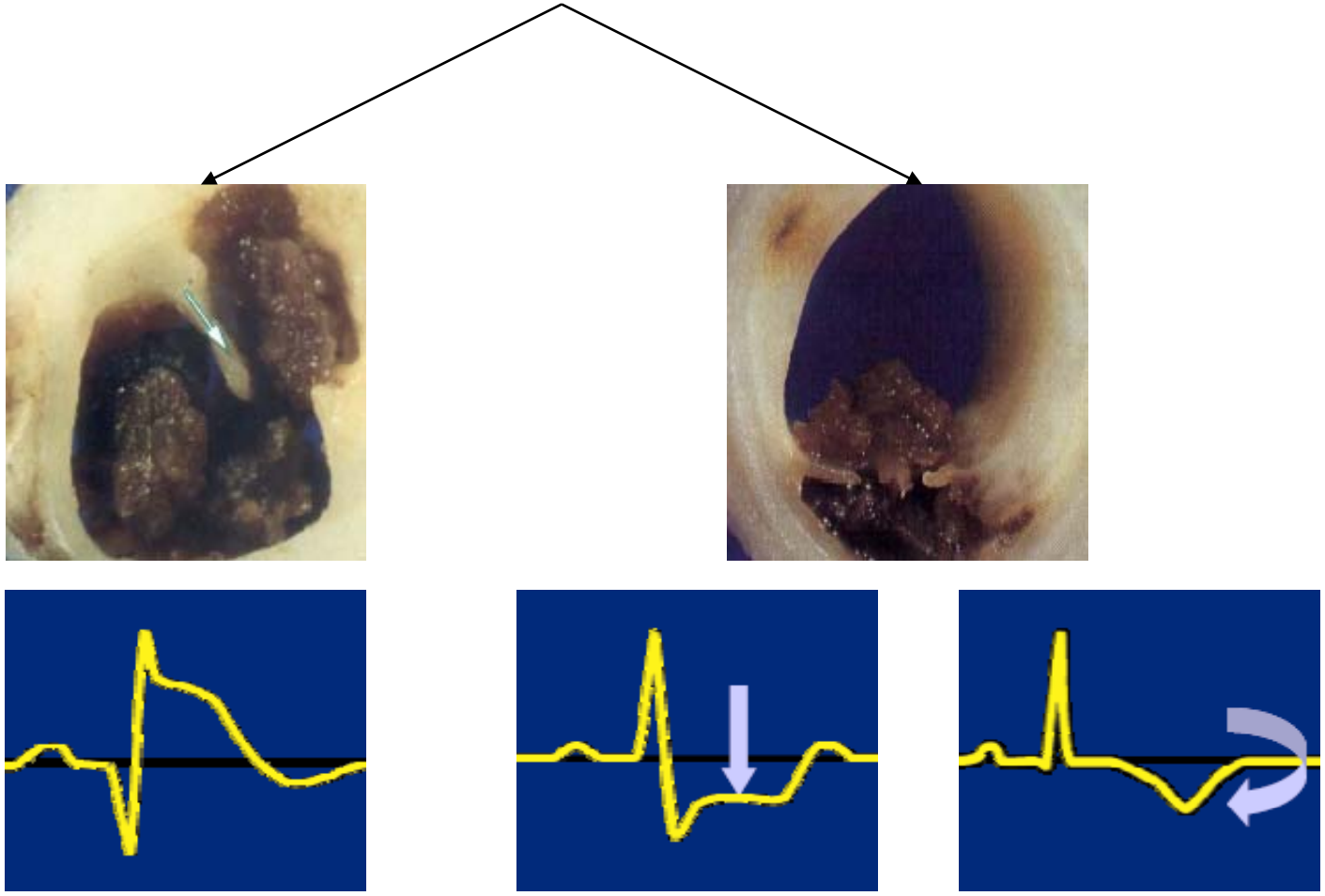
Clinical Management of MI

- Diagnosis
- Risk Stratification
- Immediate treatment
- Long term treatment

What do you need to diagnose MI?

- Symptoms
- ECG changes
- Biomarker evidence of myocardial necrosis

Acute Coronary Syndromes



ST elevation

ST depression

T wave inversion

or normal ECG

ESC NSTE-ACS Guidelines 2007

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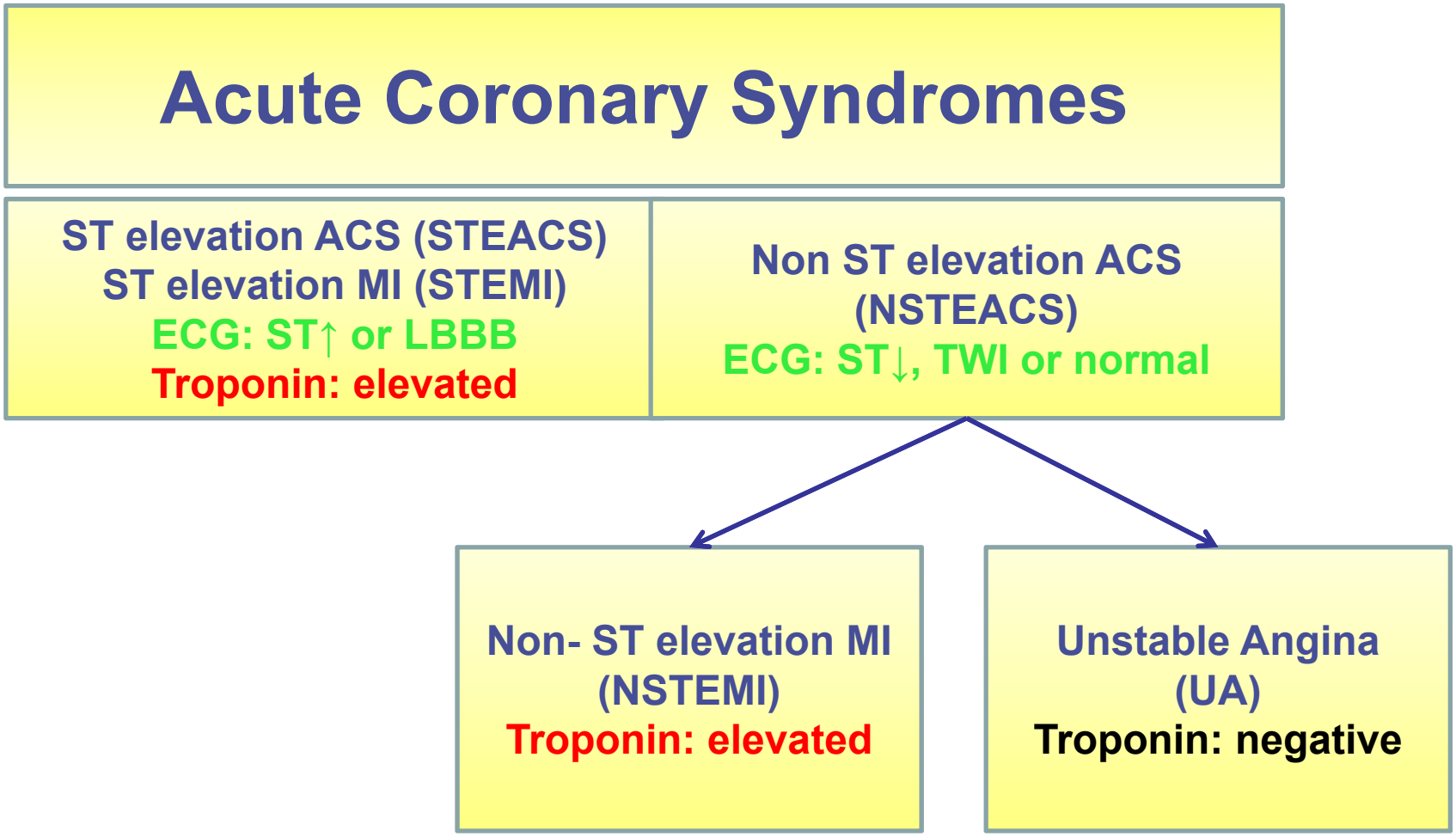
Clinical Terminology

