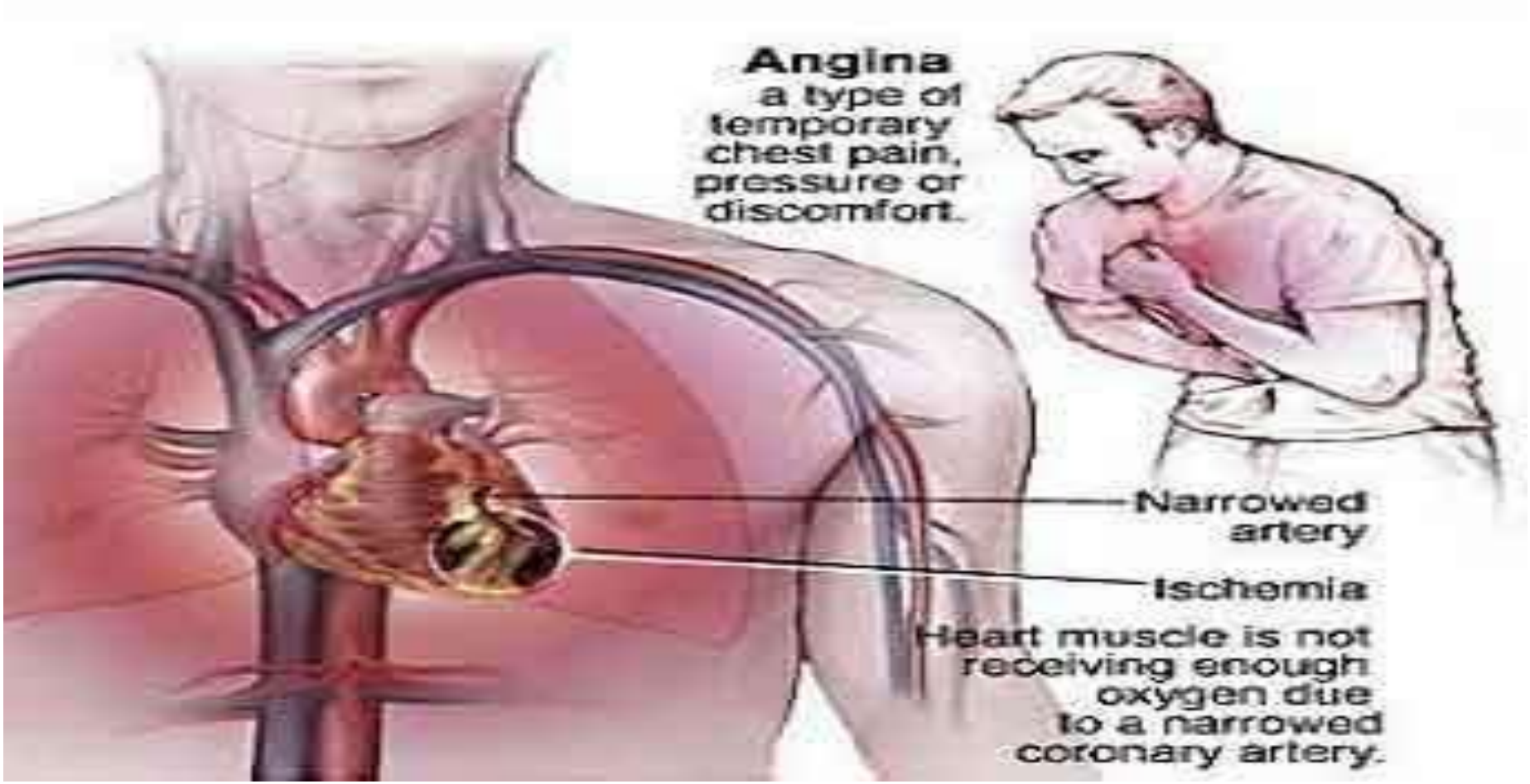
Ischemic Heart Disease



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Terminology/Definition

- **Ischemic heart disease (IHD)**, also known as **coronary artery disease (CAD)**, is defined as: **a lack of oxygen "ischemia" and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction**

- **Common clinical manifestations of IHD are stable angina and acute coronary syndrome**

