Acute Coronary Syndrome

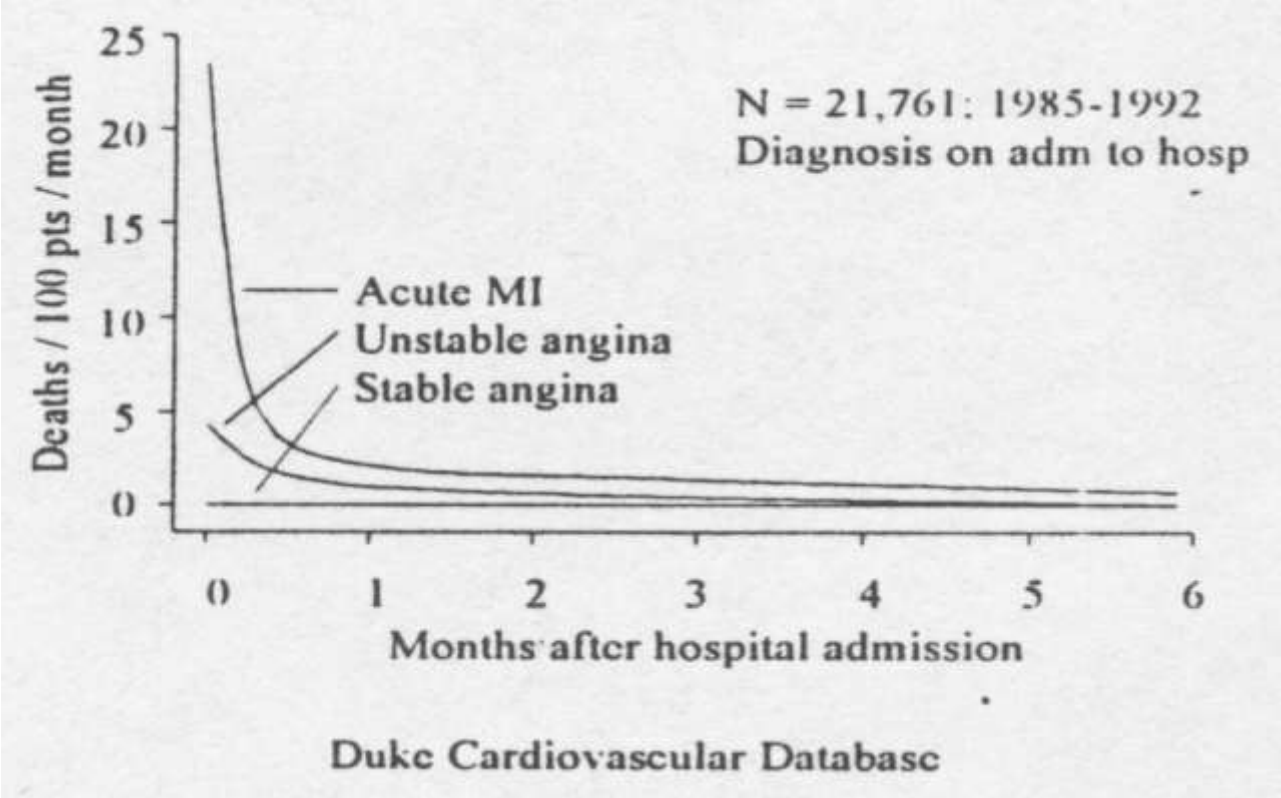
Worldwide Statistics

- > 4 million patients are admited with unstable angina and actue MI
- > 900,000 patients undergo PTCA with or without stent

Myocardial Ischemia

- Spectrum of presentation
  - Silent ischemia
  - Exertion-induced angina
  - Unstable angina
  - Acute myocardial infarction

