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مستشفى الباطنة التخصصى
Specialized Medical Hospital

Acute Coronary Syndrome: noninvasive therapy

By

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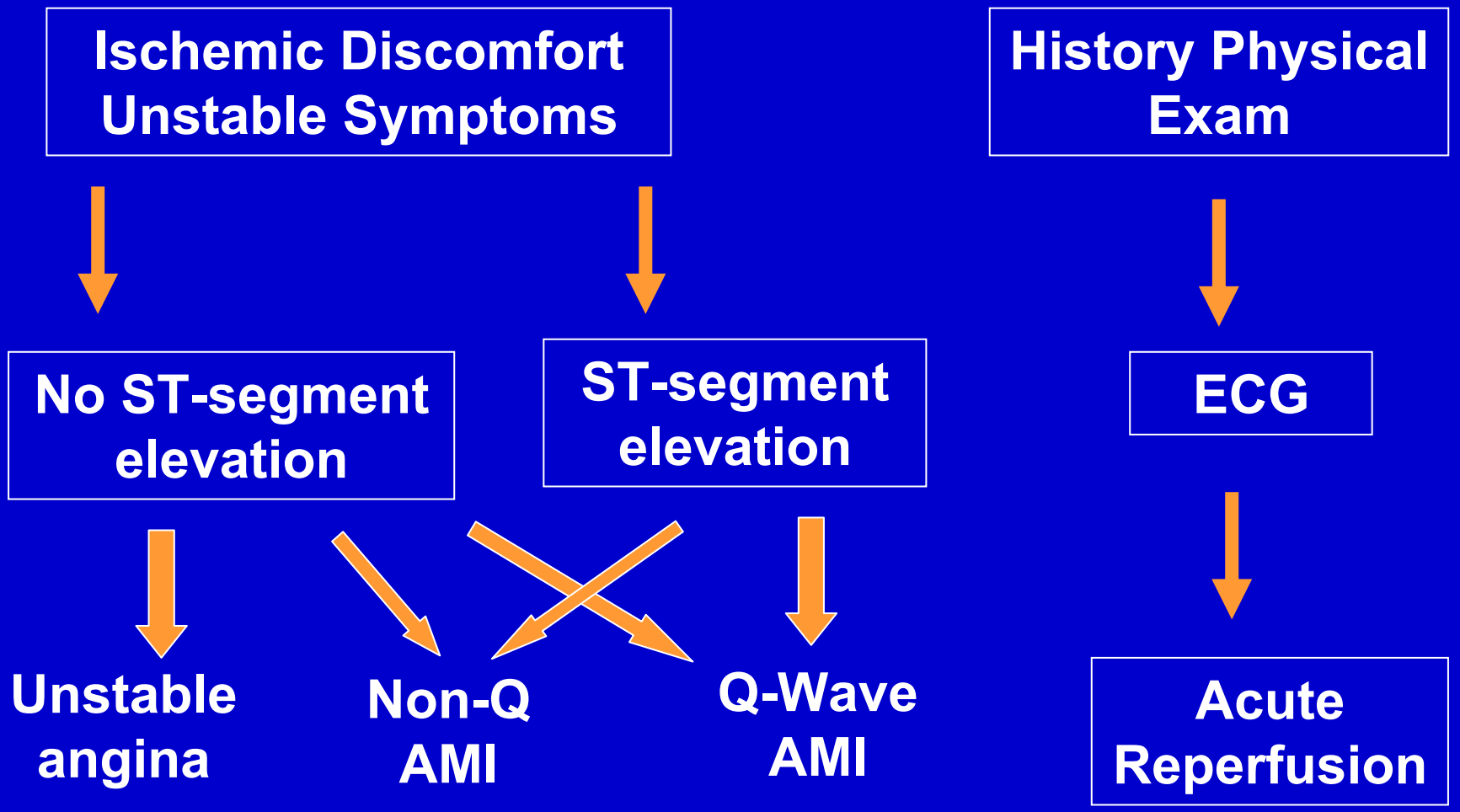
Definitions

- **Acute Coronary Syndrome:**
- Any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It encompasses AMI (ST-segment elevation and depression, Q wave and non-Q wave) as well as UA.
- **UA/NSTEMI:** constitutes a clinical syndrome that is usually, but not always, caused by atherosclerotic CAD and associated with an increased risk of cardiac death.

Acute Coronary Syndrome



Presentation of UA/USTEMI

- Rest angina
  - At rest & prolonged > 20 min.
- New-onset angina
  - New onset of at least CCS class III
- Increasing angina
  - Previously diagnosed, now more frequent, longer in duration, or lower in threshold.

Predictors of high risk for death

- Age > 65 years
- Class III or IV angina
- Tachycardia or Bradycardia
- Hypotension
- Rales
- ST depression
- Positive markers

Braunwald classification of U.A

- Class I: Exertional angina
  - New onset, severe accelerated angina of less than 2 minutes duration.
  - Angina precipitated by less exertion.
  - No rest angina in the last 2 months .
- Class II: rest angina: (sub acute)
  - Rest angina within the lost month, but now within 45h. Of presentation.
- Class III: rest angina: (acute)
  - Rest angina with 48 h of presentation.

Clinical circumstances

- **Secondary unstable angina:** caused by a non-cardiac conditions such as: anemia, infection, thyrotoxicosis or hypoxemic.
- **Primary unstable angina.**
- **Post myocardial infarction unstable angina** within 2 weeks of documented MI.

Why risk stratify? Why risk stratify?

