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# **Pharmacotherapy of Acute Coronary Syndrome (ACS)**

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# Definition

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- Acute coronary syndromes (ACSs) include
  - all clinical syndromes compatible with **acute myocardial ischemia** resulting from **an imbalance between myocardial oxygen demand and supply**.
- In contrast to stable angina,
  - an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus.

# Cont...

- ACSs are classified according to ECG changes into
  - ST-segment-elevation ACS (STE ACS or STEMI) and
  - Non-ST-segment-elevation ACS (NSTEMI), which includes
    - non-ST-segment-elevation myocardial infarction (NSTEMI) and
    - unstable angina (UA)
- After a STEMI, pathologic Q waves are seen frequently on the ECG and usually indicate transmural MI.
- Non-Q-wave MI, which is seen predominantly in NSTEMI, is limited to the sub-endocardial myocardium.



# Cont...

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- NSTEMI differs from UA in that
  - ischemia is **severe enough** to produce myocardial **necrosis**, resulting in release of detectable amounts of bio-chemical markers, primarily troponin I or T and creatine kinase myocardial band (CK-MB) from the necrotic myocytes into the bloodstream

# Comparison of ACSs

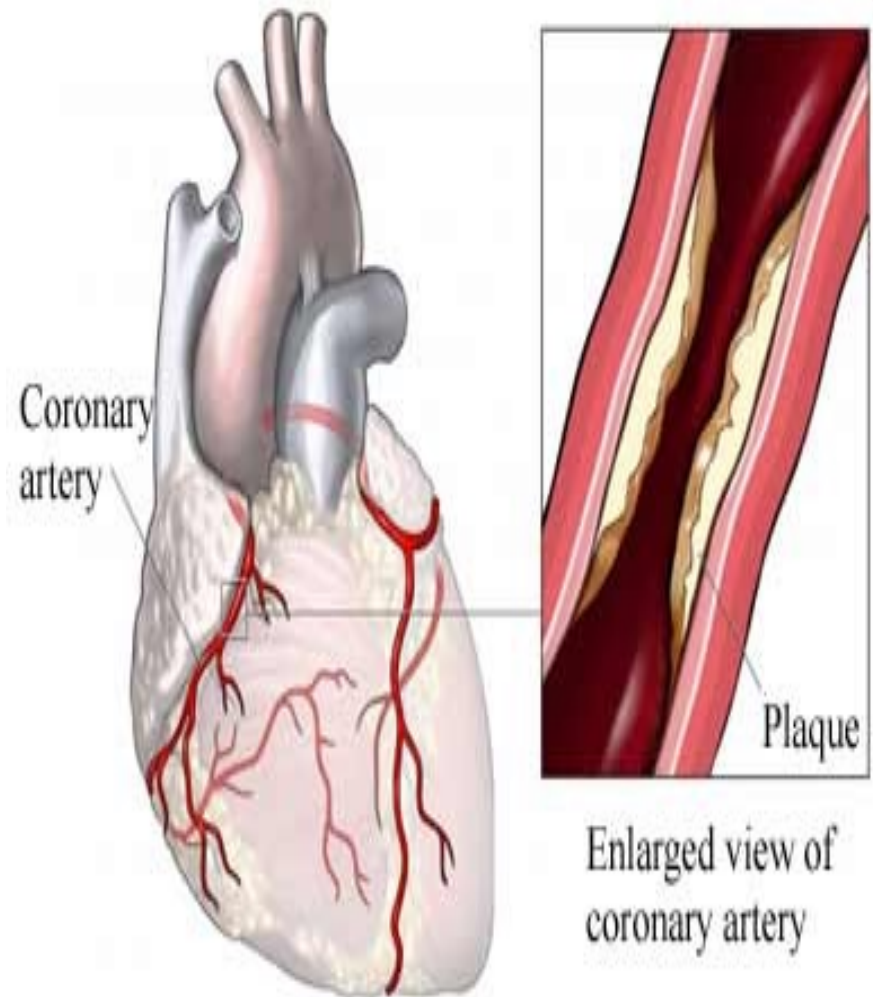
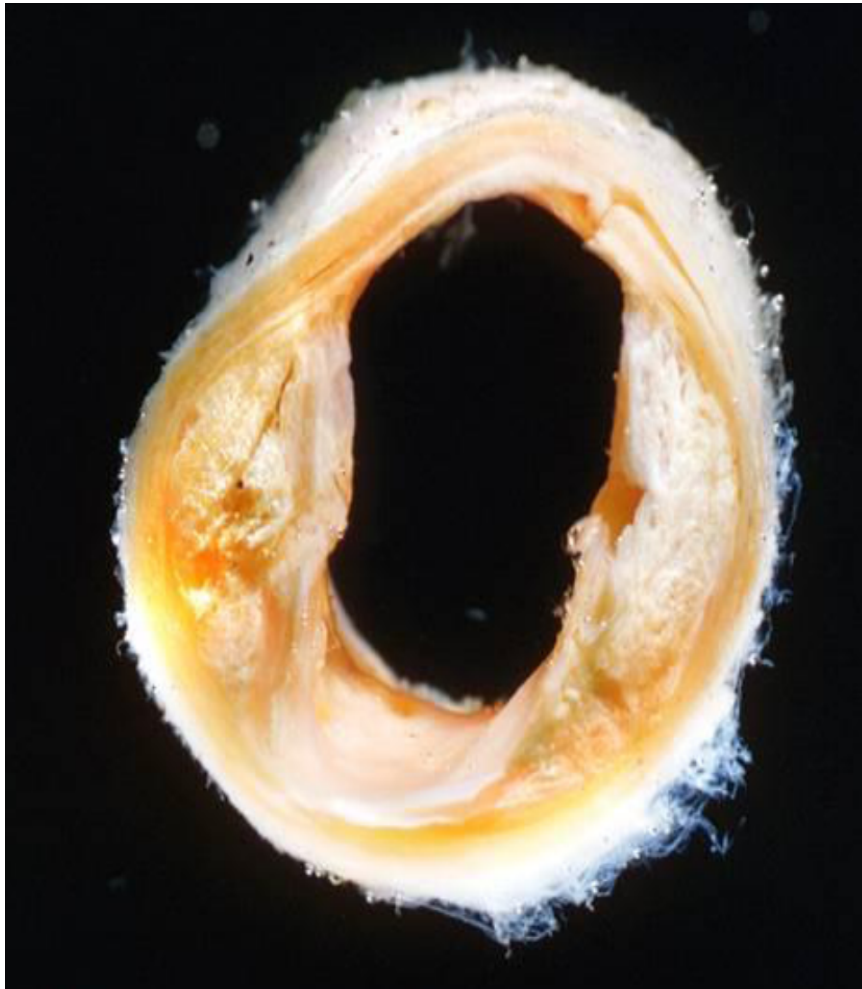
	<b>Unstable Angina</b>	<b>NSTEMI</b>	<b>STEMI</b>
Symptoms present	+	+	+
ECG changes	None	ST segment depression, T wave inversion, or no changes	ST segment elevation
Biochemical marker	No changes	Increased troponins & CK MB	Increased troponins & CK MB

# Pathophysiology

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- **Atherosclerotic plaques**
  - The formation of atherosclerotic plaques is the underlying cause of coronary artery disease (CAD) and ACS in most patients.
  - Endothelial dysfunction leads to the formation of fatty streaks in the coronary arteries and eventually to atherosclerotic plaques.
  - Factors responsible for development of atherosclerosis include:
    - hypertension, age, male gender, tobacco use, diabetes mellitus, obesity, and dyslipidemia