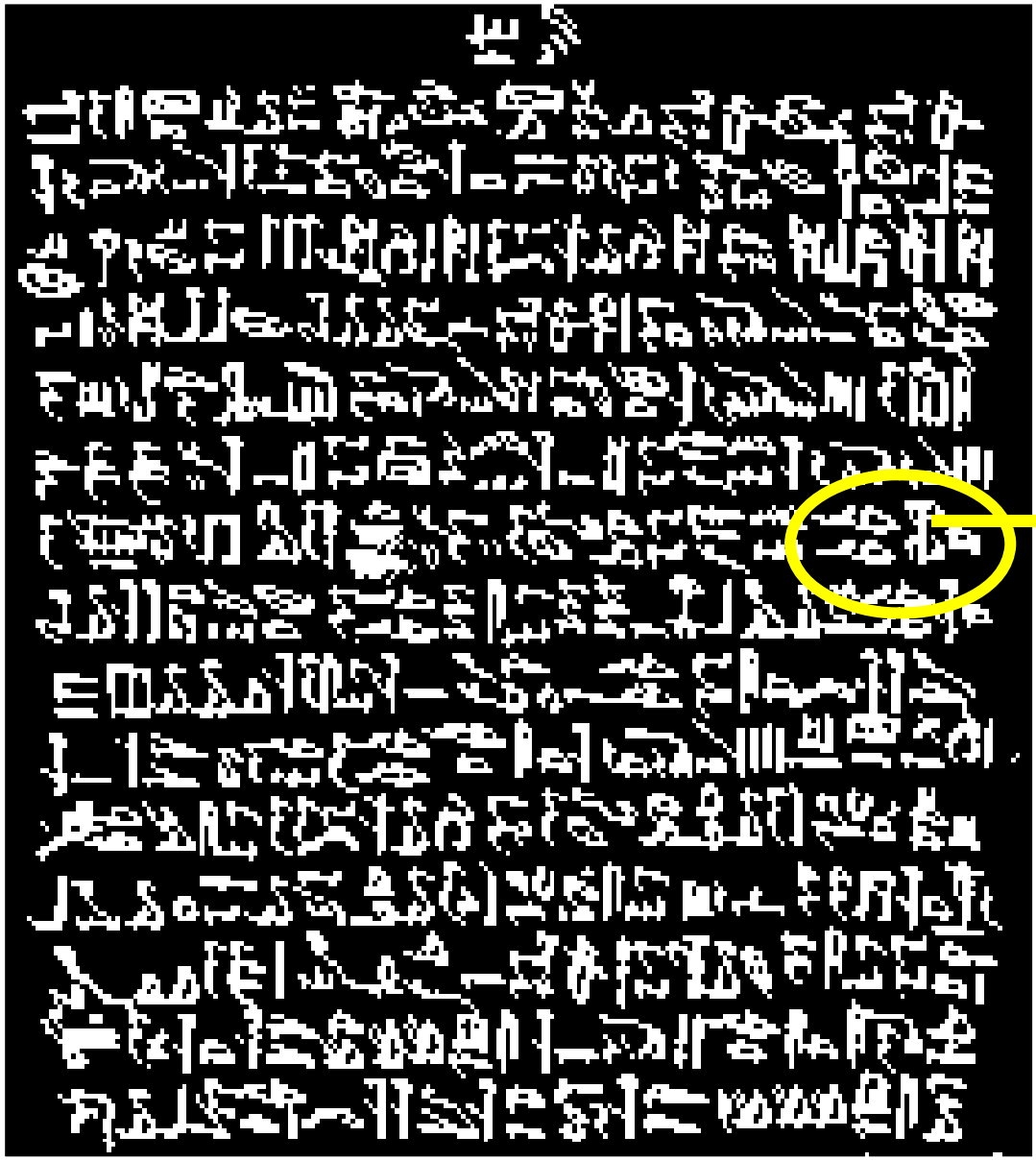


Management Goals

- Make the correct diagnosis
- Assess risk
  - Death, re-MI, heart failure
  - Complications of treatment (bleeding)
- Rapidly administer appropriate treatment
- Reduce risk of major adverse events
  - Death, MI, heart failure, re-hospitalisation

Clinical Assessment

- History
- Physical examination
- Investigations
- Differential diagnosis
- Management plan



…a man with severe chest pain going down the arms: Death is near …

The Ebers Papyrus 2600 B.C.

with kind permission from J.C. Kaski

MEDICAL TRANSACTIONS,

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IN

LONDON.

VOLUME THE SECOND.

LONDON:
Printed for S. BAKER, and J. DODSLEY.
M.DCC.LXXII.

VI. *Some Account of a Diſorder of the Breaſt. By* WILLIAM HEBERDEN, *M. D. F. R. S.*

Read at the COLLEGE, JULY 21, 1768.

THERE is a diſorder of the breaſt, marked with ſtrong and peculiar ſymptoms, conſiderable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The ſeat of it, and ſenſe of ſtrangling and anxiety with which it is attended, may make it not improperly be called Angina pectoris.