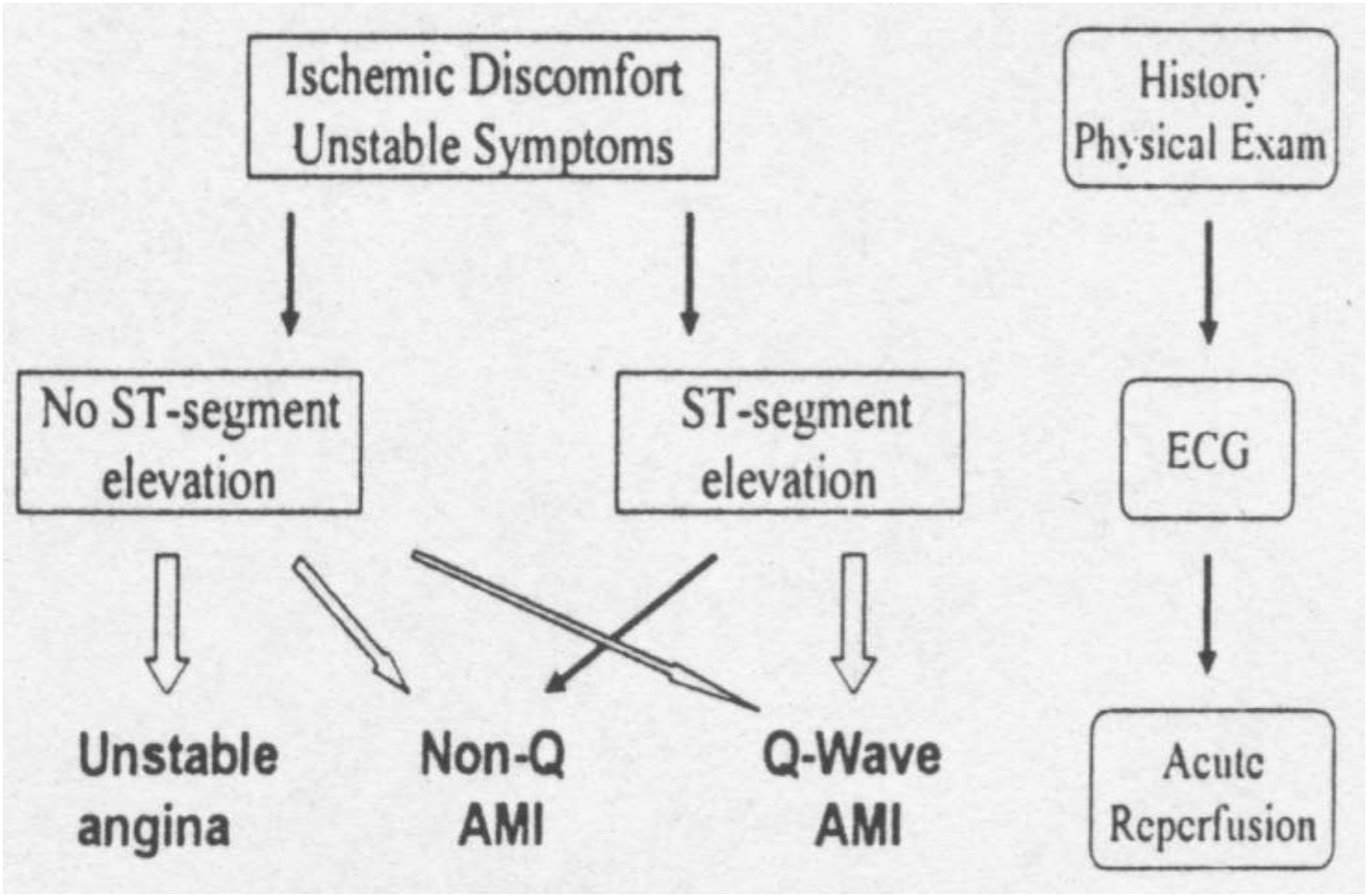
Cumulative 6-month mortality from ischemic heart disease



Ischemic Heart Disease evaluation

- Based on the patient's
  - History / physical exam
  - electrocardiogram
- Patients are categorized into 3 groups
  - Non- cardiac chest pain
  - Unstable angina
  - Myocardial infarction