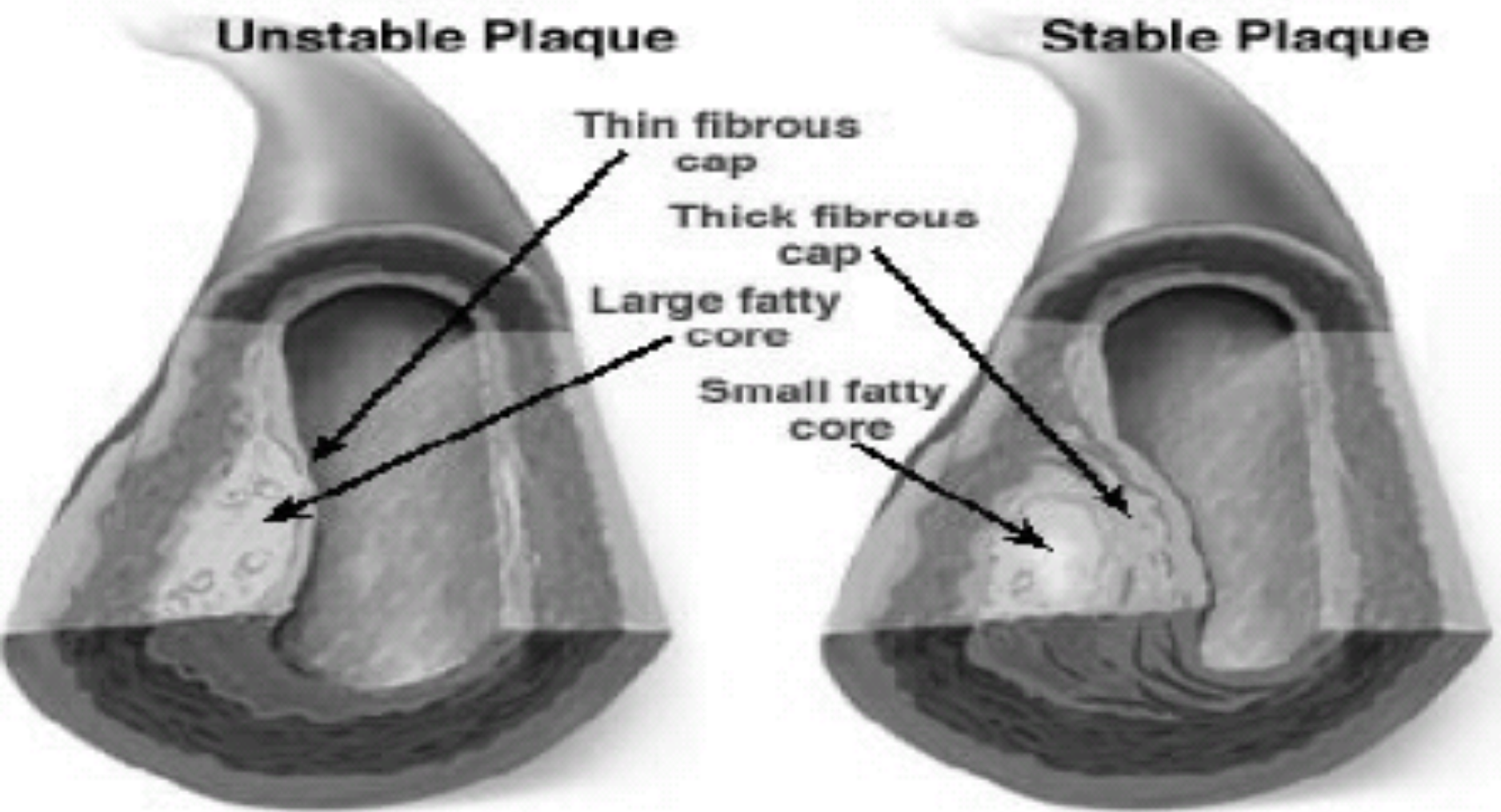
# Atherosclerotic plaque



# Cont...

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- The cause of ACS in **more than 90%** of patients is rupture, fissuring, or erosion of an unstable atheromatous plaque.
- Plaques most susceptible to rupture have
  - an eccentric shape
  - thin fibrous cap
  - large fatty core
  - high content of inflammatory cells such as macrophages and lymphocytes
  - limited amounts of smooth muscle and
  - significant compensatory enlargement.



**As plaque builds up, it can become either stable or unstable. Unstable plaque is more prone to sudden rupture, a potentially life-threatening event.**

# Cont...

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- A partially or completely occlusive clot forms on top of the ruptured plaque.
- Exposure of collagen and tissue factor induce platelet adhesion and activation, which promote release of adenosine diphosphate and thromboxane A2 from platelets.
- These produce vasoconstriction and potentiate platelet activation.

# Cont...

Thrombus formed  
occluding 100%



- A change in the conformation of the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges (the final common pathway of platelet aggregation).
- Simultaneously, activation of the extrinsic coagulation cascade occurs as a result of exposure of blood to the thrombogenic lipid core and endothelium, which are rich in tissue factor.
- This pathway ultimately leads to the formation of a fibrin **clot/thrombus** composed of fibrin strands, cross-linked platelets, and trapped red blood cells.



# Cont...

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- Ventricular remodeling occurs after an MI and is characterized by changes in the size, shape, and function of the left ventricle that may lead to cardiac failure.
- Factors contributing to ventricular remodeling include
  - neurohormonal factors (e.g., activation of the renin-angiotensin-aldosterone and sympathetic nervous systems)
  - hemodynamic factors
  - mechanical factors
  - changes in gene expression and
  - modifications in myocardial matrix metalloproteinase activity and their inhibitors.

# Cont...

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- This process may lead to cardiomyocyte hypertrophy, loss of cardiomyocytes, and increased interstitial fibrosis, which promote both systolic and diastolic dysfunction.
- **Complications of MI** include
  - cardiogenic shock, heart failure, valvular dysfunction, various arrhythmias, pericarditis, stroke secondary to left ventricular (LV) thrombus embolization, venous thromboembolism, and LV free-wall rupture.

# Causes of CAD

Type	Comments
Atherosclerosis	Most common cause. Risk factors: hypertension, hypercholesterolemia, diabetes mellitus, smoking, family history of atherosclerosis.
Spasm	Coronary artery vasospasm can occur in any population but is most prevalent in Japanese. Vasoconstriction appears to be mediated by histamine, serotonin, catecholamines, and endothelium-derived factors. Because spasm can occur at any time, the chest pain is often not exertion-related.
Emboli	Rare cause of coronary artery disease. Can occur from vegetations in patients with endocarditis.
Congenital	Congenital coronary artery abnormalities are present in 1 to 2% of the population. However, only a small fraction of these abnormalities cause symptomatic ischemia.

# Clinical Presentation

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- The predominant symptom of ACS is
  - **midline anterior chest discomfort** (most often occurring at rest)
  - **severe new-onset angina** or increasing angina that lasts at least 20 minutes.
  - The discomfort may **radiate** to the shoulder, down the left arm, to the back, or to the jaw.
  - Accompanying symptoms may include **nausea, vomiting, diaphoresis, or shortness of breath.**

# Cont...

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- Elderly patients, patients with diabetes, and women are less likely to present with classic symptoms.
- There are no specific features indicative of ACS on physical examination.
- However, patients with ACS may present with signs of acute heart failure or arrhythmias.

# Presentation of ACS

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## **General**

- The patient typically is in acute distress and may develop or present with cardiogenic shock.

## **Symptoms**

- The classic symptom of ACS is midline anterior chest discomfort. Accompanying symptoms may include arm, back or jaw pain, nausea, vomiting, or shortness of breath.
- Patients less likely to present with classic symptoms include elderly patients, diabetic patients, and women.

## **Signs**

- No signs are classic for ACS.
- However, patients with ACS may present with signs of acute heart failure, including jugular venous distension, rales, and  $S_3$  sound on auscultation.
- Patients may present with arrhythmias and therefore may have tachycardia, bradycardia, or heart block.

# Diagnosis

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- **A 12-lead ECG**

- A 12-lead ECG should be obtained within 10 minutes of patient presentation.
- Key findings indicating myocardial ischemia or MI are
  - ST-segment elevation
  - ST-segment depression and
  - T-wave inversion.
- These changes in certain groupings of leads help to identify the location of the involved coronary artery.

# Cont...

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- The appearance of a **new left bundle-branch block** accompanied by chest discomfort is **highly specific for acute MI**.
- Some patients with myocardial ischemia have no ECG changes,
  - So biochemical markers and other risk factors for CAD should be assessed to determine the patient's risk for experiencing a new MI or other complications.



# Cont...

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- **Biochemical markers**

- Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI.
- An evolving MI is defined as:
  - a typical rise and gradual fall in troponin I or T or
  - a more rapid rise and fall of CK-MB
- Typically, blood is obtained immediately and
  - 2 additional times in the first 12 to 24 hours after presentation.

# Cont...

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- An MI is identified if at least
  - **one** troponin value or
  - **two** CK-MB values are  $>$  MI decision limit
- Both troponins and CK-MB are detectable within 6 hours of MI.
- Troponins remain elevated for up to **10 days**, whereas CK-MB returns to normal within **48 hours**.
- The most **specific** test for MI is elevated Troponin

# Cont...

## **Laboratory tests**

- Troponin I or T and creatine kinase MB are measured.
- Blood chemistry tests are performed with particular attention to potassium and magnesium, which may affect heart rhythm, and glucose, which when elevated places the patient at higher risk for morbidity and mortality.
- Serum creatinine level is measured to identify patients who may need dosing adjustments for some pharmacotherapy and patients who are at high risk for morbidity and mortality.
- Baseline complete blood count and coagulation tests (activated partial thromboplastin time and international normalized ratio) should be obtained because most patients will receive antithrombotic therapy, which increases the risk for bleeding.
- Fasting lipid panel is obtained.

## **Other diagnostic tests**

- The 12-lead electrocardiogram is the first step in management. Patients are risk stratified into two groups: ST-segment elevation ACS and suspected non-ST-segment elevation ACS.
- During hospitalization, measurement of left ventricular function, such as an echocardiogram, is performed to identify patients with low ejection fractions (<40%) who are at high risk for death following hospital discharge.
- Selected low-risk patients may undergo early stress testing.

# Cont...

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- Patient symptoms, past medical history, ECG, and troponin or CK-MB determinations are used to stratify patients into
  - low, medium, or high risk of death or MI or
  - likelihood of needing urgent coronary angiography and percutaneous coronary intervention (PCI).