THOSE, who are afflicted with it, are ſeized, while they are walking, and more particularly when they walk ſoon after eating, with a painful and moſt diſagreeable ſenſation in the breaſt, which ſeems as if it would

Symptoms

- Chest discomfort
  - Central, band like, constricting
  - Radiating to neck, jaw, arms
- Dyspnoea
- Nausea, vomiting
- Sweating
- Preceding crescendo angina
- Time of onset of persistent symptoms

Risk Factors

- Increased age
- Cigarette smoking
- Diabetes mellitus
- Dyslipidaemia
- Hypertension
- Obesity
- Family history

Past Cardiac History

- Previous MI or angina
- CABG
- PCI
- Coronary angiogram
- Obtain dates/locations, if possible

Co-morbidities

- Recent TIA/stroke
- Chronic kidney disease
- Anaemia
- Pregnancy
- Recent bleeding, trauma, surgery
- Chronic lung disease
- Chronic liver disease

Physical Examination

- Airway, Breathing, Circulation
- Signs of shock
  - Cool, clammy, ashen, SBP<80 mm Hg, HR >100
- Signs of cardiac failure
  - ↑ HR, ↑ RR, ↑JVP, basal creps, gallop, ↓O_2 sats
- Murmur (MR, VSD, AS, AR, pericardial rub)
- Peripheral pulses, BP both arms – clinical exclusion of dissection
- Exclude acute neurological event

Investigations

- Serial 12 lead ECG's
- Biomarkers
  - Troponin (I or T)
- Metabolic
  - Glucose
  - Lipids
  - Renal function
  - Liver function
- Haematology
  - FBC
  - Coagulation screen
  - Group + Save
- CXR
- Echocardiogram

Differential Diagnosis

Common

- Pulmonary embolism
- Pneumonia
- Viral pleuritis
- Gastro-oesophageal reflux
- Costochondritis
- Anxiety/panic disorder

Uncommon

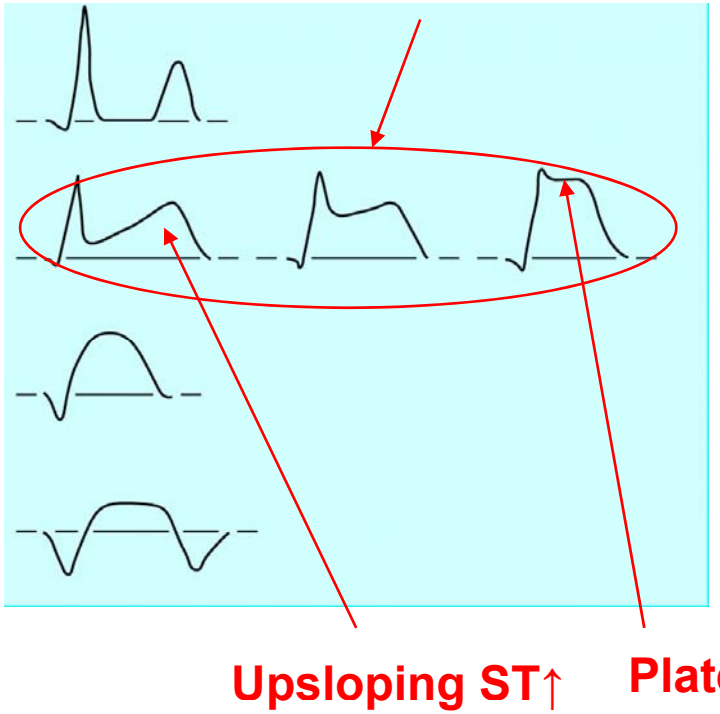
- Pericarditis
- Cardiac tamponade
- Aortic dissection
- Aortic stenosis
- Mitral valve prolapse
- Pneumothorax
- Pulmonary hypertension
- Peptic ulcer disease
- Oesophageal spasm
- Acute cholecystitis
- Pancreatitis
- Herpes zoster
- Gastritis

What can you get from the ECG?

- Diagnosis
  - Is there ST elevation or LBBB?
  - Is there ST depression?
  - Is there T wave inversion?
- Prognosis
  - Establish location
  - Estimate infarct size
- Complications
  - Arrhythmia

Evolution of ECG in acute STEMI

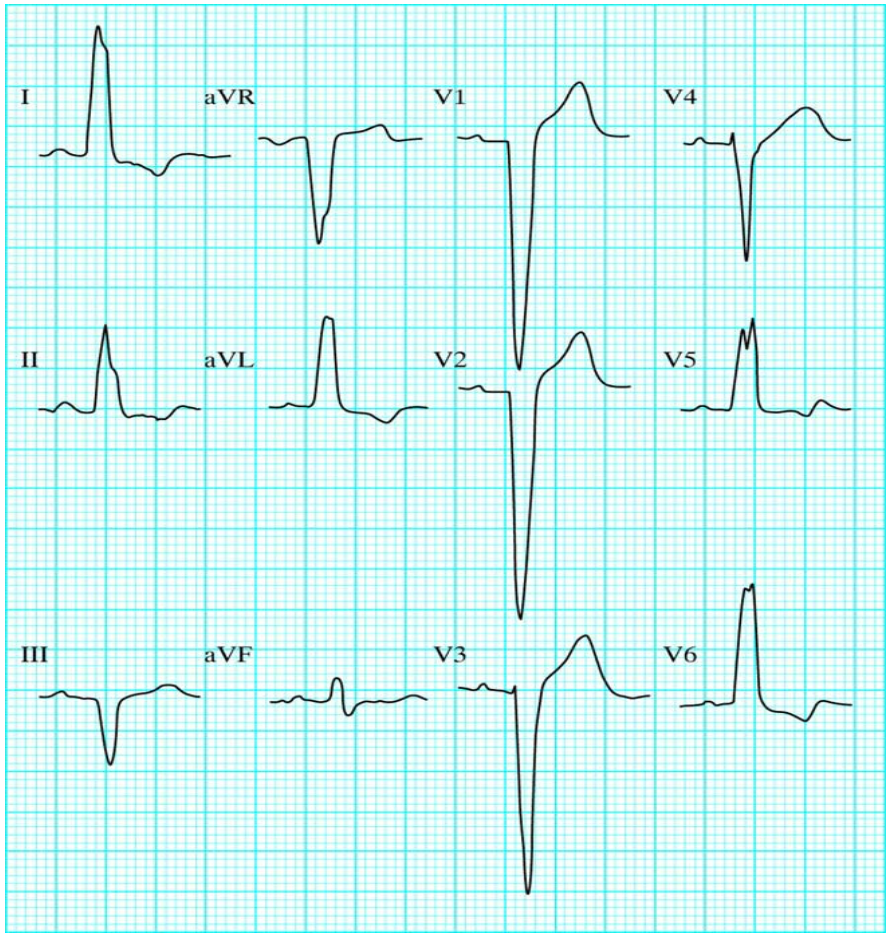
- Hyperacute T wave
- ST elevation
- Q waves + Loss of R wave
- T wave inversion