- Admission triage
- Prognostication
- Treatment

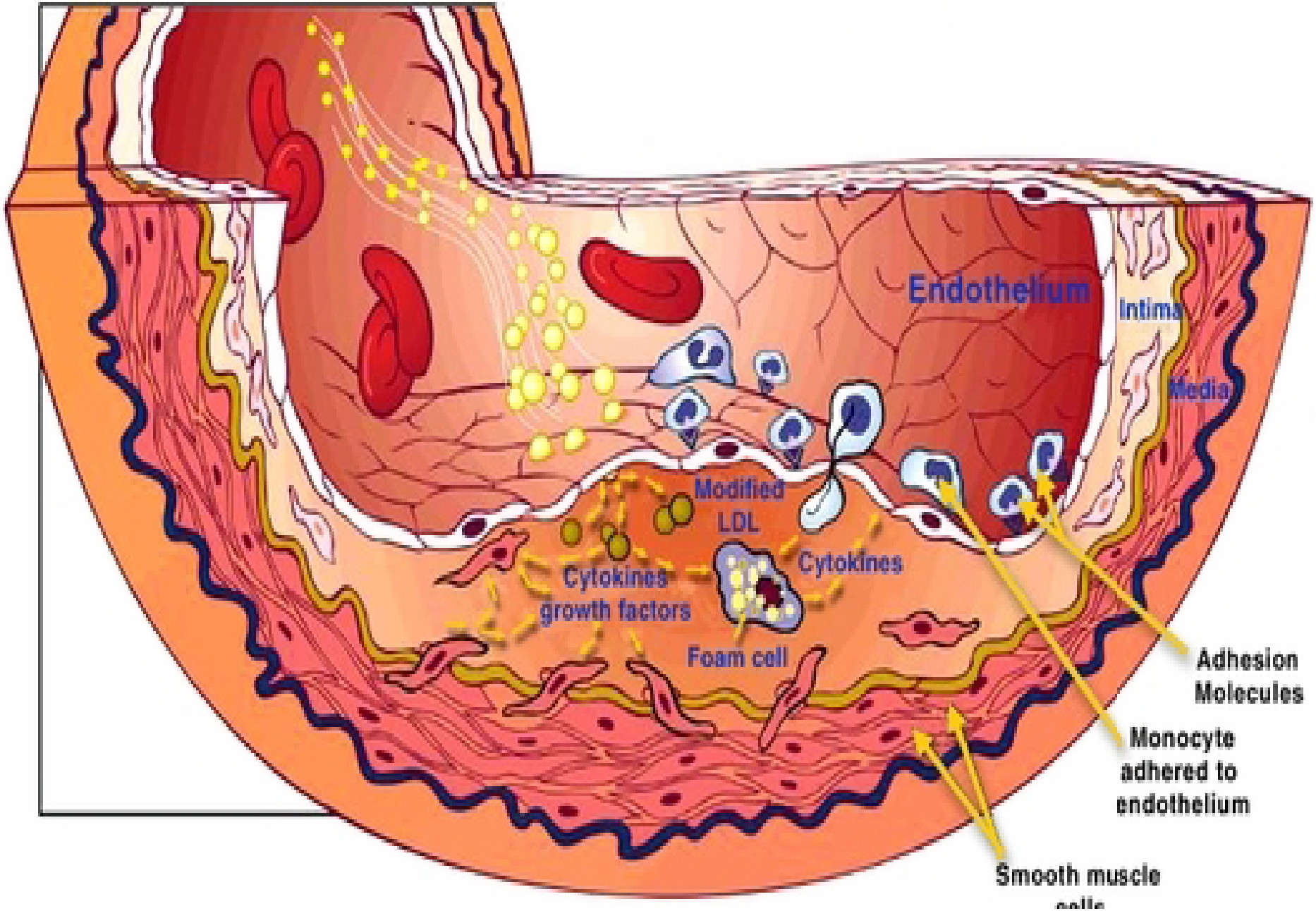
Tools for Immediate Risk Assessment

- Patient Characteristics
- Presenting Signs and Symptoms
  - Braunwald classification of UA
  - Killip HF classification
- ECG
- Laboratory Data

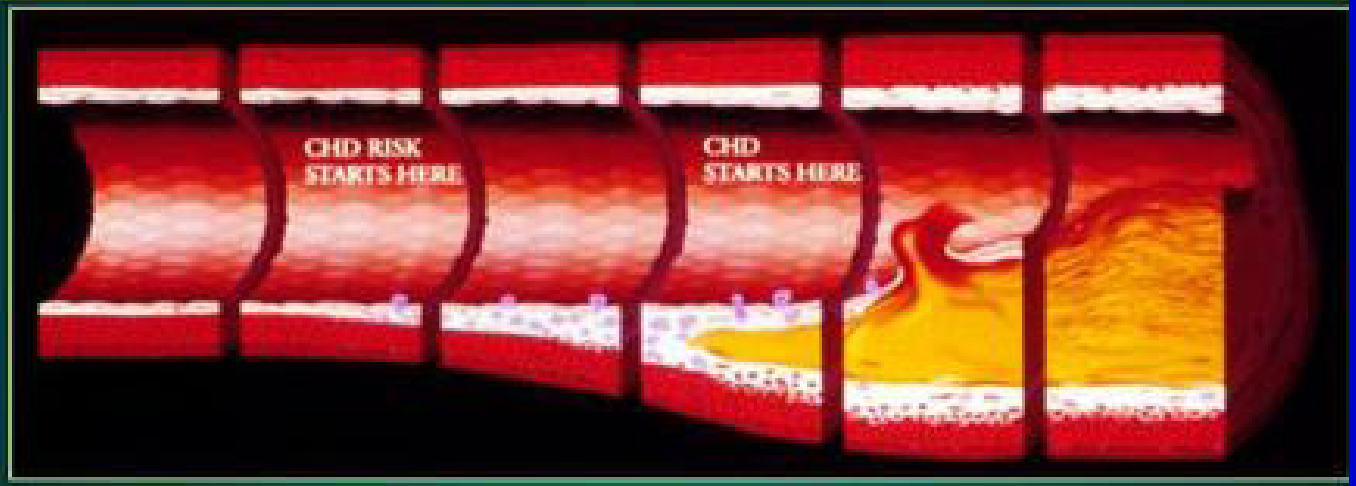
Pathogenesis of UA/NSTEMI

- **Causes:** (not mutually exclusive)
  - Nonocclusive thrombus on pre-existing plaque
  - Dynamic obstruction (coronary spasm or vasoconstriction)
  - Progressive mechanical obstruction
  - Inflammation and/or infection
  - Secondary UA