## TIMI Risk Score for Non-ST-Segment Elevation Acute Coronary Syndromes

### Past Medical History

Age  $\geq 65$  years

$\geq 3$  Risk factors for CHD

- Hypercholesterolemia
- HTN
- TM
- Smoking
- Family history of premature CHD

Known CAD (50% stenosis of coronary artery)

Use of aspirin within the past 7 days

Using the TIMI Risk Score

One point is assigned for each of the seven medical history and clinical presentation findings. The score (point) total is calculated, and the patient is assigned a risk for experiencing the composite end point of death, myocardial infarction or urgent need for revascularization as follows:

### High Risk

TIMI risk score 5–7 points

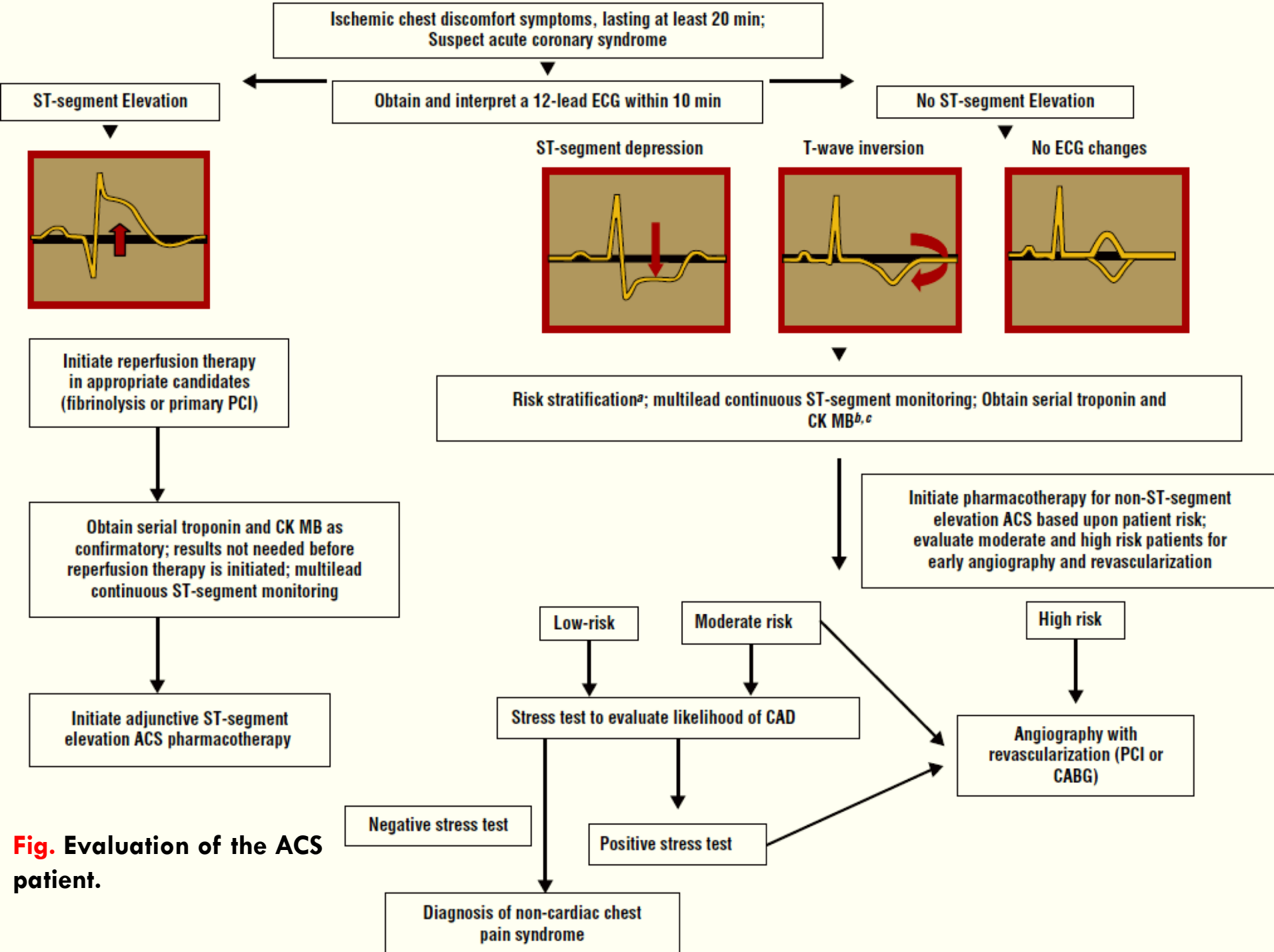
### Medium Risk

TIMI risk score 3–4 points

### Low Risk

TIMI risk score 0–2 points

<sup>a</sup>Troponin I, troponin T, or creatinine kinase MB greater than the MI detection limit.



**Fig. Evaluation of the ACS patient.**

# Desired Outcome

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- **Short-term goals** of therapy include:
  - early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA)
  - prevention of complications and death
  - prevention of coronary artery re-occlusion
  - Relief of ischemic chest discomfort and
  - maintenance of normoglycemia.

# Treatment

## General Approach

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- General treatment measures include
  - hospital admission
  - oxygen administration if saturation is less than 90%
  - continuous multilead ST-segment monitoring for arrhythmias and ischemia
  - glycemic control
  - frequent measurement of vital signs
  - bed rest for 12 hours in hemodynamically stable patients
  - use of stools softeners to avoid Valsalva maneuver and
  - pain relief.



# Cont...

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- **Blood chemistry tests** that should be performed include
  - **K and Mg** (which may affect heart rhythm)
  - **Blood Glucose** (which when elevated places the patient at higher risk for morbidity and mortality)
  - **SCr** (to identify patients who may need drug dosing adjustments)
  - **CBC**
  - **Coagulation tests** (because most patients receive antithrombotic therapy, which increases bleeding risk) and
  - **Fasting lipid panel** (obtained within the first 24 hours of hospitalization)

# Cont...

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- It is important to triage and treat patients according to their risk category
- Patients with **STE ACS** are at **high risk of death**
  - coronary re-perfusion should be initiated immediately (without evaluation of biochemical markers).
- Patients with NSTEMI ACS who are considered to be **at low risk**
  - should have serial biochemical markers obtained.
  - If they are negative, the patient may be
    - admitted to a general medical floor with ECG monitoring,
    - undergo a noninvasive stress test, or
    - may be discharged

# Cont...

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- **High-risk NSTEMI ACS patients**
  - should undergo early coronary angiography (within 24 to 48 hours) and revascularization if a significant coronary artery stenosis is found.
- **Moderate-risk patients with positive biochemical markers**
  - typically undergo angiography and revascularization, if indicated.
- **Moderate-risk patients with negative biochemical markers**
  - may initially undergo a noninvasive stress test, with only those having a positive test proceeding to angiography

# Treatment

## Non-pharmacologic Therapy

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- For patients with **STE ACS**,
  - either fibrinolysis or primary PCI is the treatment of choice for re-establishing coronary artery blood flow when the patient presents within **3 hours of symptom onset**.
  - Primary PCI may be associated with a lower mortality rate than fibrinolysis,
    - possibly because PCI opens more than 90% of coronary arteries compared with less than 60% opened with fibrinolytics.

# Cont...

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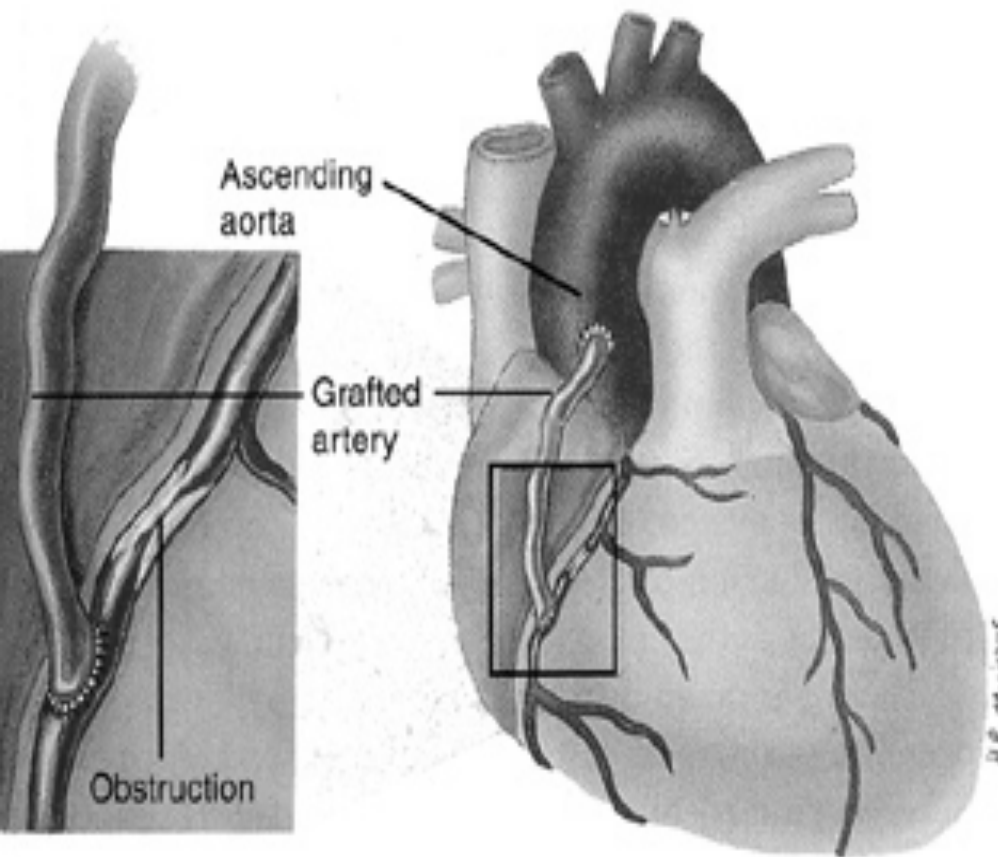
- The risks of intracranial hemorrhage (ICH) and major bleeding are also **lower with PCI** than with fibrinolysis.
- Primary PCI is **generally preferred**
  - if institutions have skilled interventional cardiologists and other necessary facilities
  - in patients with cardiogenic shock
  - in patients with contraindications to fibrinolytics and
  - in patients presenting with symptom onset greater than 3 hours