Morris F, Brady WJ. *BMJ* 2002;324:831-4

LBBB

- QRS >120msec
- QS or RS in V1
- notched broad R wave V5/V6
- no Q in I, V5, V6



Morris F, Brady WJ. *BMJ* 2002;324:831-4

Differential Diagnosis of ST Elevation

- Acute pericarditis
- Acute myocarditis
- Hyperkalaemia
- Brugada syndrome
- ARVD
- Massive PE
- Acute aortic dissection
- Prinzmetal's angina
- LV aneurysm
- Subarachnoid haemorrhage
- post-DC shock
- Early repolarization/High "take-off"/normal variant

Wang et al. NEJM 2003;349:2128-35

Acute STEMI – ECG Criteria

- ST↑
  - >2mm in 2 contiguous leads V1-V3 or
  - >1 mm in at least 2 contiguous other leads
- LBBB (if no previous ECGs available, then LBBB should be presumed to be new)

ECG – Localize Infarct Territory

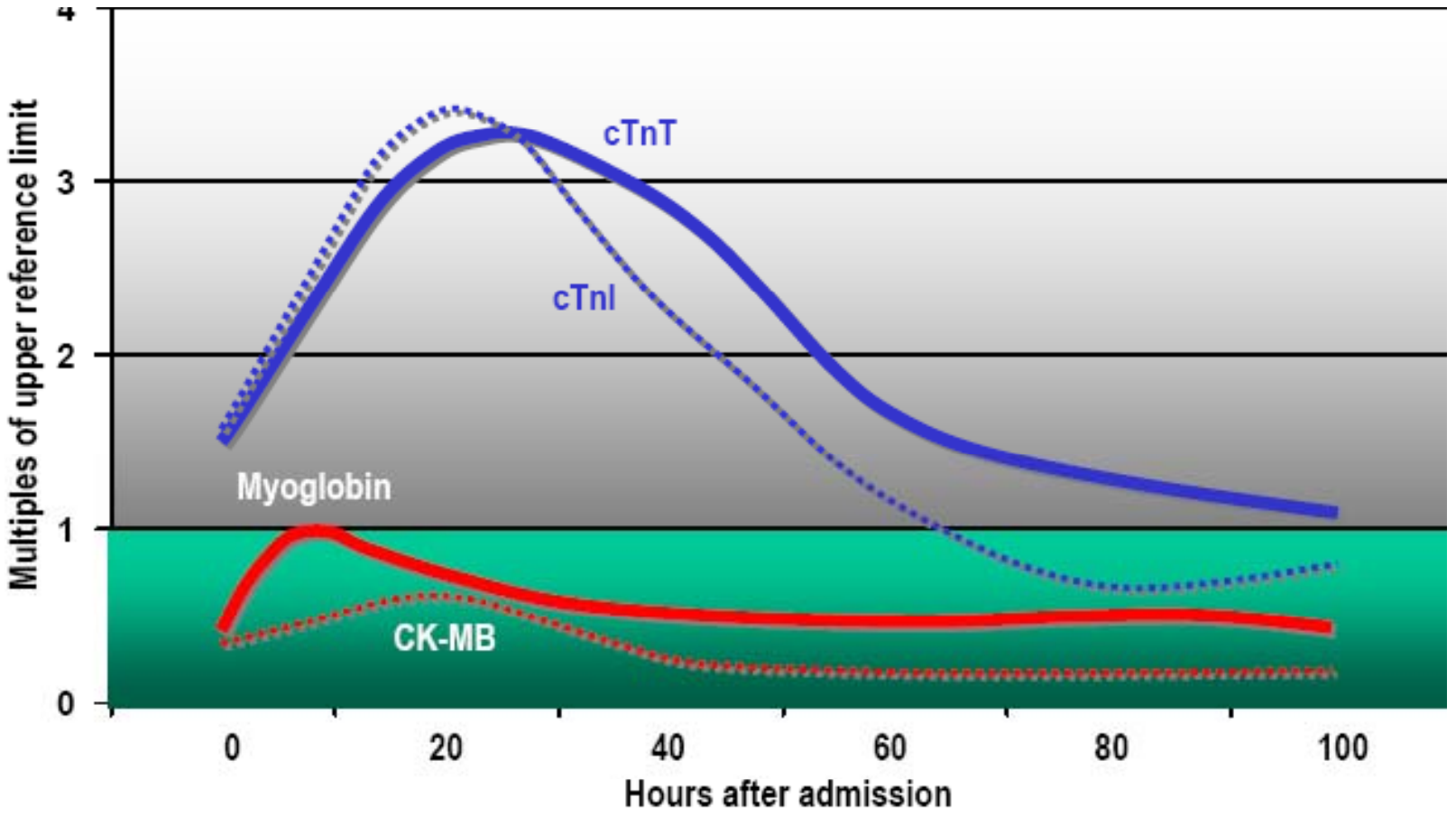
- Antero-septal: ST↑ V1-V4 or LBBB (LAD)
- Inferior: ST↑ II, III, aVF (RCA)
- Lateral: ST↑ I, aVL, V5, V6 (LCx)
- Posterior: ST↑ V7-V9; ST↓ V1-3; dominant R V1 (LCx)
- RV: ST↑ V4R-V6R (RCA)

ECG and Prognosis

- Prognosis worsens as the number of leads showing ST↑ increases
- Location and 30 d mortality (GISSI)
  - Anterior – 16.3%
  - Multi-site – 10.3%
  - Lateral – 9.7%
  - Inferior – 6.2%