Epidemiology

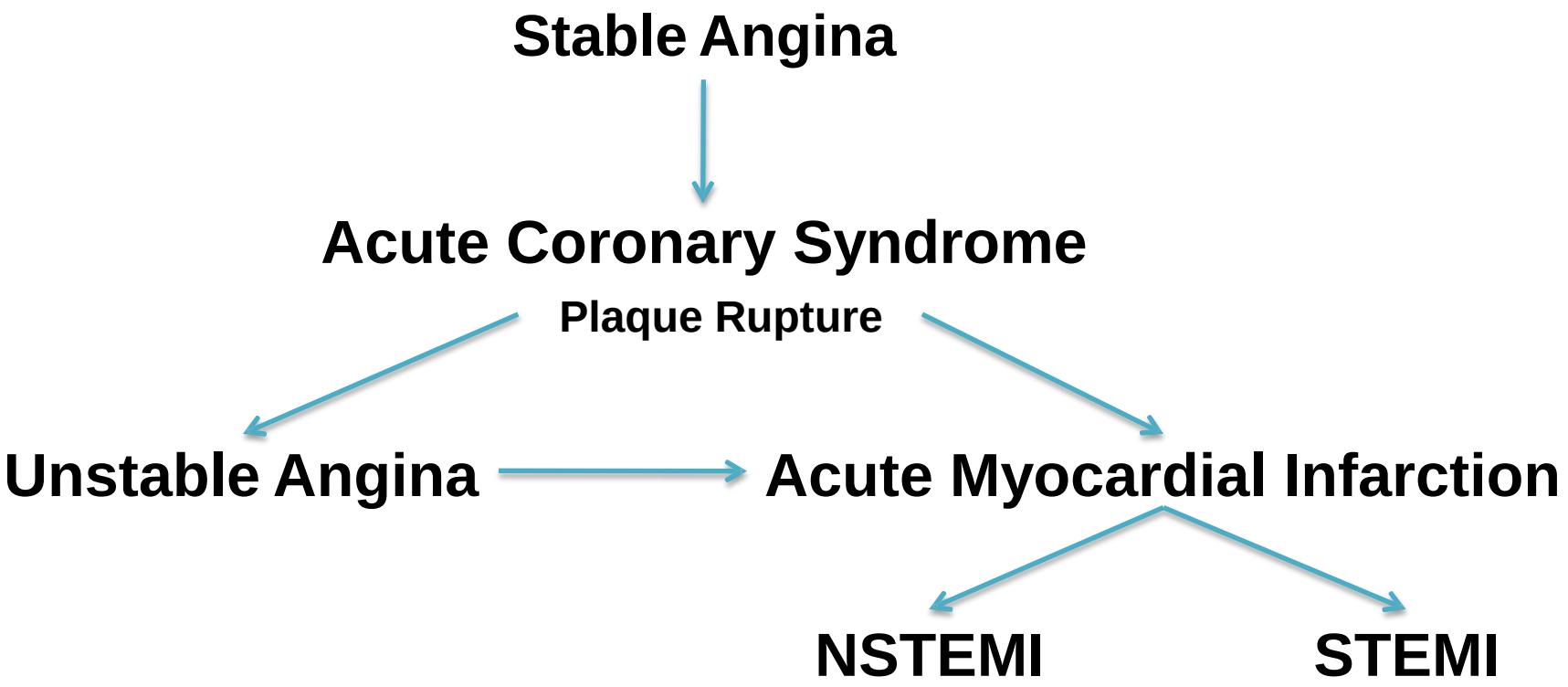
- In India CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013.

- **60 to 79 year old** :~ 23% of men and 15% of women have prevalent IHD, and these figures rise to 33% and 22% among men and women **80 years of age**.

- Although **IHD is widely known** to be the **number 1 cause** of **death in men**, this is **also the case for women**, among whom this condition accounts for 27% of deaths.