# Cont...

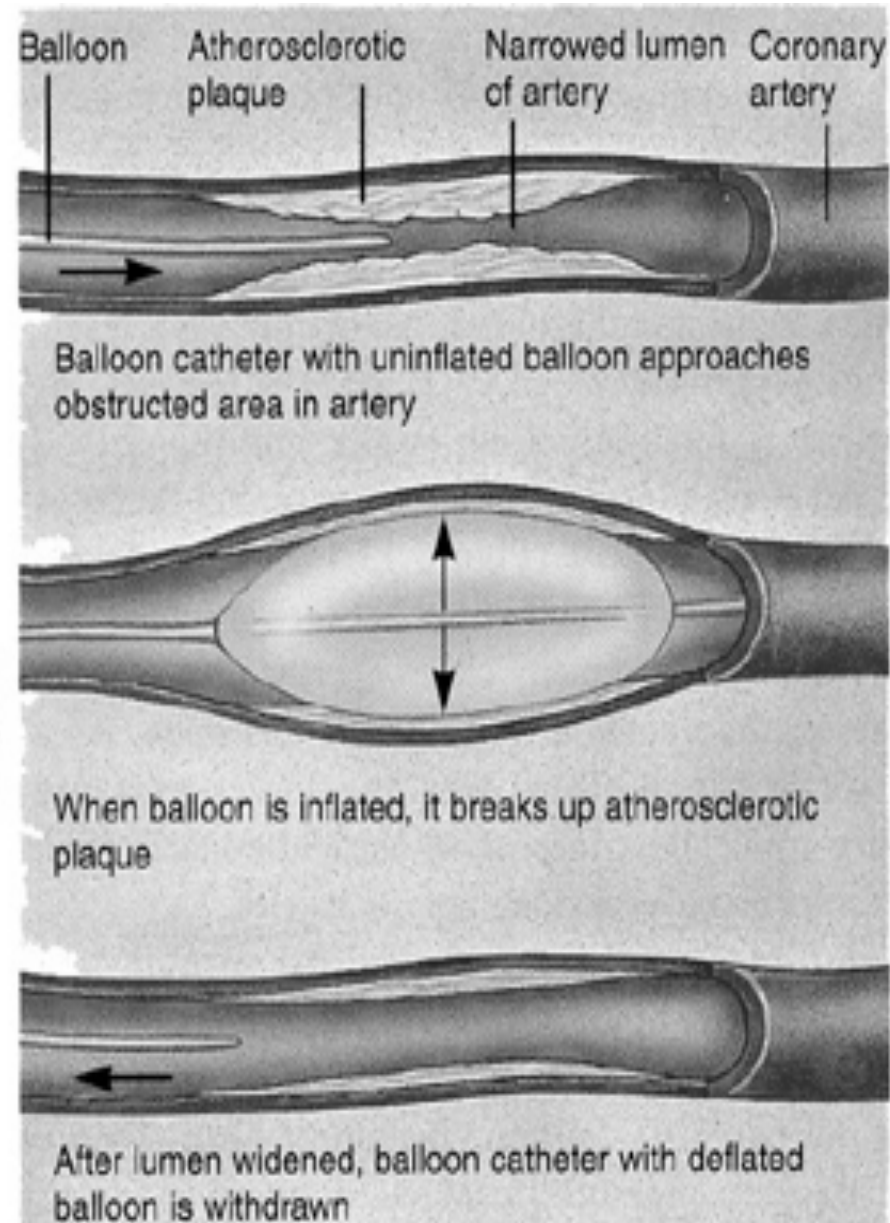
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- In patients with **NSTE ACS**,
  - Either PCI or coronary artery bypass grafting (CABG) revascularization as an early treatment for **high-risk patients**, and
  - such an approach also be considered for **moderate-risk patients**.
  - An early invasive approach results in
    - fewer MIs
    - less need for revascularization procedures over the next year after hospitalization and
    - lower cost than the conservative medical stabilization approach

# PCI and CABG



Coronary artery bypass grafting (CABG)



# Treatment

## Early Pharmacotherapy For STE ACS

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- According to ACC/AHA practice guidelines, early pharmacologic therapy should include:
  - Intranasal oxygen, if  $\text{SaO}_2 < 90\%$
  - Sublingual Nitroglycerin
  - Aspirin
  - $\beta$ -blocker
  - UFH or enoxaparin and
  - Fibrinolysis in eligible candidates



# Cont...

- **Morphine** is administered to patients with refractory angina as an analgesic and venodilator that lowers preload.
- These agents should be **administered early**, while the patient is still in the emergency department.
- An **ACEI** should be started within 24 hours of presentation, particularly in patients with the following conditions if there are no contraindications.
  - LVEF  $\leq 40\%$  (predictor of mortality)
  - Signs of HF or an anterior wall MI
- **IV NTG** and  $\beta$ Bs should be administered to **selected patients** without contraindications.

# Fibrinolytic Therapy

- **A fibrinolytic agent** is indicated
  - in patients with **STE ACS** presenting within 12 hours of the onset of chest discomfort who have **at least**
    - 1 mm of STE in two or more continuous ECG leads or
    - a new left bundle-branch block.
  - It should also be considered in patients with those findings and **persistent symptoms of ischemia** who present within 12 to 24 hours of symptom onset.
  - The mortality benefit of fibrinolysis is highest with early administration and diminishes after 12 hours.
  - It is **not necessary** to obtain the results of biochemical markers before initiating fibrinolytic therapy.

# Cont...

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- **Absolute contraindications** to fibrinolytic therapy include: (Primary PCI is preferred in these situations)
  - previous ICH (hemorrhagic stroke) at any time
  - ischemic stroke within 3 months
  - active internal bleeding
  - known intracranial neoplasm
  - known structural vascular lesion
  - suspected aortic dissection and
  - significant closed head or facial trauma within 3 months

# Cont...

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- Patients with **relative contraindications** to fibrinolytics include: (may receive therapy if the perceived risk of death from MI is higher than the risk of major hemorrhage)
  - Severe, uncontrolled hypertension (BP > 180/110)
  - History of prior ischemic stroke longer than 3 months prior, dementia or known intracranial pathology not considered an absolute contraindication
  - Current anticoagulant use

# Cont...

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- known bleeding diathesis
- traumatic or prolonged cardiopulmonary resuscitation or major surgery within 3 weeks
- non-compressible vascular puncture
- recent (within 2 to 4 weeks) internal bleeding
- Pregnancy
- active peptic ulcer
- history of severe, chronic poorly controlled hypertension &
- for streptokinase, prior administration ( $>5$  days) or prior allergic reactions.