Acute Coronary Syndrome



Acute Coronary Syndrome

- The spectrum of clinical conditions ranging from:
  - Unstable angina
  - Non-Q wave MI
  - Q-wave MI
- Characterized by the common pathophysiology of a disrupted atherosclerotic plaque

- Angina at rest (> 20 minutes)
- New-onset (<2 months) exertional angina (at least CCSC III in severity)
- Recent (< 2 months) acceleration of angina (increase in severity of at least one CCSC class to at least CCSC class III)

Unstable Angina Likelihood of CAD

- Previous history of CAD
- Presence of risk factors
- Older age
- ST-T wave ischemic ECG changes

Unstable Angina precipitating factors

- Inappropriate tachycardia
  - Anemia,fever,hypoxia,tachyarrhythmias,thyrotoxicosis
- High afterload
  - Aortic valve stenosis,LVH
- High preload
  - High cardiac output, chamber dilatation
- Inotropic state
  - Sympathomimetic drugs,cocaine intoxication

Unstable Angina prognostic indicators

- Presence of ST-Twave changes with pain
- Hemodynamic deterioration
  - Pulmonary edema, new mitral regurgitation
  - 3rd heart sound, hypotension
- Other predictors
  - Left ventricular dysfunstion extensive CAD, age, comorbid conditions(diabetes mellitus, obstructive pulmonary disease, renal failure, malignancy)

Unstable Angina Pathogenesis

- Plaque disruption
- Acute thrombosis
- vasoconstriction

Unstable Angina Pathogenesis

- Plaque disruption
  - Passive plaque disruption

    soft plaque with high concentration of cholesteryl esters and a thin fibrous cap
  - Active plaque disruption

    Macrophage-rich area with enzymes that may degrade and weaken the fibrous cap; predisposing it to rupture

Unstable Angina Pathogenesis

- Acute thrombosis
  - Vulnerable plaque
    - Disrupted plaque with ulceration
    - Occurring in 2/3 of unstable patients
    - The exposed lipid-rich core abunant in cholesteryl ester is highly thrombogenic
  - Systemic Hyperconagulables State
    - Distrupted plaque with erosion
    - Occurring in 1/3 of unstable patients

Unstable Angina Pathogenesis

- Vasoconstriction
  - The culprit lesion in response to deep arterial damage or plaque disruption
  - Area of dysfuncitonal endothelium near the culprit lesion
  - Platelet-dependent and thrombin-dependent vasoconstriction, mediated by serotonin and thromboxane A_2

Acute Coronary Syndrome

- Process of resolution
  - Spontaneous thrombolysis
  - Vasoconstricion resolution
  - Presence of collateral circulation
- Delayed or absence or resolution may lead to non-Q-wave or Q-wave myocardial infarction

Non-Q-Wave MI clues to diagnosis

- Prolonged chest pain
- Associated symptoms from the autonomic nervous system
  - Nausea, vomiting, diaphoresis
- Persistent ST-segment depression after resolution of chest pain

Prinzmetal's Angina clues to diagnosis

- Transient ST-segment elevation during chest pain
- Intermittent chest pain
  - Often repetitive
  - Usually at rest
  - Typically in the early morning hours
  - Rapidly relieved by nitroglycerine
- Syncope (rare), Raynaud's, migraine

Unstable Angina Risk Stratification

- Low risk
  - New-onset exertional angina
  - Minor chest pain during exercise
  - Pain relieved promptly by nitroglycerine
- Management
  - Can be managed safety as an outpatient (assuming close follow-up and rapid investigation)

Unstable Angina Risk Stratification

- intermediate risk
  - Prolonged chest pain
  - Diagnosis of rule-out MI
- Management
  - Observe in the ER or Chest Pain Unit
  - Monitor clinical status and ECG
  - Obtain cardiac enzyme (troponin T or I) every 8 to 12 hours