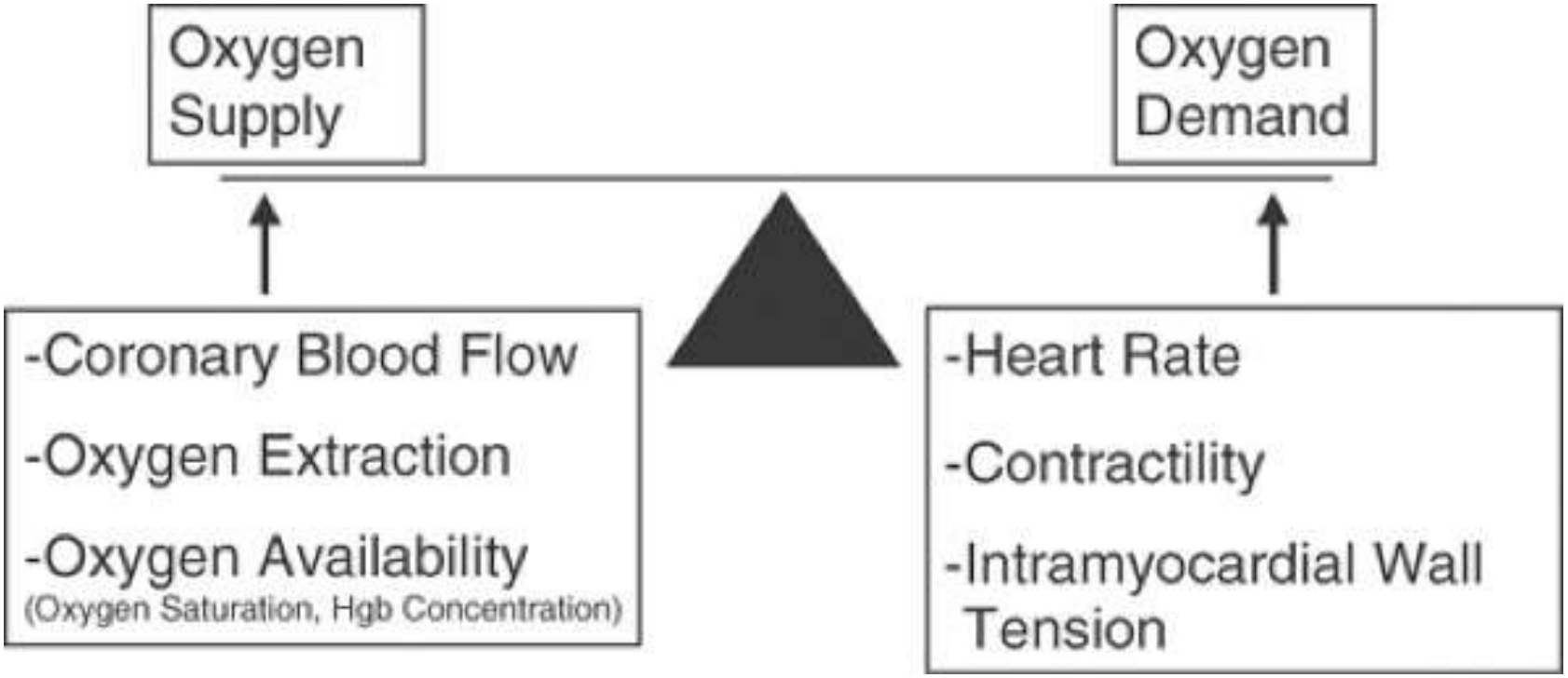
- **IHD** accounts for the **vast majority** of the **mortality and morbidity of cardiac disease.**

Cardiovascular Event Pathway



Pathophysiology

Determinants of myocardial oxygen supply & demand



As the consequences of IHD are a result of increased demand in the face of a fixed supply of oxygen in most situations, alterations in MVO_2 are critically important in producing ischemia and for interventions intended to alleviate ischemia

Pathophysiology

- **Reductions** in **coronary** blood **flow** (secondary to **atherosclerotic plaques**, **vasospasm**, or **thrombus formation)** and **arterial oxygen content** (secondary to **hypoxia**) decrease **myocardial oxygen supply.**

- Because the coronary arteries fill during diastole, decreases in diastolic filling time (e.g**.,** **tachycardia**) can also **reduce coronary perfusion** and myocardial oxygen supply.

- **In chronic stable angina**, ***atherosclerotic plaques*** are the most common cause of coronary artery **narrowing** and reductions in coronary blood flow. **In contrast, in ACS**, ***disruption of an atherosclerotic plaque*** with subsequent **thrombus** (**blood clot**) formation causes **abrupt** **reductions** in **coronary blood flow** and **oxygen supply.**

Pathophysiology

- **Conditions** that can **reduce the oxygen-carrying capacity** of blood:
  - **Anemia**
  - **Carbon monoxide poisoning**, and
  - **Cyanotic congenital heart**

→ potentially causing **ischemia** in the face of **adequate coronary perfusion.**

- **Coronary heart disease (CHD)** refers to the failure of coronary circulation to supply adequate circulation to cardiac muscle and surrounding tissue.
  - Common manifestations of coronary heart disease (CHD) include:
    - Angina pectoris, whether stable (SA) or unstable (USA)
    - myocardial infarction (MI),
    - heart failure (HF),
    - arrhythmias,
    - Sudden cardiac death (SCD).