## Indications and Contraindications to Fibrinolytic Therapy According to ACC/AHA Guidelines for Management of Patients with ST-Segment Elevation Myocardial Infarction

### Indications

1. Ischemic chest discomfort at least 20 minutes in duration but  $\leq 12$  hours since symptom onset and ST-segment elevation of at least 1 mm in height in  $\leq 2$  contiguous leads or New or presumed new left bundle-branch block
2. Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset and ST-segment elevation of at least 1 mm in height in  $\geq 2$  contiguous leads

### Absolute contraindications

Active internal bleeding (not including menses)  
Previous intracranial hemorrhage at any time; ischemic stroke within 3 months  
Known intracranial neoplasm  
Known structural vascular lesion (e.g., arteriovenous malformation)  
Suspected aortic dissection  
Significant closed head or facial trauma within 3 months

### Relative contraindications

Severe, uncontrolled hypertension on presentation (blood pressure  $>180/110$  mm Hg)  
History of prior ischemic stroke  $>3$  months, dementia, or known intracranial pathology not covered above under absolute contraindications  
Current use of anticoagulants  
Known bleeding diathesis  
Traumatic or prolonged ( $>10$  minutes) CPR or major surgery ( $<3$  weeks)  
Noncompressible vascular puncture (e.g., a recent liver biopsy or carotid artery puncture)  
Recent (within 2–4 weeks) internal bleeding  
For streptokinase administration, previous streptokinase use ( $>5$  days) or prior allergic reactions  
Pregnancy  
Active peptic ulcer  
History of severe, chronic poorly controlled hypertension

# Cont...

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- Practice guidelines indicate that a more fibrin-specific agent (**alteplase, reteplase, tenecteplase**) is preferred over the non–fibrin-specific agent streptokinase.
- Fibrin-specific agents **open** a greater percentage of infarct arteries, which results in **smaller infarcts** and **lower mortality** (*open artery hypothesis*)
- Eligible patients should be treated as soon as possible, but preferably **within 30 minutes** from the time they present to the ED, with one of the following regimens:

# Cont...

- **Alteplase:** *Bolus followed by 90 minutes of infusion, weight based dosing*
  - 15 mg IV bolus followed by
  - 0.75 mg/kg infusion (max 50 mg) over 30 min, followed by
  - 0.5 mg/kg infusion (max 35 mg) over 60 min
  - overall max dose is **100 mg**
- **Reteplase:** *Two bolus doses 30 minutes apart*
  - 10 units IV over 2 minutes
  - followed 30 minutes later with another 10 units IV over 2 minutes.



# Cont...

- **Tenecteplase:** *Single IV bolus dose given over 5 seconds based on patient weight:*
  - 30 mg if <60 kg
  - 35 mg if 60-69.9 kg
  - 40 mg if 70-79.9 kg
  - 45 mg if 80-89.9 kg
  - 50 mg if  $\geq 90$  kg
- **Streptokinase:** *One dose over 60 minutes infusion*
  - 1.5 million units in 50 mL of normal saline or 5% dextrose in water IV over 60 minutes.

# Cont...

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- **ICH and major bleeding**
  - ICH and major bleeding are the most serious side effects.
  - The risk of ICH is higher with fibrin-specific agents than with streptokinase.
  - However, the risk of systemic bleeding other than ICH is higher with streptokinase than with fibrin-specific agents.

# Cont...

## Comparison Between Fibrinolytic Agents

Agent	Fibrin Specificity	TIMI-3 Blood Flow Complete Perfusion at 90 Minutes	Systemic Bleeding Risk/ ICH Risk	Administration
Streptokinase (Streptase)	+	35%	+++ / +	Infusion over 60 minutes
Alteplase (rt-PA) (Activase)	+++	50%–60%	++ / ++	Bolus followed by infusions over 90 minutes, weight-based dosing
Reteplase (rPA) (Retavase)	++	50%–60%	++ / ++	Two bolus doses, 30 minutes apart
Tenecteplase (TNK-tPA) (TNKase)	++++	50%–60%	+ / ++	Single bolus dose, weight-based dosing

# Aspirin

- Aspirin should be administered to all patients without contraindications **within the first 24 hours of hospital admission.**
- It provides an **additional mortality benefit** in patients with STE ACS when given with fibrinolytic therapy.
- In patients experiencing an ACS,
  - non-enteric-coated aspirin, **162 to 325 mg** should be chewed and swallowed as soon as possible after the onset of symptoms or immediately after presentation to the ED regardless of the reperfusion strategy being considered.

# Cont...

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- A daily maintenance dose of **75 -162 mg** is recommended thereafter and **should be continued indefinitely.**
- For patients undergoing PCI and receiving stents, the recommended dose is **325 mg** once daily
  - for at least **30 days** with bare metal stents
  - for **3 months** with a sirolimus-eluting stent
  - for **6 months** with a paclitaxel-eluting stent

followed by  
**75 -162 mg**  
od dosing  
thereafter.

# Cont...

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- **Low-dose aspirin** is associated with a reduced risk of major bleeding, particularly GI bleeding.
- Other GI disturbances (e.g., dyspepsia, nausea) are infrequent with low-dose aspirin.
- Ibuprofen should **not** be administered on a regular basis concurrently with aspirin
  - because it may block aspirin's antiplatelet effects.

# Thienopyridines

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- **Clopidogrel**

- is recommended for patients with an aspirin allergy.
- A 300- 600 mg loading dose is given on the first hospital day, followed by a maintenance dose of 75 mg daily.
- It should be continued indefinitely.
- For patients treated with fibrinolytics and in those receiving no revascularization therapy, clopidogrel either 75 mg or 300 mg on day 1 followed by 75 mg once daily should be given for at **least 14 to 28 days in addition to aspirin.**

# Cont...

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- For patients undergoing primary PCI, clopidogrel is administered as a 300-to 600-mg loading dose followed by a 75 mg/day maintenance dose, in combination with aspirin 325 mg once daily, to prevent sub-acute stent thrombosis and long-term CV events.
- The most frequent side effects of clopidogrel are **nausea, vomiting, and diarrhea** (5% of patients).
- Thrombotic thrombocytopenia purpura (**TTP**) has been reported rarely.
- The most serious side effect of clopidogrel is **hemorrhage**.



# Cont...

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- **Ticlopidine**

- is associated with **neutropenia** that requires frequent monitoring of the CBC during the first 3 months of use.
- For this reason, clopidogrel is the preferred thienopyridine for ACS and PCI patients

# Glycoprotein IIb/IIIa Receptor Inhibitors

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- **Abciximab**

- is a first-line GP IIb/IIIa inhibitor for patients undergoing primary PCI who have not received fibrinolytics.
- It should not be administered to STE ACS patients who will not be undergoing PCI.
- Abciximab is preferred over **eptifibatide** and **tirofiban** in this setting because it is the most widely studied agent in primary PCI trials.

# Cont...

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- Abciximab, in combination with aspirin, a thienopyridine, and UFH (administered as an infusion for the duration of the procedure),
  - reduces mortality and re-infarction without increasing the risk of major bleeding.
- The dose of abciximab is
  - 0.25 mg/kg IV bolus given 10 to 60 minutes before the start of PCI, followed by
  - 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hours.

# Cont...

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- GP IIb/IIIa inhibitors may increase the risk of **bleeding**, especially if given in the setting of recent (<4 hours) administration of fibrinolytic therapy.
- An immune-mediated **thrombocytopenia** occurs in about 5% of patients

# Anticoagulants

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- **UFH**

- is a first-line anticoagulant for STE ACS, both for medical therapy and PCI.
- UFH should be initiated in the emergency department and continued for **at least 48 hours** in patients who will receive chronic warfarin after acute MI.
- If a patient undergoes PCI, **UFH is discontinued immediately after the procedure**

# Cont...

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- If a fibrinolytic agent is administered, UFH is given concomitantly with alteplase, reteplase, and tenecteplase,
  - but UFH is not administered with streptokinase because no benefit of combined therapy has been demonstrated.
- Rates of re-infarction are higher if UFH is not given with the fibrin-selective agents.
- For STE ACS, the dose of UFH is
  - 60 units/kg IV bolus (maximum 4,000 units) followed by
  - a continuous IV infusion of 12 units/kg/hour (max 1,000 units/hour)

# Cont...

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- The dose is titrated to maintain the activated partial thromboplastin time (aPTT) between **50-70 seconds**.
- The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with fibrinolytics and at 4 to 6 hours in patients not receiving thrombolytics.

# Cont...

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- Besides **bleeding**, the most frequent adverse effect of UFH is immune-mediated **thrombocytopenia**, which occurs in up to 5% of patients.
- LMWHs may be an alternative to UFH in STE ACS.
- Enoxaparin may produce a modest benefit over UFH in reducing the risk of death or nonfatal MI.
- Enoxaparin has not been studied in the setting of primary PCI.



# Nitrates

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- Immediately upon presentation,
  - one SL NTG tablet should be administered every 5 minutes for up to **three doses** to relieve chest pain and myocardial ischemia.
- Intravenous NTG should be initiated in all patients with an ACS
  - who do not have a contraindication **and** who have **persistent ischemic symptoms, heart failure, or uncontrolled high BP.**

# Cont...

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- The **usual dose** is
  - 5 to 10 mcg/min by continuous infusion, titrated up to 200 mcg/min
  - Given until relief of symptoms or limiting side effects (e.g., headache or hypotension).
  - Treatment should be continued for approximately **24 hours** after ischemia is relieved.

# Cont...

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- **NTG works**

- causes venodilation, which lowers preload and myocardial oxygen demand.
- In addition, arterial vasodilation may lower BP, thereby reducing myocardial oxygen demand.
- Arterial dilation also relieves coronary artery vasospasm and improves myocardial blood flow and oxygenation.

- Oral nitrates play a **limited role** in ACS

- because clinical trials have failed to show a mortality benefit for IV followed by oral nitrate therapy in acute MI.