Mauri et al. Am J Cardiol 1989;63:1291-5

Cardiac Enzyme Changes in ACS



ESC NSTE-ACS Guidelines 2007

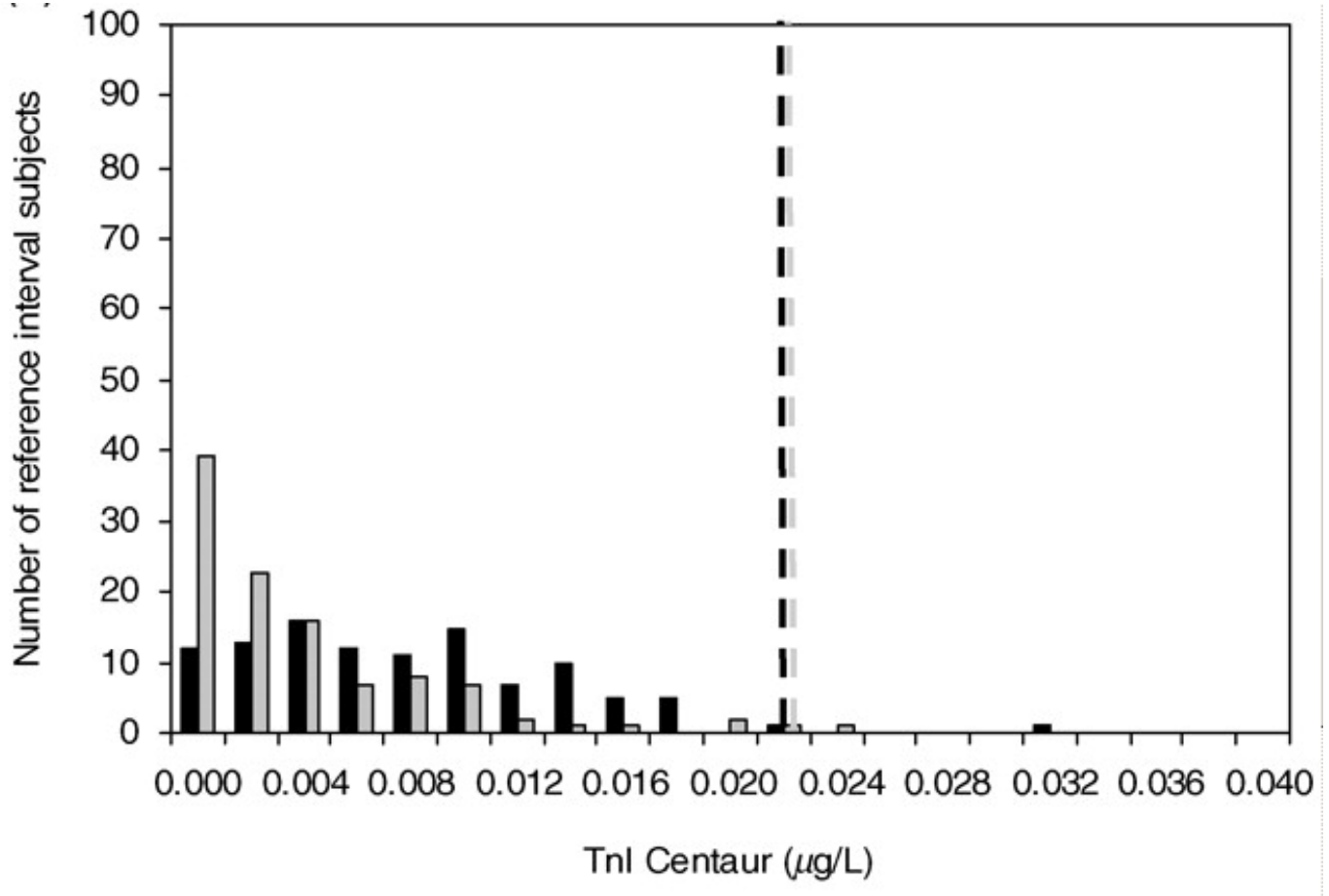
Universal Definition Acute MI

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of 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 with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Definition of Troponin Elevation

>99th centile for normal reference population
Rise or fall
Precise assay
AND symptoms, ECG changes



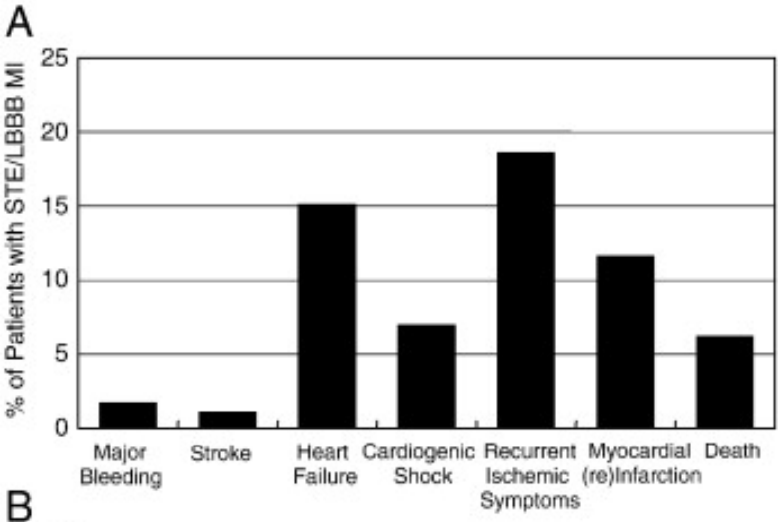
Non-ACS Causes of Troponin Elevation

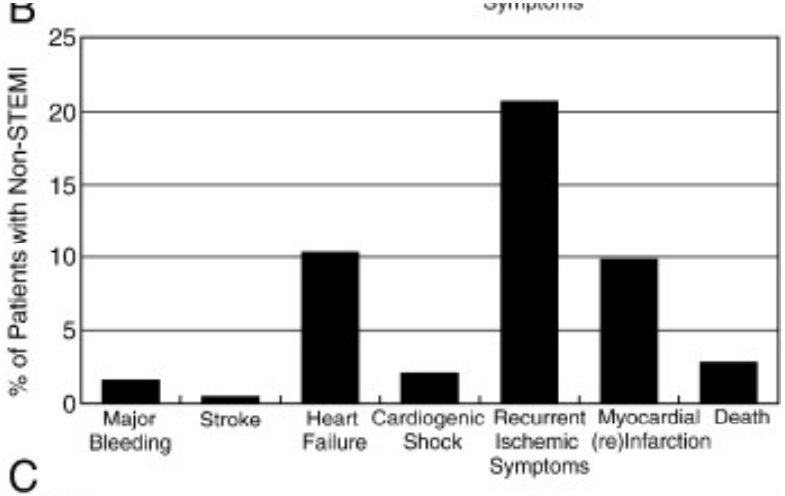
Chronic or acute renal dysfunction	Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
Severe congestive **heart failure** – acute and chronic	Hypothyroidism
Hypertensive crisis	Apical ballooning syndrome (Tako-Tsubo cardiomyopathy)
Tachy- or bradyarrhythmias	Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, sclerodermia
Pulmonary embolism, severe pulmonary hypertension	Drug toxicity, e.g. adriamycin, 5-fluorouracil, herceptin, snake venoms
Inflammatory diseases, e.g. **myocarditis**	Burns, if affecting >30% of body surface area
Acute neurological disease, including **stroke**, or subarachnoid haemorrhage	Rhabdomyolysis
Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy	Critically ill patients, especially with respiratory failure, or sepsis