Unstable Angina Risk Stratification

- High risk
  - Recurrent chest pain
  - ST-segment change
  - Hemodynamic compromise
  - Elevation in cardiac enzyme
- Management
  - Monitor in the coronary Care Unit

Risk Stratification by ECG

The risk of death or MI at 30 days is strongly related to the ECG at the time of chest pain

- ST depression 10 %
- T-wave inversion 5 %
- No ECG changes 1~2 %

Unstable Angina Therapeutic Goals

- Therapeutic Goals
  - Reduce myocardial ischemia
  - Control of symptoms
  - Prevention of MI and death
- Medical Management
  - Anti-ischemic therapy
  - Anti-thrombotic therapy

Unstable Angina Medical Therapy

- Anti-ischemic therapy
  - Nitrates, beta blockers, calcium antagonists
- Anti-thrombotic therapy
  - Anti-platelet therapy
    - Aspirin, ticlopidine, clopidolgrel, GP IIb/IIIa inhibitors
  - Anti-coagulant therapy
    - Heparin, low molecular weight heparin (LMWH), warfarin, hirudin, hirulog

Unstable Angina Anti-ischemic Therapy

- Restrict activities
- Morphine
- oxygen
- nitroglycerine
  - Pain relief, prevent silent ischemia, control hypertension, improve ventricular dysfunction
  - Nitrate free period recommended after the first 24-48 hours

Unstable Angina Anti-ischemic Therapy

- Beta-blockers
  - Lowering angina threshold
  - Prevent ischemia and death after MI
  - Particularly useful during high sympathetic tone
- Calcium antagonists
  - Particularly the rate-limiting agents
  - Nifedipine is not recommended without concomitant ß-blockade

Unstable Angina Anti-ischemic Therapy

- Thrombolytics are not indicated
- “lytic agents may stimulate the thrombogenic process and result in paradoxical aggravation of ischemia and myocardial infarction”

Platelets in Acute coronary Syndromes

- Platelets play a key role in ACS
- Sources of platelet activation(triggers)
  - Thromboxane A_2 (TXA_2)
  - ADP
  - Epinephrine
  - Collagen
  - thrombin

Unstable Angina Anti-ischemic Therapy

- Aspirin is the "gold standard"
  - Irreversible inhibition of cyclooxygenase pathway in platelets, blocking formation of thromboxane A_2, and platelet aggregation
  - In AMI, ASA reduced the risk of death by 20-25%
  - In UA, ASA reduced the risk of fatal or nonfatal MI by 71% during the acute phase, 60% at 3 months, and 52% at 2 years
  - Bolus dose of 160~325 mg, followed by maintenance dose of 80~160 mg/d