# Cont...

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- The most significant adverse effects of nitrates are
  - Tachycardia
  - Flushing
  - Headache and
  - hypotension
- Nitrates are contraindicated in patients
  - who have taken the oral phosphodiesterase-5 inhibitors
    - **sildenafil** or **vardenafil** within the prior 24 hours or
    - **tadalafil** within the prior 48 hours.

# $\beta$ -Adrenergic Blockers

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- If there are no contraindications, a BB should be administered **early** in the care of patients with STE ACS
  - **within the first 24 hours** and continued **indefinitely**.
- The benefits result from blockade of  $\beta_1$  receptors in the myocardium,
  - which reduces heart rate, myocardial contractility, and BP, thereby **decreasing myocardial oxygen demand**.
  - The reduced heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.

# Cont...

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- Because of these effects,  $\beta$ -blockers reduce
  - the risk for recurrent ischemia
  - infarct size
  - risk of re-infarction and
  - occurrence of ventricular arrhythmias.
- The usual doses of  $\beta$ -blockers are as follows:

# Cont...

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- **Metoprolol:**

- 5 mg by slow (over 1 to 2 minutes) IV bolus, repeated every 5 minutes for a total initial dose of 15 mg.
  - If a conservative regimen is desired, initial doses can be reduced to 1 to 2 mg.
- This is followed in 15 to 30 minutes by 25 to 50 mg orally every 6 hours.
- If appropriate, initial IV therapy may be omitted.

# Cont...

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- **Propranolol:**

- 0.5 to 1 mg slow IV push, followed in 1 to 2 hours by 40 to 80 mg orally every 6 to 8 hours.
- If appropriate, the initial IV therapy may be omitted

- **Atenolol:**

- 5 mg IV dose, followed 5 minutes later by a second 5-mg IV dose;
- then 50 to 100 mg orally every day beginning 1 to 2 hours after the IV dose.
- The initial IV therapy may be omitted.



# Cont...

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- **Esmolol:**

- Starting maintenance dose of 0.1 mg/kg/min IV, with titration in increments of 0.05 mg/kg/min every 10 to 15 minutes as tolerated by BP
- Given until the desired therapeutic response is obtained, limiting symptoms develop, or a dose of 0.2 mg/kg/min is reached.
- An optional loading dose of 0.5 mg/kg may be given by slow IV administration (2 to 5 minutes) for more rapid onset of action.
- Alternatively, the initial IV therapy may be omitted.

# Cont...

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- The most serious side effects early in ACS are **hypotension, bradycardia, and heart block.**
- Initial acute administration of  $\beta$ -blockers is not appropriate for patients presenting with **DHF**
- However, therapy may be attempted in most patients before hospital discharge after treatment of acute heart failure.

# Calcium Channel Blockers

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- In the setting of STE ACS, CCBs are reserved for patients who have contraindications to BBs.
- They are used for **relief of ischemic symptoms only.**
- Patients who had been prescribed CCBs for hypertension who are not receiving BBs and who do not have a contraindication
  - should have the CCBs discontinued and a BB initiated.

# Cont...

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- Dihydropyridine channel blockers (e.g., nifedipine) have **little benefit** on clinical outcomes beyond symptom relief.
- The role of verapamil and diltiazem appears to be limited to symptom relief or control of heart rate
  - in patients with supraventricular arrhythmias in whom  $\beta$ -blockers are contraindicated or ineffective.

# Cont...

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- Patients with **variant (Prinzmetal's) angina** or **cocaine-induced ACS**
  - may benefit from CCBs as initial therapy because they can **reverse coronary vasospasm**.
  - BBs generally should be **avoided** in these situations because they may worsen vasospasm through an unopposed  $\beta$ 2-blocking effect on smooth muscle

ST-segment elevation ACS

Oxygen (if  $O_2$  saturation  $<90\%$ )  
SL NTG, aspirin, clopidogrel,  
IV NTG

**Fig: Initial  
pharmacotherapy  
for STE-ACS**

Symptoms  $\leq 12$  hours

Symptoms  $> 12$  hours

Reperfusion therapy

Primary PCI

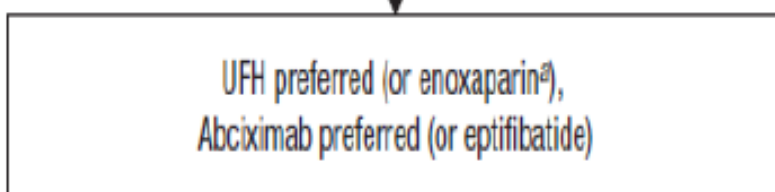
Fibrinolysis

UFH preferred (or enoxaparin<sup>a</sup>),  
Abciximab preferred (or eptifibatide)

IV UFH or IV and SC enoxaparin (for  
selected patients)

PCI or CABG or fibrinolysis for selected  
patients; for PCI during hospitalization,  
administer abciximab or eptifibatide at  
time of PCI and clopidogrel

$\beta$ -blocker (oral or IV), statin, ACE inhibitor (or ARB), eplerenone (or spironolactone)



# Treatment

## Early Pharmacotherapy For NSTEMI-ACS

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- Early pharmacotherapy for NSTEMI ACS is similar to that for STE ACS **except**:
  - fibrinolytic therapy is **not administered**
  - GP IIb/IIIa receptor blockers are administered to **high-risk patients** and
  - there are **no standard quality performance measures** for patients with NSTEMI ACS with UA.

# Cont...

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- According to **ACC/AHA practice guidelines**, early pharmacotherapy should include:
  - intranasal oxygen, if  $\text{SaO}_2$  is  $<90\%$
  - SL NTG (IV therapy for selected patients)
  - aspirin
  - an oral  $\beta$  –blocker (IV therapy optional) and
  - an anticoagulant (UFH, LMWH [enoxaparin], fondaparinux or bivalirudin).
  - Morphine (administered to patients with refractory angina)
- **These agents should be administered early, while the patient is still in the ED.**



# Fibrinolytic Therapy

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- Fibrinolytics are **not indicated** in any patient with NSTEMI ACS,
  - even those who have positive biochemical markers that indicate infarction.
  - The risk of death from MI is lower in these patients, and the hemorrhagic risks of fibrinolytic therapy outweigh the benefit.

# Aspirin

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- Aspirin reduces the risk of death or developing MI by about **50%** compared with no antiplatelet therapy in patients with NSTEMI ACS.
- Dosing of aspirin is the **same** as for STE ACS, and aspirin is continued indefinitely.

# Thienopyridines

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- **Clopidogrel**

- The addition of clopidogrel started on the first day of hospitalization as a 300- to 600-mg loading dose followed the next day by 75 mg/day orally is recommended for most patients.
- Although aspirin is the mainstay of anti-platelet therapy in ACS, **addition of clopidogrel may further reduce morbidity and mortality.**

# Cont...

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- current guidelines for patients with NSTEMI ACS recommend that clopidogrel be administered for at least
  - 12 months for patients undergoing PCI with placement of either a bare-metal or drug-eluting stent and
  - up to 15 months for patients with a drug-eluting stent, where the risk of thrombotic occlusion may be greater.
- For medical therapy of NSTEMI ACS, clopidogrel should be administered for up to 12 months for patients not at high risk of bleeding

# Cont...

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- Because of the potential increased risk for bleeding with combination antiplatelet therapy,
  - a low dose of aspirin (75 to 100 mg/day) is recommended for maintenance therapy with clopidogrel.
- In patients undergoing CABG,
  - Clopidogrel, but not aspirin, should be withheld at least 5 days and **preferably 7 days** before the procedure

# Glycoprotein IIb/IIIa Receptor Inhibitors

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- Administration of tirofiban or eptifibatide is recommended for **high-risk** NSTEMI ACS patients
  - as medical therapy without planned revascularization.
- Administration of either abciximab or eptifibatide (alternatively tirofiban) is recommended
  - for NSTEMI ACS patients undergoing PCI.
- Tirofiban and eptifibatide are also indicated
  - in patients with continued or recurrent ischemia despite treatment with aspirin, clopidogrel and an anticoagulant.

# Anticoagulants

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- For patients with NSTEMI ACS undergoing planned early angiography and revascularization with PCI,
  - UFH, LMWH (enoxaparin), fondaparinux or bivalirudin should be administered.
  - Therapy should be continued
    - for up to 48 hours for UFH
    - until the patient is discharged (a maximum of 8 days) for either enoxaparin or fondaparinux and
    - until the end of the PCI or angiography procedure (or up to 42 hours after PCI) for bivalirudin.

# Cont...

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- In patients initiating **warfarin** therapy,
  - **UFH** or LMWHs should be continued until the INR with warfarin is in the therapeutic range.
  - For NSTEMI ACS, the dose of UFH is 60 to 70 units/kg IV bolus (maximum 5,000 units) followed by a continuous IV infusion of 12 to 15 units/kg/hour (maximum 1,000 units/hour).
  - The dose is titrated to maintain the aPTT between 1.5 and 2.5 times control.