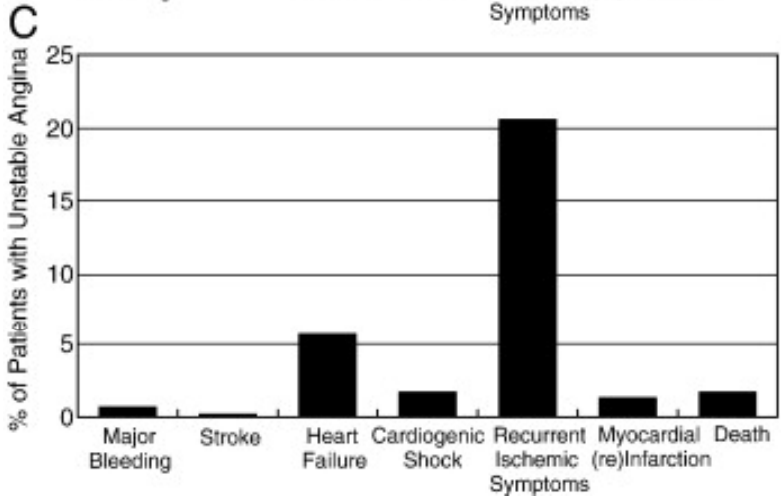
High Risk Features

- Age >75y
- Cardiac arrest
- Cardiogenic shock
- Heart failure
- Diabetes mellitus, chronic kidney disease, ♀
- Murmur
  - MR, VSD
- ECG
  - LBBB > ST↑ > ST↓ > TWI > normal
  - Anterior > Posterior > Lateral > Inferior

Clinical Outcomes after ACS







Goodman et al Am Heart J 2009

Clinical Diagnosis of ACS

Feature	High Likelihood Any of the following:	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following:*	Low Likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age greater than 70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5 to 1 mm or T-wave inversion greater than 1 mm	T-wave flattening or inversion less than 1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Clinical Risk Stratification

Feature	High Risk *At least 1 of the following features must be present:*	Intermediate Risk *No high-risk feature, but must have 1 of the following:*	Low Risk *No high- or intermediate-risk feature but may have any of the following features:*
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (greater than 20 min) rest pain	Prolonged (greater than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (greater than 20 min) or relieved with rest or sublingual NTG Nocturnal angina New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (greater than 20 min) rest pain but with intermediate or high likelihood of CAD (see Table 6)	Increased angina frequency, severity, or durationAngina provoked at a lower threshold New onset angina with onset 2 weeks to 2 months prior to presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age greater than 75 years	Age greater than 70 years	
ECG	Angina at rest with transient ST-segment changes greater than 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression less than 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (e.g., TnT or TnI greater than 0.1 ng per ml)	Slightly elevated cardiac TnT, TnI, or CK-MB (e.g., TnT greater than 0.01 but less than 0.1 ng per ml)	Normal

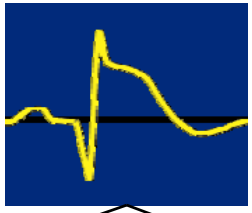
Management Goals

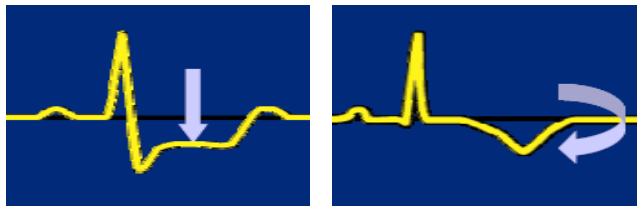
- Reduce MI size
- Stabilise plaques
- Manage thrombosis
- Manage LV remodelling

Reduce MI size

- Open the artery as quickly as possible
  - PPCI or fibrinolysis
  - Adenosine, nitroprusside, nicardipine, Gp IIb/IIIa antagonists (reduce no-reflow)
- Drugs
  - β blockers
  - *Cyclosporine*
  - *Sodium nitrite*
- Other
  - *Post-conditioning*
  - *Progenitor cells*