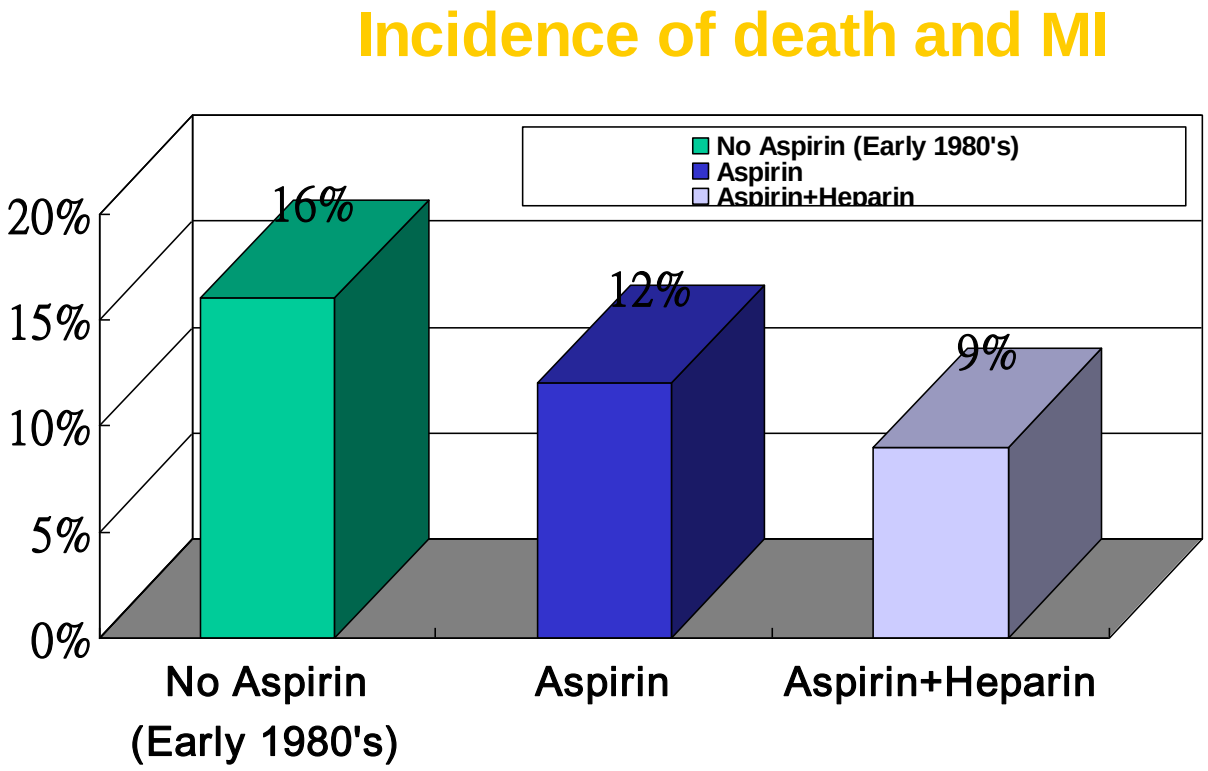
GP IIb/IIIa Receptor Final Pathway to Platelet Aggregation

- Platelet activation and aggregation are early events in the development of coronary thrombosis
- GP IIb/IIIa receptors on activated platelets undergo a conformational change allowing recognition and binding of fibrinogen
- Fibrinogen”acts like glue”,bridging GP IIb/IIIa recptors on adjacent platelets, leading to platelet aggregation

GP IIb/IIIa Receptor KVGFFGR

- There are approcimately 50,000 GP IIb/IIIa receptors on each platelet
- KVGFFGR is a specific region within GP IIb/IIIa receptor that is thought to be involved in platelet activation

Incidence of Ischemic Events



Unstable Angina Anti-Platelet Therapy

- Thienopyridines
  - Ticlopidine (Ticlid; Roche)
  - Clopidogrel (Plavix; BMS)

block platelet aggregation induced by ADP and the transformation of GP IIb/IIIa into its high affinity state

Unstable Angina Anti-Platelet Therapy

- Ticlopidine
  - In a open-label, randomized study in patients with unstable angina
  - Ticlopidine 250 mg bid vs. placebo reduced the risk of fatal or nonfatal MI by 46% at 6 months
  - Benefit not seen at 7 days, but became apparent after 10 days of therapy (the time required for full antiplatelet activity)
  - An alternative for patient with asprin intolerance

Unstable Angina Anti-Platelet Therapy

- Clopidogrel
  - CAPRIE(Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events)
  - 19,000 patients randomly assigned to clopidogrel(75 mg/d) or to Aspirin(325mg/d)
  - There are 8.7% reduction in the combined incidence of stoke, MI, or death(P≒0.043)
  - Patients with MI did better with aspirin
  - Patients with PVD or stroke did better with clopidogrel

Unstable Angina Anti-Platelet Therapy

- GP IIb/IIIa inhibitors
  - Abciximab (monocional antibody)
  - Eptigibatide (peptidic inhibitor)
  - Lamifiban and tirofiban (non-peptides)

direct occupancy of the GP Iib/Iia receptor by a monoclonal antibody or by synthetic compounds mimicking the RGD sequence for fibrinogen binding prevents platelet aggregation