# Cont...

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- LMWHs are administered by a fixed, weight-based dose:
- **Enoxaparin:**
  - 1 mg/kg Sc every 12 hours
  - extend the interval to 24 hours if creatinine clearance is less than 30 mL/min
- **Dalteparin:**
  - 120 units/kg Sc every 12 hours (maximum single bolus dose of 10,000 units)

# Nitrates

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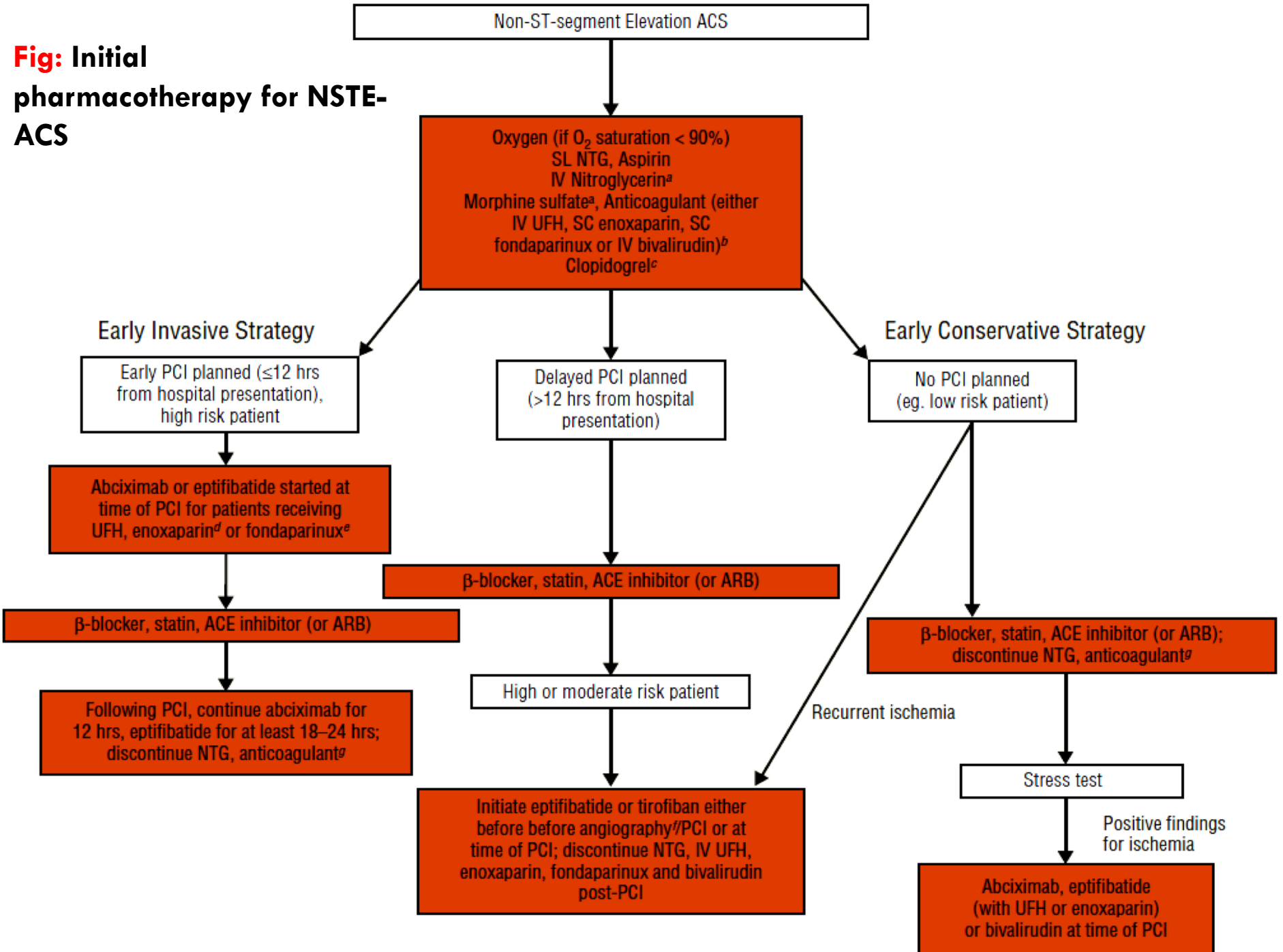
- In the absence of contraindications,
  - SL followed by IV NTG should be administered to all patients with NSTEMI ACS.
  - IV NTG is continued for approximately 24 hours after ischemia relief.

# β-Blockers

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- In the absence of contraindications, oral β-blockers should be administered to all patients with NSTEMI ACS.
- IV β-blockers should be considered in
  - hemodynamically stable patients who present with persistent ischemia, hypertension or tachycardia.
- The drugs are continued **indefinitely**.
- **CCBs** should not be administered to most patients with ACS.

**Fig: Initial pharmacotherapy for NSTEMI-ACS**



# Secondary Prevention After Myocardial Infarction

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## Desired Outcome

- The long-term goals after MI are to:
  - control modifiable CHD risk factors
  - prevent development of SHF
  - prevent recurrent MI and stroke
  - prevent death, including sudden cardiac death

# Pharmacotherapy

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- **General Approach**

- Pharmacotherapy that has been proven to decrease mortality, heart failure, re-infarction or stroke should be started before hospital discharge for secondary prevention.
- The ACC/AHA guidelines suggest that after MI from either STE or NSTEMI ACS,
  - patients should receive **indefinite treatment** with **aspirin, BB** and **ACEI**

# Cont...

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- All patients should receive SL NTG or lingual spray and instructions for use in case of recurrent ischemic chest discomfort.
- Clopidogrel should be considered for most patients, but the duration of therapy is individualized according to the type of ACS and whether the patient is treated medically or undergoes stent implantation.

# Cont...

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- All patients should receive annual influenza vaccination .
- Selected patients also should be treated with long-term warfarin anticoagulation.
- For all ACS patients, treatment and control of modifiable risk factors such as hypertension, dyslipidemia, and diabetes mellitus are essential.



# Aspirin

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- Aspirin decreases the risk of death, recurrent MI, and stroke after MI.
- All patients should receive aspirin indefinitely (or clopidogrel if there are aspirin contraindications).
- The risk of major bleeding from chronic aspirin therapy is approximately 2% and is dose related.
- Therefore, after an initial dose of 325 mg, chronic low doses of 75 to 81 mg are recommended unless a stent is placed.

# Thienopyridines

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- For patients with NSTEMI ACS, clopidogrel decreases the risk of death, MI, or stroke.
- Most patients with NSTEMI ACS should receive clopidogrel, in addition to aspirin, for up to 12 months.
- For patients with STEMI treated medically without revascularization, clopidogrel can be given for 14 to 28 days.
- If a stent has been implanted, clopidogrel can be continued for up to 12 months in patients at low risk for bleeding.

# Anticoagulation

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- **Warfarin** should be considered in selected patients after an ACS, including those with
  - an LV thrombus
  - extensive ventricular wall motion abnormalities on cardiac echocardiogram and
  - a history of thromboembolic disease or chronic atrial fibrillation.

# Beta Blockers and Calcium Channel Blockers

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- After an ACS, patients should receive a  $\beta$ -blocker indefinitely, regardless of whether they have residual symptoms of angina.
- Therapy should continue indefinitely in the absence of contraindications or intolerance.
- A CCB can be used to prevent anginal symptoms in patients
  - who cannot tolerate or have a contraindication to a  $\beta$ -blocker but should not be used routinely in the absence of such symptoms

# Nitrates

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- All patients should be prescribed a short-acting SL NTG or lingual NTG spray to relieve anginal symptoms **when necessary**.
- Chronic long-acting nitrates have not been shown to reduce CHD event after MI.
  - Therefore, chronic long-acting oral nitrates are not used in ACS patients who have undergone revascularization unless the patient has chronic stable angina or significant coronary stenosis that was not revascularized.

# ACEIs and ARBs

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- ACEIs should be initiated in all patients after MI to reduce
  - Mortality
  - decrease re-infarction and
  - prevent the development of heart failure
- Data suggest that most patients with CAD benefit from an ACEI
- The dose should be low initially and titrated to the dose used in clinical trials if tolerated

# Cont...

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- Example doses include the following:
  - **Captopril:** 6.25 to 12.5 mg initially; target dose 50 mg two or three times daily.
  - **Enalapril:** 2.5 to 5 mg initially; target dose 10 mg twice daily.
  - **Lisinopril:** 2.5 to 5 mg initially; target dose 10 to 20 mg once daily.
  - **Ramipril:** 1.25 to 2.5 mg initially; target dose 5 mg twice daily or 10 mg once daily.
  - **Trandolapril:** 1 mg initially; target dose 4 mg once daily.

# Cont...

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- ARB may be prescribed for
  - patients with ACEI cough and a low LVEF and heart failure after MI.
- Example doses include the following:
  - **Candesartan**: 4 to 8 mg initially; target dose 32 mg once daily.
  - **Valsartan**: 40 mg initially; target dose 160 mg twice daily.