ACS





PPCI
Transfer <1h
DTB <60 min
Cardiogenic shock
CI to lysis

Lysis
Pre-hospital
Pain to Rx <2h
If transfer >2h:
Lytic+GpIIbIIIa

Fail to reperfuse → Rescue PCI

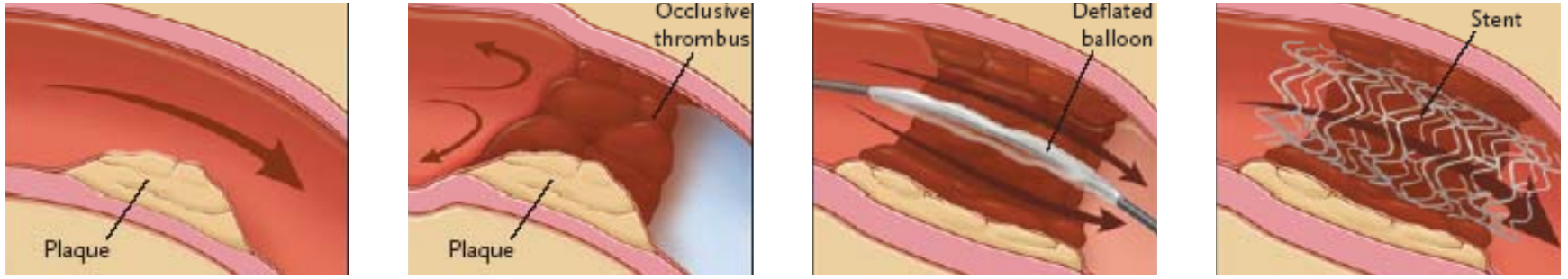
PCI within 24h

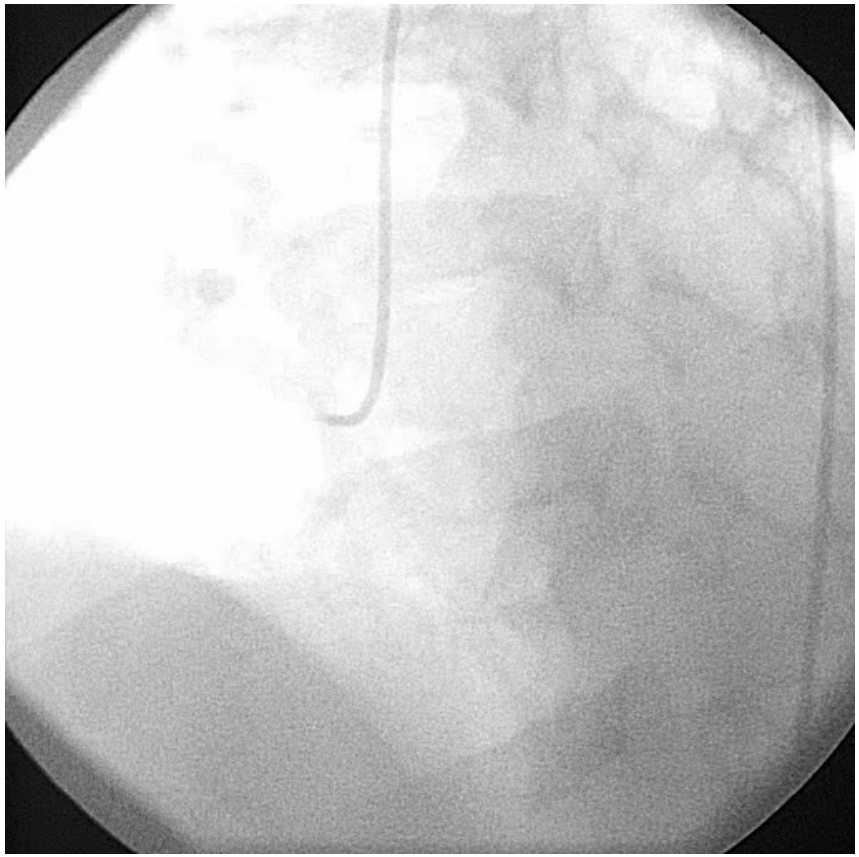
Medical Rx
Risk Stratification

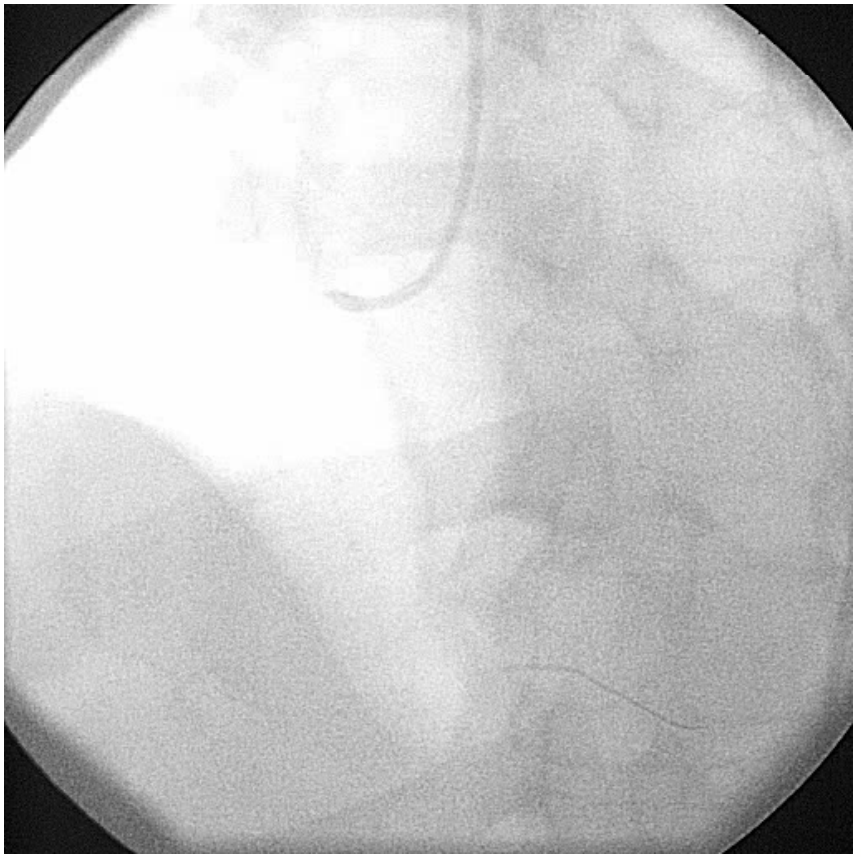
High/Intermediate Risk → Angiography ± Revasc. within 96h

Low Risk → Medical Rx ± Revasc.