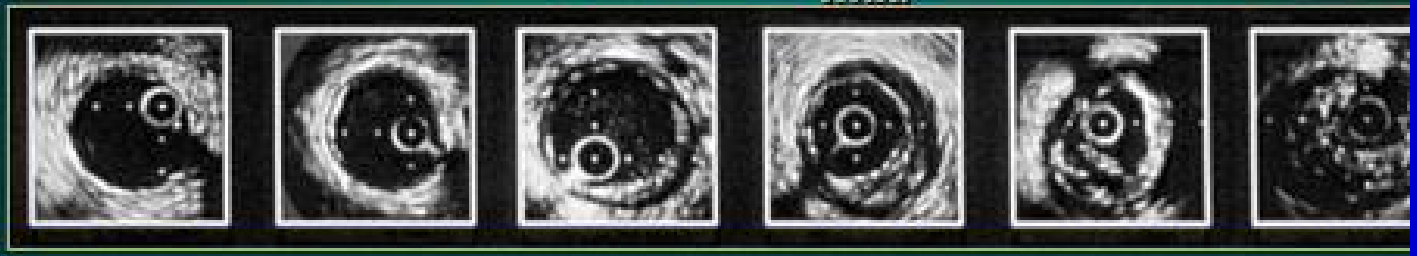
Schematic View of Atherogenesis



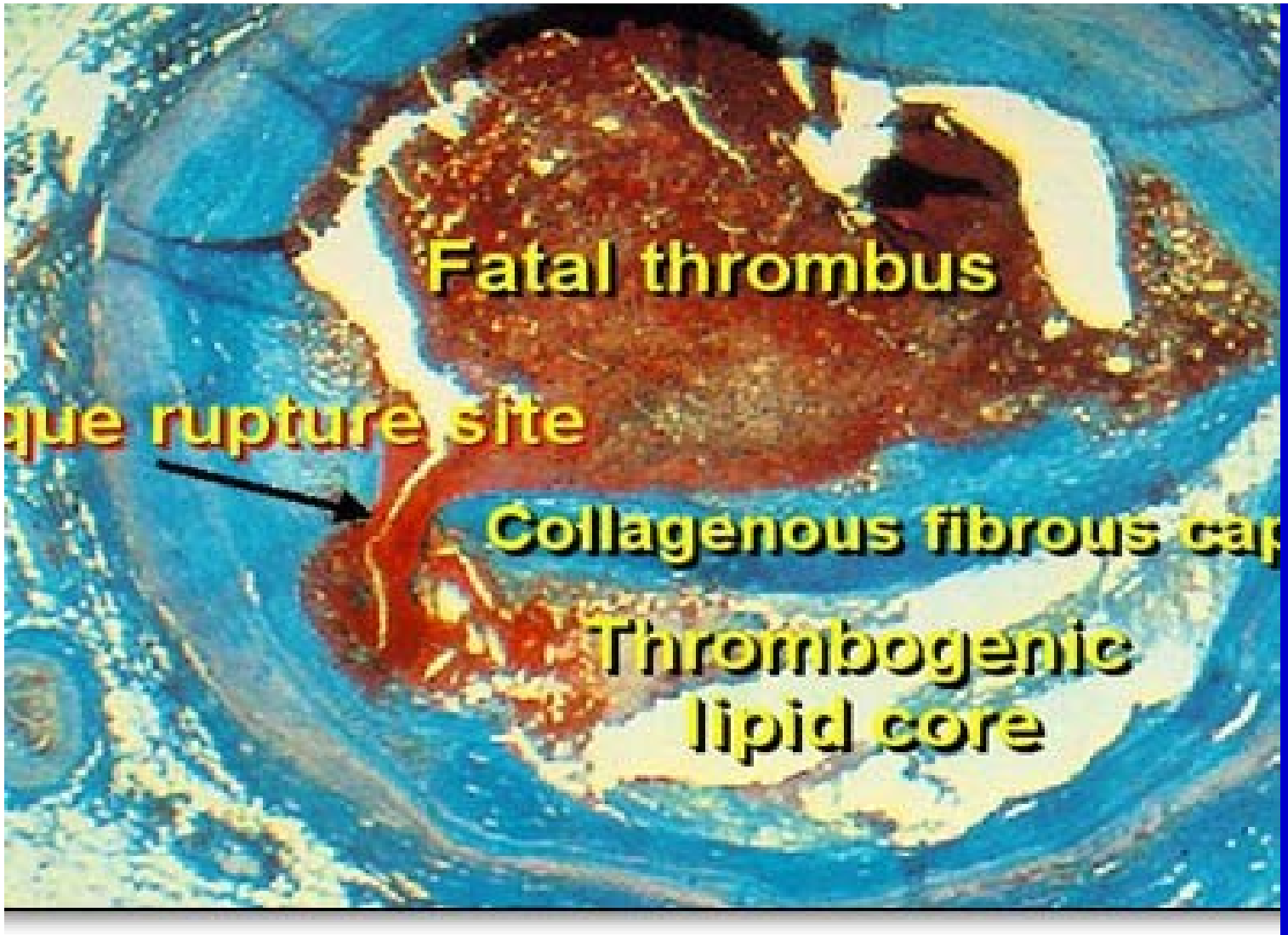
Structure of Thrombus Following Plaque Disru



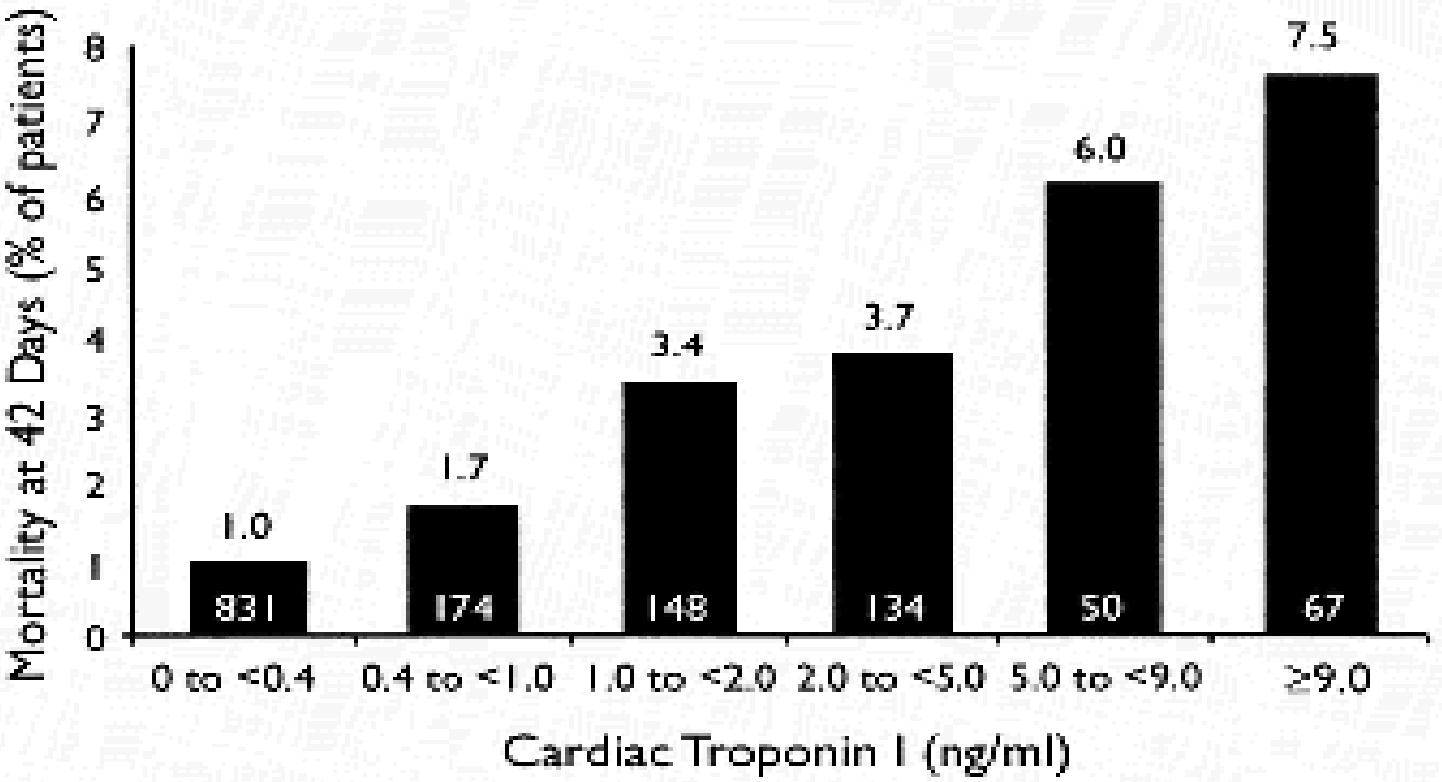
Healthy Artery | Early stages of atherosclerosis | Inflammatory process | Early atherosclerotic lesion | Vulnerable plaque | Stable plaque