# Aldosterone Antagonists

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- Either eplerenone or spironolactone, should be considered within the first 2 weeks following MI
  - in all patients already receiving an ACE inhibitor who experienced HF symptoms during hospitalization for MI and have an LVEF of 40% or less to reduce mortality
  - The drugs are continued indefinitely.

# Cont...

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- Example oral doses include the following:
  - **Eplerenone:** 25 mg initially; target dose 50 mg once daily.
  - **Spironolactone:** 12.5 mg initially; target dose 25 to 50 mg once daily.

# Lipid-Lowering Agents

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- There are now overwhelming data supporting the benefits of statins for patients with CAD in the **prevention of total mortality, cardiovascular mortality, and stroke**
- All patients with CAD should receive **dietary counseling AND pharmacotherapy** in order to reach LDL cholesterol <100 mg/dL.
- Newer recommendations from the National Cholesterol Education Program give an optional LDL goal of <70 mg/dL in selected patients.

# Cont...

- **Statins**

- are the preferred agents for **lowering LDL cholesterol** and should be prescribed at or near discharge in most patients.
- Atorvastatin
  - Starting Dose: 80 mg orally once daily
  - Maintenance Dose: 10–80 mg orally once daily
- Rosuvastatin
  - Starting Dose: 20 mg orally once daily
  - Maintenance Dose: 5–40 mg once daily

- **A fibrate derivative or niacin**

- should be considered in selected patients with a low HDL cholesterol (<40 mg/dL) and/or a high triglyceride level (>200 mg/dL).

# Fish Oils

## (Marine-Derived Omega-3 Fatty Acids)

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- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
  - are omega-3 polyunsaturated fatty acids that are most abundant in fatty fish such as sardines, salmon, and mackerel.
- A diet high in EPA plus DHA or supplementation with these fish oils reduces
  - the risk of cardiovascular mortality
  - re-infarction and
  - stroke in patients who have experienced an MI.

# Cont...

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- The AHA recommends that CHD patients consume approximately **1 g EPA plus DHA per day**, preferably from oily fish.
- Because of variable fish oil content, one would need to consume from four to more than 14 6-oz servings of fish per week to provide 7 g of the fish oils.
- Because the average diet provides only 10% to 20% of that amount, supplements may be considered in selected patients.

# Cont...

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- Approximately three 1-g fish oil capsules per day should be consumed to provide 1 g of EPA/DHA, depending on the brand.
- Alternatively, the prescription drug **LOVAZA** (omega-3-acid ethyl esters) can be used at a dose of 1 g/day.
- **Higher doses** of EPA/DHA (2 to 4 g/day) may be considered for managing **hypertriglyceridemia**.
- Adverse effects of fish oils include **fishy after-taste**, **nausea** and **diarrhea**.

# Evaluation Of Therapeutic Outcomes

- Monitoring parameters for efficacy of therapy for both STE and NSTEMI ACS include:
  - relief of ischemic discomfort
  - return of ECG changes to baseline
  - absence or resolution of heart failure signs.
- Monitoring parameters for adverse effects are dependent upon the individual drugs used.
- In general, the most common adverse reactions from ACS therapies are **hypotension** and **bleeding**.



Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding, gastrointestinal upset; baseline CBC and platelet count; CBC platelet count every 6 months
Clopidogrel	Bleeding, TTP (rare), diarrhea, rash	Clinical signs of bleeding ; baseline CBC and platelet count; CBC and platelet count every 6 months following hospital discharge
Unfractionated heparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleedinga ; baseline CBC, platelet count, aPTT and INR; aPTT every 6 hours until target then every 24 hours; daily CBC; platelet count every 2 days (minimum, preferably every day)
Low-molecular-weight heparins (enoxaparin and dalteparin)	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding; baseline CBC, platelet count, SCr, aPTT and INR; daily CBC, platelet count every 2–3 days (minimum, preferably every day); SCr daily
Fondaparinux	Bleeding	Clinical signs of bleeding, baseline CBC, platelet count, INR, SCr, and aPTT; daily CBC and SCr
Bivalirudin	Bleeding	Clinical signs of bleeding baseline CBC, platelet count, INR, SCr, and aPTT; daily CBC and SCr

Drug	Adverse Effects	Monitoring
Fibrinolytics	Bleeding, especially intracranial hemorrhage	Clinical signs of bleeding, baseline CBC, platelet count, INR, and aPTT; mental status every 2 hours for signs of intracranial hemorrhage; daily CBC
Glycoprotein IIb/IIIa receptor blockers	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding, baseline CBC and platelet count; daily CBC; platelet count at 4 hours after initiation then daily
Intravenous nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
$\beta$ -Blockers	Hypotension, bradycardia, heart block, bronchospasm, heart failure, fatigue, depression, sexual dysfunction, nightmares, masking hypoglycemia symptoms in diabetic patients	BP, RR, HR, 12-lead ECG, and clinical signs of heart failure every 5 minutes during bolus intravenous dosing; BP, RR, HR, and clinical signs of heart failure every shift during oral administration during hospitalization, then BP and HR every 6 months following hospital discharge
Diltiazem or verapamil	Hypotension, bradycardia, heart block, heart failure, gingival hyperplasia, constipation	BP and HR and signs of clinical heart failure every shift during oral administration during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
Amlodipine	Hypotension, dependent peripheral edema, gingival hyperplasia	BP every shift during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months

Drug	Adverse Effects	Monitoring
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, angioedema (ACE inhibitors >ARBs)	BP every 2 hours x 3 for first dose, then shift during oral administration during hospitalization, then once every 6 months following hospital discharge; baseline SCr and potassium; daily SCr and potassium while hospitalized, then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in selected patients (e.g., those taking spironolactone or eplerenone or with renal insufficiency); counsel patient on throat, tongue, and facial swelling
Aldosterone antagonists	Hypotension, hyperkalemia, prerenal azotemia	BP and HR every shift during oral administration during hospitalization, then once every 6 months; baseline SCr and serum potassium concentration; SCr and potassium at 48 hours, monthly for 3 months then every 3 months thereafter
Statins	Myalgia, myopathy, elevated LFTs, rhabdomyolysis, teratogenic in first trimester	Baseline LFTs, then repeat LFTs at 6 weeks and when patient titrated to target maintenance dose; if LFTs >3 times upper limit of normal, decrease dose or discontinue; if myalgia and/or brown urine, monitor creatine kinase for rhabdomyolysis
Morphine sulfate	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose

# Conclusions

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- The AHA and ACC published evidence-based practice guidelines for the treatment of patients with STE and NSTEMI ACS. (2013/14 guidelines available with me, can take if interested! )
- Mainstays of therapy include risk stratification, primary PCI for STE MI, early angiography & revascularization with either PCI or CABG for patients with NSTEMI ACS at high risk of MI and death.
- Pharmacotherapy for acute treatment includes sublingual NTG, anti-platelets and anticoagulants.

# Cont...

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- Routine pharmacotherapy for secondary prevention of recurrent ACS, MI and CHD death includes: aspirin, a thienopyridine, statin, Beta-blocker and either an ACE inhibitor or an ARB.
- Ensuring selection of evidence-based therapies for all patients without contraindications results in lower mortality.
- Encouraging adherence and persistence of pharmacotherapy is also important role for pharmacists.

# Case Study #1

A 65-year-old man presents to the ED of a hospital with no interventional cardiology services with STE MI 2 hours after the onset of symptoms. He has a history of HTN 10 years and hemorrhagic stroke 10 years ago. His current BP is 105/55 mm Hg and his HR is 98 beats/minute. He has no signs and symptoms of acute HF. He received aspirin 325 mg orally and was started on an IV NTG infusion.

What additional pharmacotherapy should be administered in the emergency department to prevent death, stroke, or re-infarction?

- A. Unfractionated heparin, clopidogrel
- B. Reteplase, bivalirudin and metoprolol
- C. Prasugrel, enoxaparin, and metoprolol
- D. Enoxaparin and abciximab

# Case Study #2

A 65-year-old man presents to the ED of a hospital with no interventional cardiology services 6 hours with NSTEMI 6 hours since the onset of chest discomfort. His current BP is 130/80 mm Hg and his HR is 88 beats/minute. On physical examination he has rales and an S3. His 12-lead ECG shows ST-segment depression and his troponin is elevated.

In addition to aspirin and IV NGT, what additional pharmacotherapy should be administered at this time to treat symptoms, and prevent death, stroke, and re-infarction?

- A. Clopidogrel, fondaparinux, metoprolol, furosemide
- B. Prasugrel, enoxaparin, furosemide, enalapril
- C. Reteplase, unfractionated heparin, metoprolol, enalapril
- D. Alteplase, bivalirudin, furosemide, captopril

# Case Study #3

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Which of the following characteristics describes a patient with ACS patient who is at the highest risk of immediate death?

- A. ST-segment elevation and heart failure symptoms
- B. ST-segment depression and heart failure symptoms
- C. T-wave inversion and positive troponin
- D. ST-segment depression and positive troponin