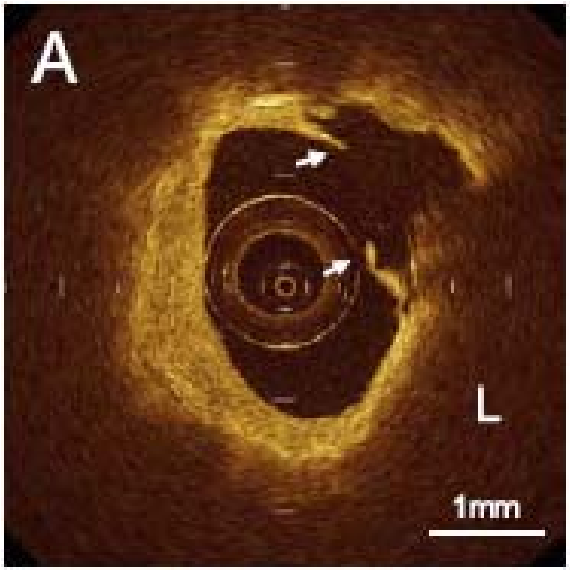
PPCI for STEMI

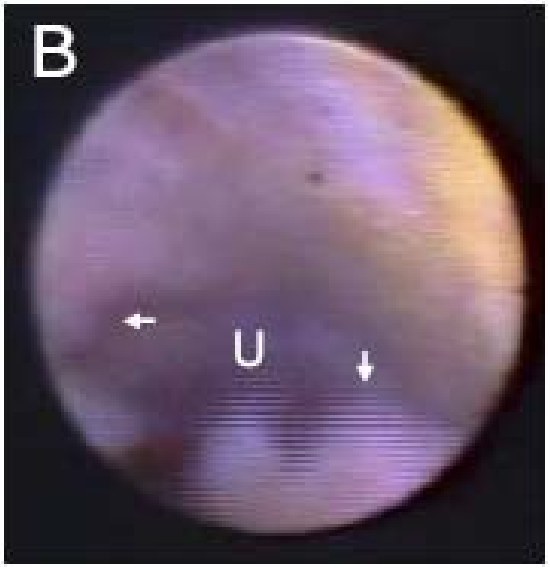


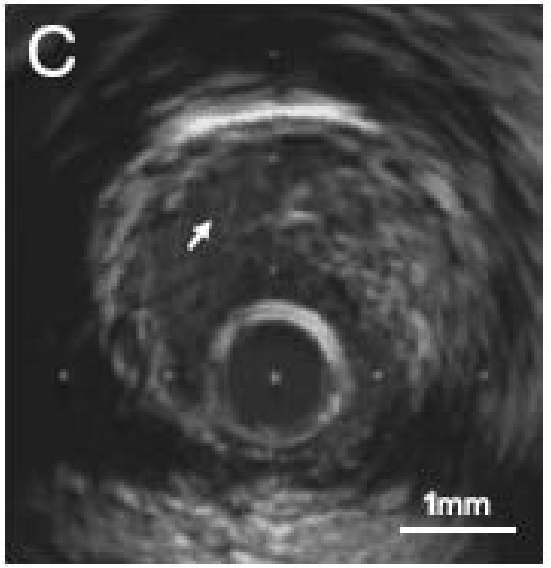




Plaque Rupture In Vivo







OCT **Angioscopy** **IVUS**

Kubo et al. JACC 2007

STEACS Immediate Drug Treatment

PPCI

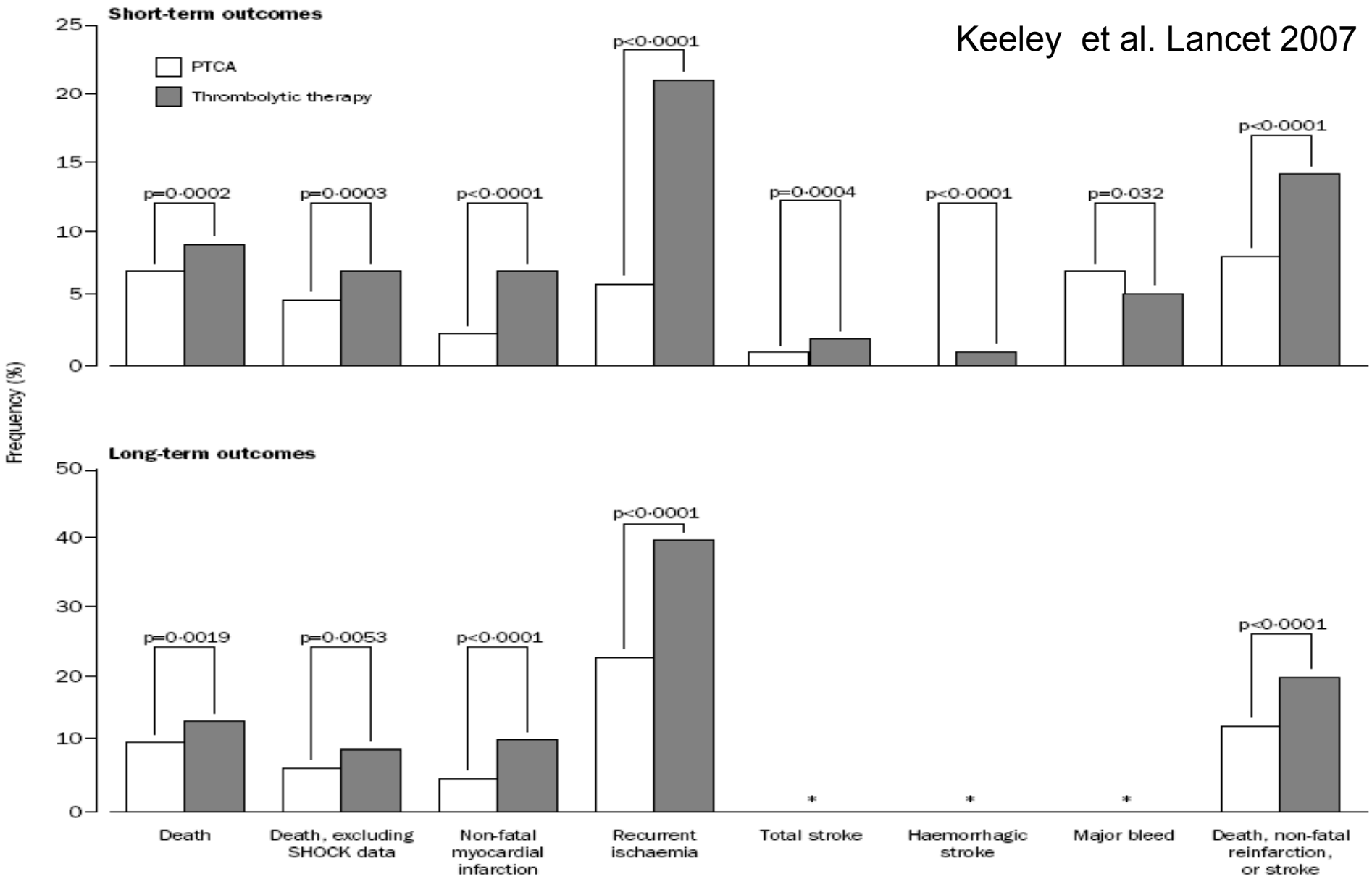
- Aspirin 300mg
- P2Y12 receptor antagonist
  - Clopidogrel 600mg *(CURRENT-OASIS7)*
  - Prasugrel 60mg *(TRITON-TIMI38, HR 0.81, NNT=46)*
  - Ticagrelor 180 mg *(PLATO, HR 0.84, NNT=54)*
- Antithrombin
  - UFH
  - Enoxaparin *(ATOLL)*
  - Bivalirudin *(HORIZONS-AMI)*

Lysis

- Fibrin specific
  - Tenecteplase
- Aspirin 300mg
- P2Y12 receptor antagonist
  - Clopidogrel 300mg *(CLARITY-TIMI28)*
- Antithrombin
  - UFH
  - Enoxaparin *(EXTRACT-TIMI25)*
  - Fondaparinux *(OASIS-6)*

PPCI v Fibrinolysis

Keeley et al. Lancet 2007



Manage Thrombotic Burden/Risk

Acute

- Thrombectomy
- Drugs
  - Oral: Aspirin, clopidogrel, prasugrel, ticagrelor
  - SC: LMWH, fondaparinux
  - IV: Bivalirudin, GpIIb/IIIa inhibitors, fibrinolytics, *Factor Xa inhibitors*

Recurrent

- Oral antiplatelet drugs
- Anticoagulants
  - *Direct thrombin inhibition*
  - *Factor Xa inhibitors*

Plaque Stabilisation

Mechanical

- Stent

Drugs

- Statins (high dose)
- ACE inhibitors

Manage LV Remodelling

Non-Drug

- CRT-P/D
- Progenitor cells

Drugs

- β blockers
- ACE inhibitors
- Angiotensin receptor blockers
- Aldosterone receptor antagonists

QUESTIONS?

Imperial College London

Royal Brompton & Harefield NHS
NHS Foundation Trust

NHS
National Institute for Health Research