Intravascular ultrasound (IVUS) images compiled by the Cleveland Clinic Foundat


Fatal thrombus
que rupture site
Collagenous fibrous cap
Thrombogenic
lipid core

Troponin I Levels to Predict the Risk of Mortality in Acute Coronary Syndromes



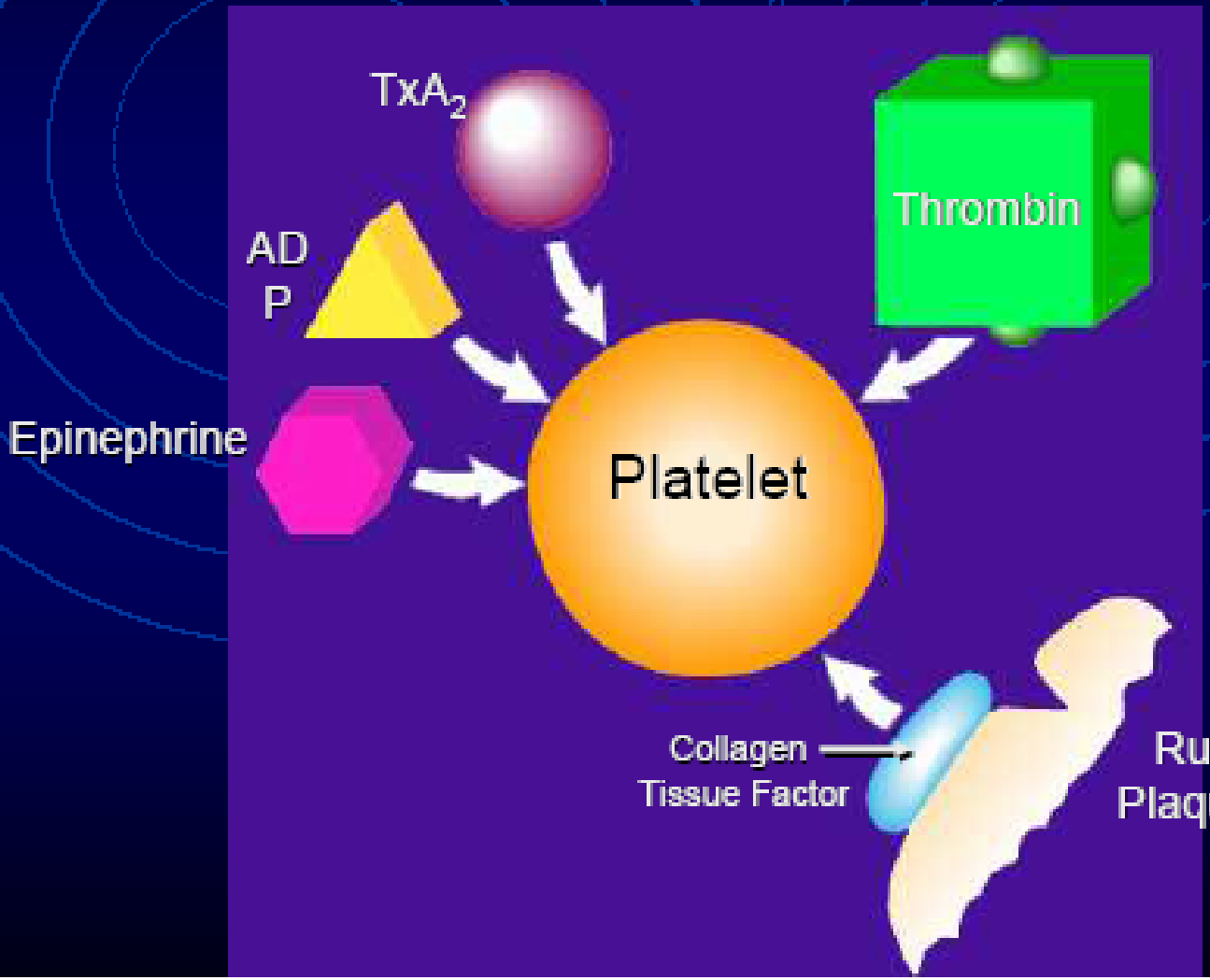
Risk Ratio	1.0	1.8	3.5	3.9	6.2	7.8
95% Confidence Interval	—	0.5–6.7	1.2–10.6	1.3–11.7	1.7–22.3	2.6–23.0

Platelets in Acute Coronary Syndromes

- Platelets play a key role in ACS
- Sources of platelet activation (triggers)
- thromboxane A2(TXA2)
- ADP
- Epinephrine
- Collagen
- thrombin

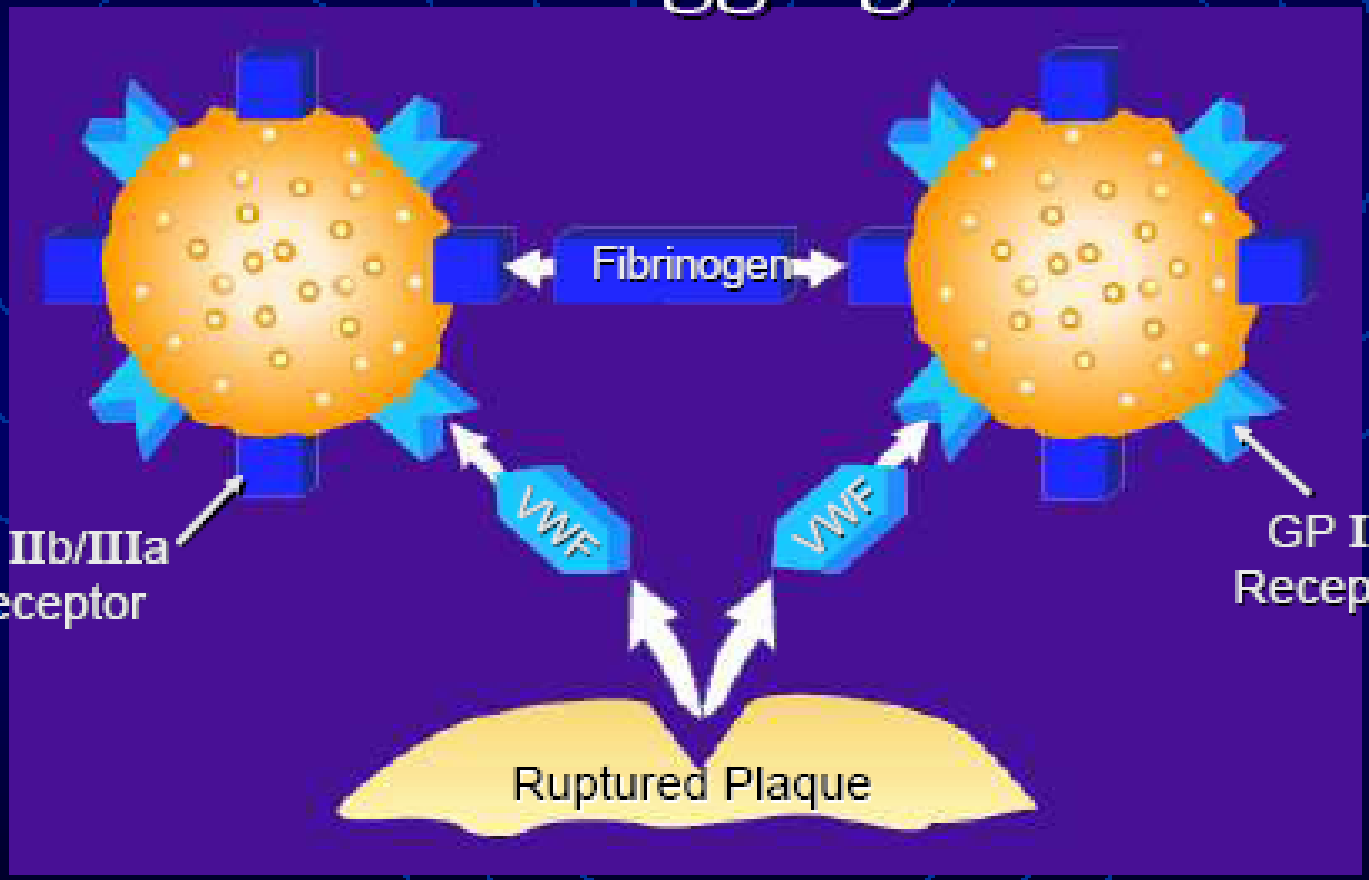
Thrombotic Process – Pathophysiology

Platelet Activation



Thrombotic Process – Pathophysiology

Platelet Aggregation



Demographics:

- Patients with UA/NSTEMI are:
  - Older
  - Higher incidence of risk factors.
  - Prior history of MI and revascularization procedures as PCI or CABG.
- Differential diagnosis:
  - Exclude mimics of angina:
    - Costochondritis
    - Pneumonia
    - Pericarditis.
    - Aortic dissection.
    - Pneumothorax.
    - Pulmonary embolism.
    - Hypertensive emergencies
    - thyrotoxicosis
    - Systemic infection.

Laboratory evaluation

- **E.C.G: include**
  - ST-segment depression.
  - Transient ST elevation.
  - T-wave inversion.
- **Cardiac enzymes**
  - CK- MB.
  - Troponins.

Cont.

- **Other biochemical markers:**
  - C.R.P
  - VEGF
  - b FGF
  - IAM-1
  - E-selectin.
  - P-selectin.
  - CD 40 ligand.

Non-invasive stress testing:

- **Can be done only in low-risk patients with the following characteristic:**
  - Who remain pain free for 24 – 48 hs after admission.
  - Who have undetectable biomarkers.
  - Normal or non-diagnostic ECG.
  - Present with a typical symptoms.
  - Have a few cardiac risk factors.

Indications for cardiac catheterization in UA

- Prior revascularization.
- CHF.
- Depressed LV function (EF <50%).
- Malignant ventricular arrhythmias.
- Persistent or recurrent angina.
- Large perfusion defect or noninvasive functional test.
- Significant valvular H.D.

ACC/AHA Risk Stratification

Feature	High Risk	Intermediate Risk	Low Risk
History	Accelerating tempo of ischemic sx in 48hrs	Prior MI, PVD, CVD, CABG, ASA use	New-onset CCS III or IV angina in past 2 wks without prolonged (>20 min) rest pain but with mod. or high likelihood of CAD
Character of Pain	Prolonged, ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with mod. or high likelihood of CAD	
Clinical Findings	Pulmonary edema New or Worse MR S3 or new/worse rales Hypotension, brady/tachycardia Age>75 yrs	Age >70 yrs	
ECG	Rest angina +transient ST changes >0.05mV New BBB Sustained VT	T-wave inversions >0.2 mV Pathological Q waves	Normal or unchanged during CP
Cardiac Markers	Markedly elevated (TnT or TnI >0.1 ng/mL)	Slightly elevated (TnT >0.01 but <0.1 ng/mL	Normal

Management

- **Goals:**
  - Immediate relief of ischemia
  - Prevention of serious adverse outcomes
- **Approach**
  - Anti-ischemic therapy
  - Anti-platelet therapy
  - Anti-coagulant therapy
  - Ongoing risk stratification
  - Invasive procedures

Anti-Ischemic therapy for Continuing Ischemia

- Bed rest with ECG monitoring
- O_2 to maintain Sa O_2 > 90%
- NTG IV
- Beta-blockers
- Morphine
- IABP if ischemia or hemodynamic instability persists
- ACE I for control of hypertension or LV dysfunction, after AMI.

Antiplatelet and Anticoagulation Therapy

- Oral Antiplatelet therapy
  - Aspirin
  - Thienopyridines
    - Ticlopidine
    - Clopidogrel
- Heparins
  - UFH
  - LMWH
- IV Antiplatelet therapy
  - Abciximab
  - Eptifibatide
  - Tirofiban

Anticoagulants Unfractionated Heparin (UFH)

- Most widely used antithrombotic agent
- Recommendation is based on documented efficacy in many trials of moderate size
- Meta-analyses of six trials showed a 33% risk reduction in MI and death, but with a two fold increase in major bleeding

Unfractionated Heparin (UFH)

- **Disadvantages include:**
  - Poor bioavailability
  - No inhibition of clot-bound thrombin
  - Dependent on antithrombin III (ATIII) cofactor
  - Frequent monitoring (aPTT) to ensure therapeutic levels
  - Rebound ischemia after discontinuation
  - Risk of heparin-induced thrombocytopenia (HIT)

Low-Molecular-Weight Heparin (LMWH)

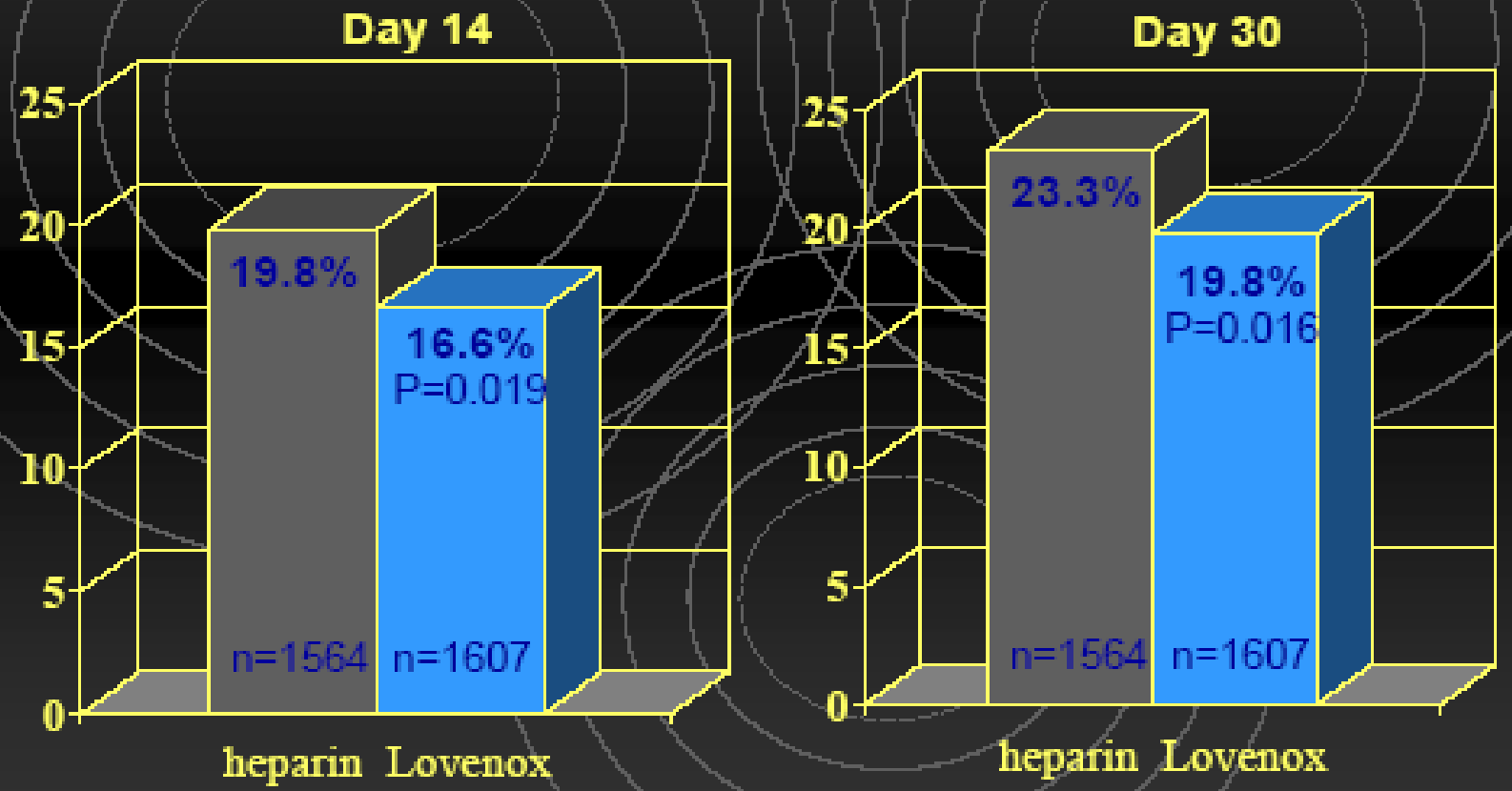
- Fraction of standard (UFH) heparin
- Advantages over UFH:
  - Greater bioavailability
  - No need to closely monitor
  - Resistant to inhibition by activated platelets
  - Lower incidence of HIT
  - Enhanced anti-factor Xa activity
- Effective subcutaneous administration
- Enoxaparin, dalteparin, reviparin, nadroparin, fraxiparin