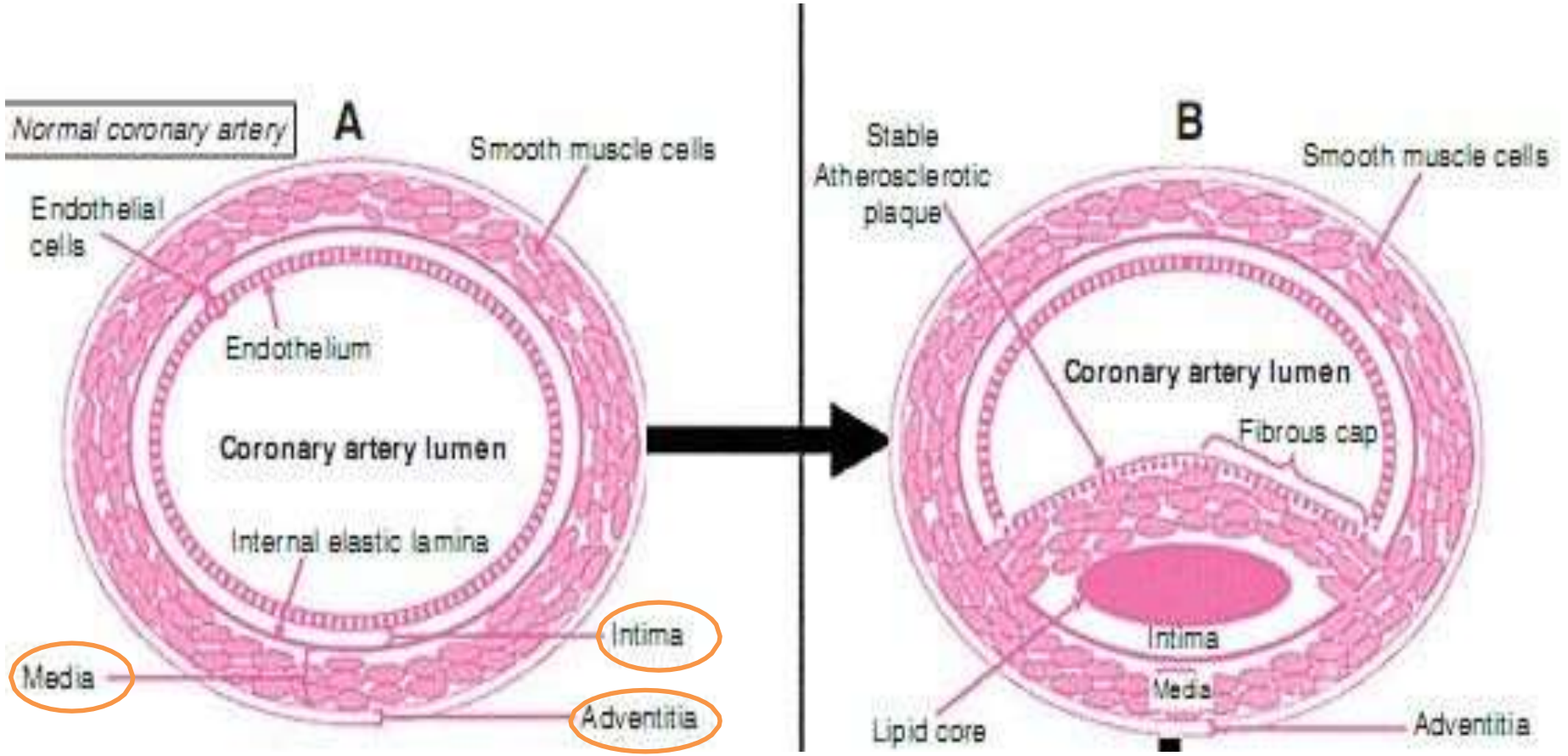
- **Ischemic heart disease (IHD),** or myocardial ischemia, is a disease characterized by reduced blood supply to the heart muscle, usually due to **coronary artery disease (CAD)** (**atherosclerosis of the coronary arteries**).