ESSENCE Trial (Efficacy and Safety of Subcutaneous Enoxaparin in non-Q-Wave Coronary Events Study)

- LMWH (enoxaparin)+ ASA vs UFH+ASA
- Patients: angina at rest or non-Q-wave MI; n = 3,171
- *Composite triple endpoint:* death/nonfatal MI/RA

ESSENCE Trial

incidence of death, MI, or recurrent angina



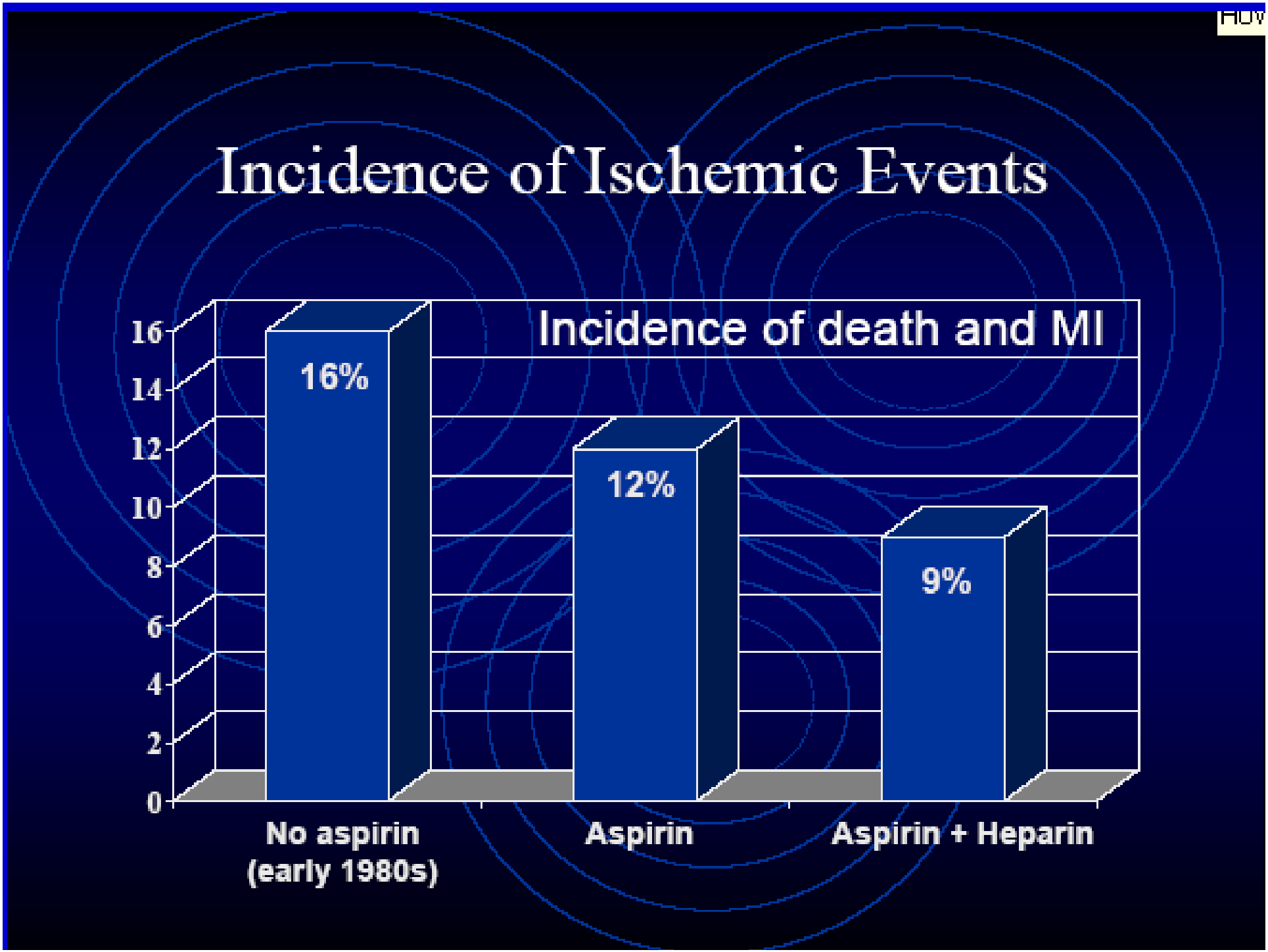
N Eng J Med 1997;337:447-452

Anti-platelet Therapy

- **Aspirin**
  - Irreversible inhibition of the cyclooxygenase pathway in platelets, blocking formation of thromboxane A2
  - Bolus dose of 160-325 mg, followed by maintenance dose of 80-325 mg/d

Aspirin

- 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


Incidence of Ischemic Events
Incidence of death and MI
16
14
12
10
8
6
4
2
0
16%
12%
9%
No aspirin
(early 1980s)
Aspirin
Aspirin + Heparin

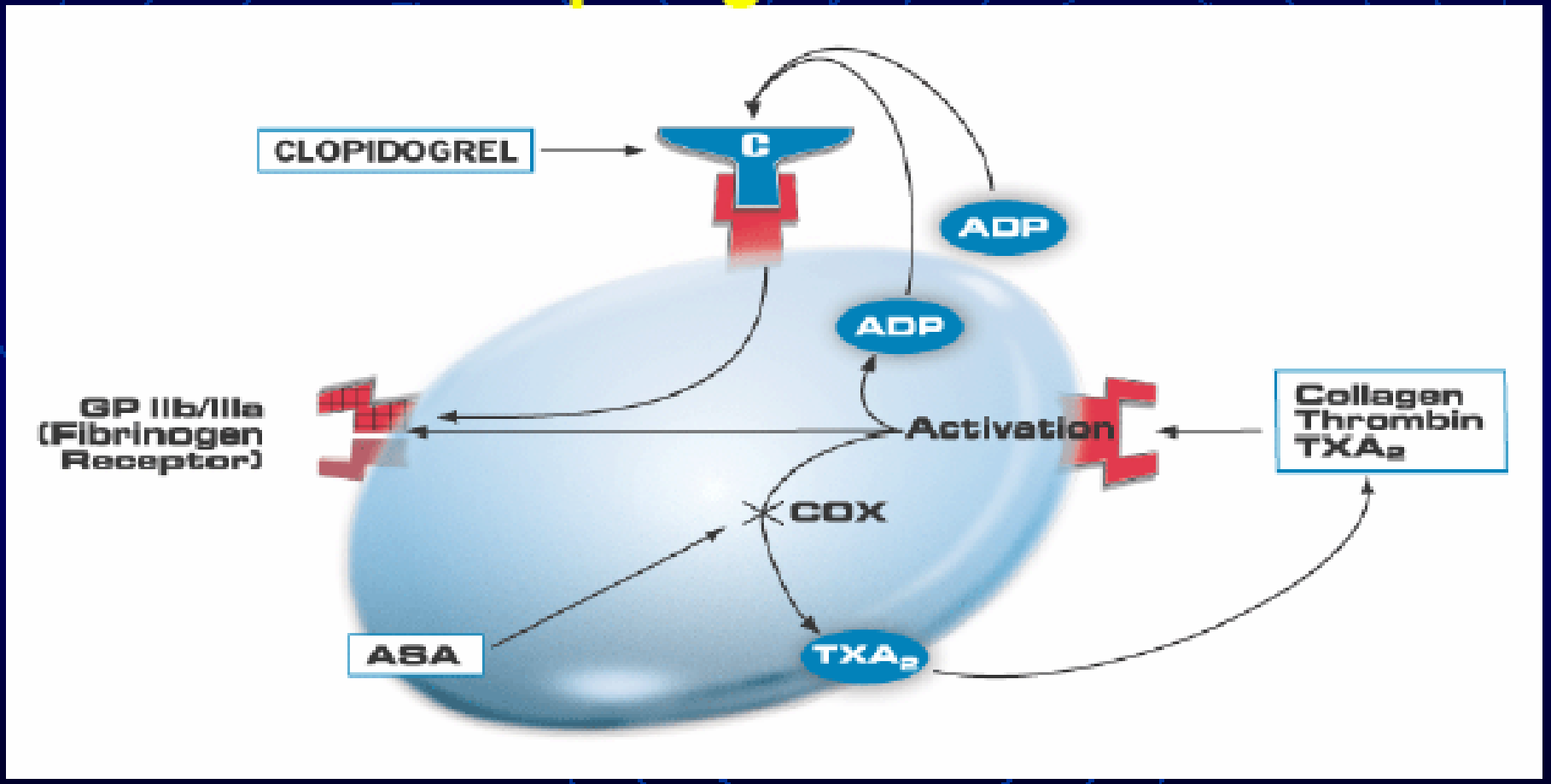
Aspirin

- Not Perfect
- Patients on ASA may present with ACS
- ASA non-responders 20-30%
- Not adequate alone for stent implantation
- Side effects

Thienopyridines

- Ticlopidine.
- Clopidogrel.
  - Block ADP receptor resulting in inhibition of transformation of GP IIb/IIIa into its high affinity state.

Complementary Mode of Action between Clopidogrel and ASA



COX, cyclooxygenase; ADP, adenosine diphosphate; TxA_2, thromboxane A_2

CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events)

- 19,185 patients randomly assigned to clopidogrel (75 mg/d) or to aspirin (325 mg/d).
- Entry criteria: recent MI, recent ischemic stroke and symptomatic PAD.
- Follow up for 1-3 years
- 8.7%RR in the combined incidence of stroke, MI, or death (P=.043) with clopidogrel.
- Patients with MI did better with aspirin.
- Patients with PVD or stroke did better with clopidogrel

Study Design

- Randomized, double-blind, parallel group, clinical trial of clopidogrel vs placebo in patients with ACS
- All patients receive ASA (75-325 mg)
- International trial (28 countries)
- 12,562 patients (482 Hospitals)•Central randomization
- 3-12 month Rx and follow-up
- Main outcomes: -CV death/MI, stroke
  -Above + refractory ischemia

Outcomes 1/2

	Plac	Clop			
	%	%	RR	CI	p
# Patients	6303	6259			
1st Co-Primary	11.41	9.30	0.80	0.72-0.90	< 0.001
•CV Death	5.47	5.08	0.93	0.79-1.08	
•MI	6.65	5.18	0.77	0.67-0.89	
•Stroke	1.38	1.20	0.86	0.63-1.18	
Non CV death	0.71	0.66	0.91	0.60-1.39	

Outcomes 2/2

	Plac	Clop			
	%	%	RR	CI	p
# Patients	6303	6259			
2nd Co-Primary	18.83	16.54	0.86	0.79-0.94	< 0.001
Refract.Ischemia	9.31	8.69	0.93	0.82-1.04	
In hospital	2.00	1.36	0.68	0.52-0.90	
After Discharge	7.59	7.57	0.99	0.87-1.13	
Severe Ischemia	5.03	3.80	0.75	0.63-0.89	< 0.001

Bleeding Complications

	Placebo	Clopidogrel	RR	95% CI	p
# Patients	6303	6259			
Major	2.7%	3.7%	1.38	1.13-1.67	0.001
•Life Threatening	1.8%	2.2%	1.21	0.95-1.56	0.13
•Other Major	0.9%	1.5%	1.70	1.22-2.35	< 0.002
Minor	2.4%	5.1%	2.12	1.75-2.56	< 0.001
Transfusion (2+Units)	2.2%	2.8%	1.30	1.04-1.62	0.02

Major/Life-Threatening Bleeds within 7 Days of CABG Surgery

	Plac	Clop	RR	p
Stopped ≤ 5 days prior to CABG	N = 476	N = 436		
Pts with Maj/LT Bleeds	6.3%	9.6%	1.53	0.06
Stopped > 5 days prior to CABG	N = 454	N = 456		
Pts with Maj/LT Bleeds	5.3%	4.4%	0.83	0.53

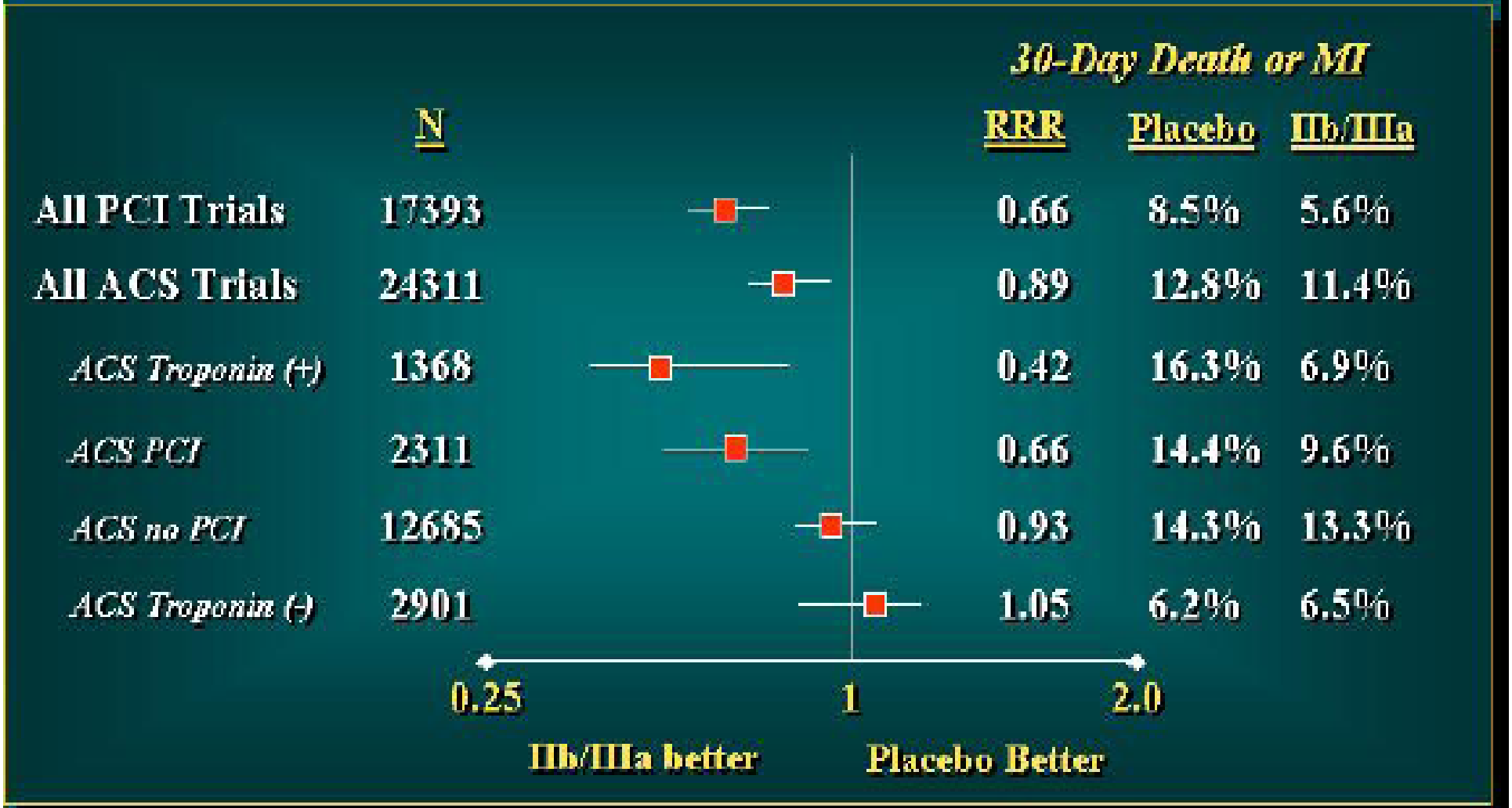
GP IIb/IIIa Receptor
Final Pathway to Platelet Aggregation

- 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 receptors on adjacent platelets, leading to platelet aggregation

IV Anti-platelet Therapy

- GP IIb/IIIa inhibitors
  - Abciximab (monoclonal antibody)
  - Eptifibatide (peptide inhibitor)
  - Lamifiban and tirofiban (non-peptides)

Overview of GP IIb/IIIa Trials by Pooled Analysis



Chew & Moliterno JACC 2000; 36:2028

IV GP IIb/IIIa ACS Trials (1998-2000)

- Patients undergoing PCI have the greatest reduction in events
- Little data to support use to reduce complications in the absence of PCI
- Should be used in high risk patients (ST changes, elevated troponin, refractory symptoms) as a bridge to catheterization

Subgroups of patients that benefit from glycoprotein IIb/IIIa inhibitors

- **Troponin- positive status: CAPTURE trial**: Abciximab therapy reduces the rate of incidence of fatal and nonfatal AMI in patients with UA with elevated troponin level than in patients with normal troponin.
- **Diabetes:** A decreased mortality at 30 days was observed in diabetics treated with glycoprotein IIb/IIIa (6.2% vs 4.6, p=0.007).

Recommendations for Antiplatelet and Anticoagulation Therapy

Class I

1. Antiplatelet therapy should be initiated promptly. Aspirin is the first choice and is administered as soon as possible after presentation and is continued indefinitely. (Level of Evidence: A)
2. Clopidogrel should be administered to patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: A)
3. In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of Evidence : A) and for upto 9 months (Level of Evidence : B)

Recommendations for Antiplatelet and Anticoagulation Therapy

Class I (Contd.)

4. In hospitalized patients for whom a PCI is planned, clopidogrel should be started and continued for at least 1 month (Level of Evidence : A) and for up to 9 months in patients who are not at high risk for bleeding (Level of Evidence : B)
5. In patients taking clopidogrel in whom CABG is planned, if possible the drug should be withheld for at least 5 days, and preferably for 7 days. (Level of Evidence :B)

Recommendations for Antiplatelet and Anticoagulation Therapy

ass I (Contd.)

Anticoagulation with subcutaneous LMWH or ntravenous UFH should be added to antiplatelet herapy with ASA and/or clopidogrel.

A platelet GP IIb/IIIa receptor antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI (Level of Evidence: A)

Early Conservative vs Invasive Strategies

ecommendations

ass I

An early invasive strategy in patients with UA/NSTE-MI and any of the following highrisk indicators. (Level of Evidence A)

a. Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy

ecommendations

ass I (Contd.)

g. Hemodynamic instability

h. PCI within 6 months

I. Prior CABG

In the absence of these findings, either an early conservative or an early invasive strategy in hospitalized patients without contraindications

pid lowering therapy

n all patients with elevated LDL or total cholesterol for primary or secondary prevention.

MIRACL study:

- 3086 patients with UA/NSTEMI.
- Atorvastation 24-96 hours after presentation.
- Fatal & nonfatal AMI, cardiac arrest or recurrent angina at 16 wk were reduced.
- These early benefits of statins are due to their "pleiotropic" or non-lipid lowering effects

ecommendations

ass I (Contd.)

b. Elevated TnT or TnI

c. New or presumably new ST-segment depression

d. Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening MR

e. High-risk findings on noninvasive stress testing

Post discharge Care

BCDE

A – Antiplatelets & Antianginals

B – Beta blocker, Blood pressure control

C – Cholesterol lowering, Cigarettes cessation

D – Diabetes control, Diet

E – Education & Exercise

onclusions:

The risks of UA/NSTEMI have been underestimated: one in eight patients will die within six months and one in ive will require emergency hospitalization.

Anti-platelets and anti-thrombin therapy improve outcome and **β-blockers and nitrates** reduce schaemia.

Glycoprotein IIb/IIIa inhibitors reduce cardiac complications, especially in those patients proceeding to ntervention.

Fibrinolytoc therapy is associated with worse

Thank You