- **Acute coronary syndrome (ACS)** is a set of signs and symptoms (syndrome) related to the heart.
  - The sub-types of acute coronary syndrome include:
    - **unstable angina** (UA, **not** associated with heart **muscle damage**),
    - two forms of myocardial infarction (**MI, heart attack**), in which heart muscle is damaged.
      - **non-ST segment** elevation myocardial infarction (NSTEMI)
      - **ST segment elevation** myocardial infarction (STEMI).

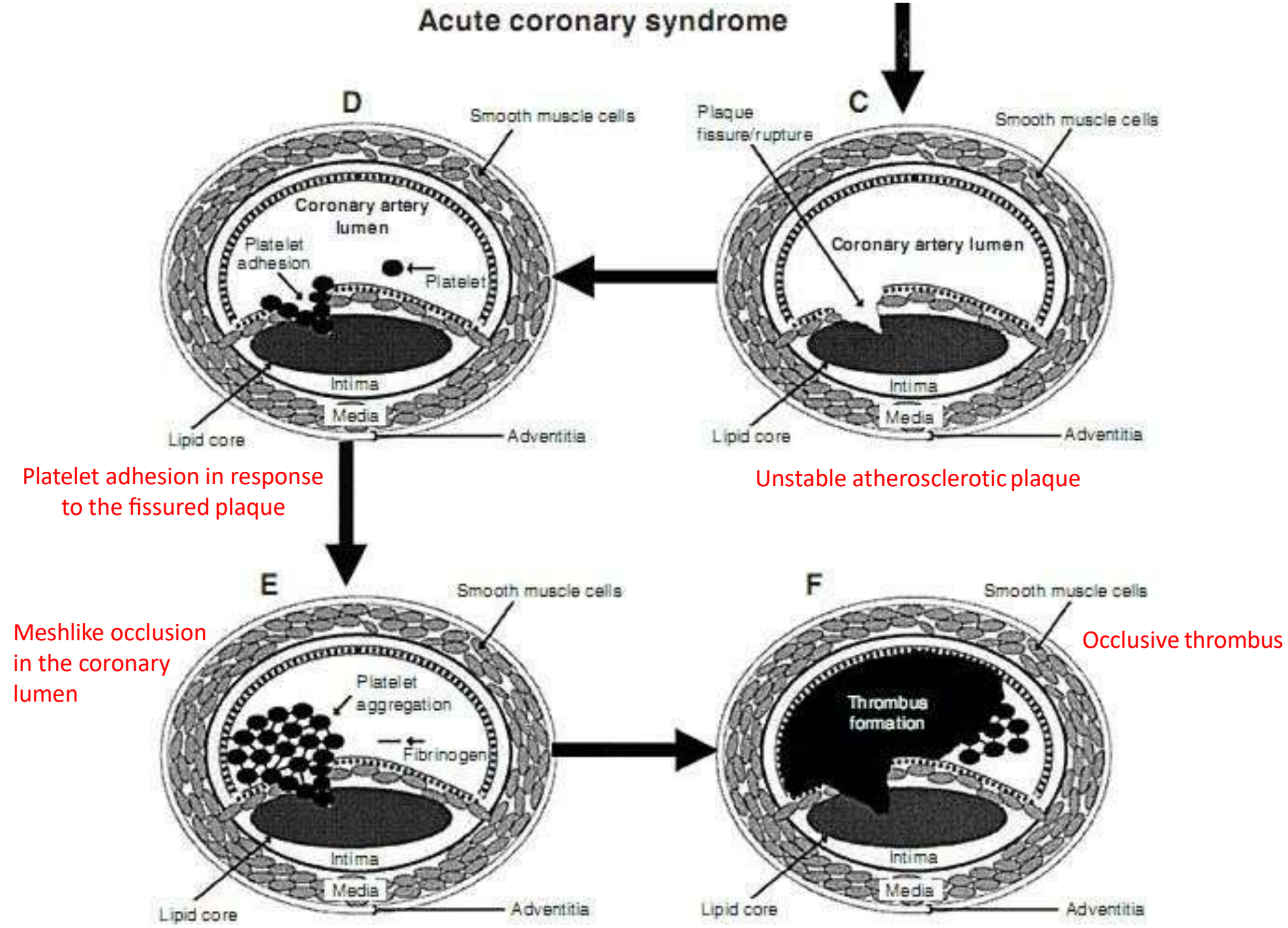
Terminology/Definitions

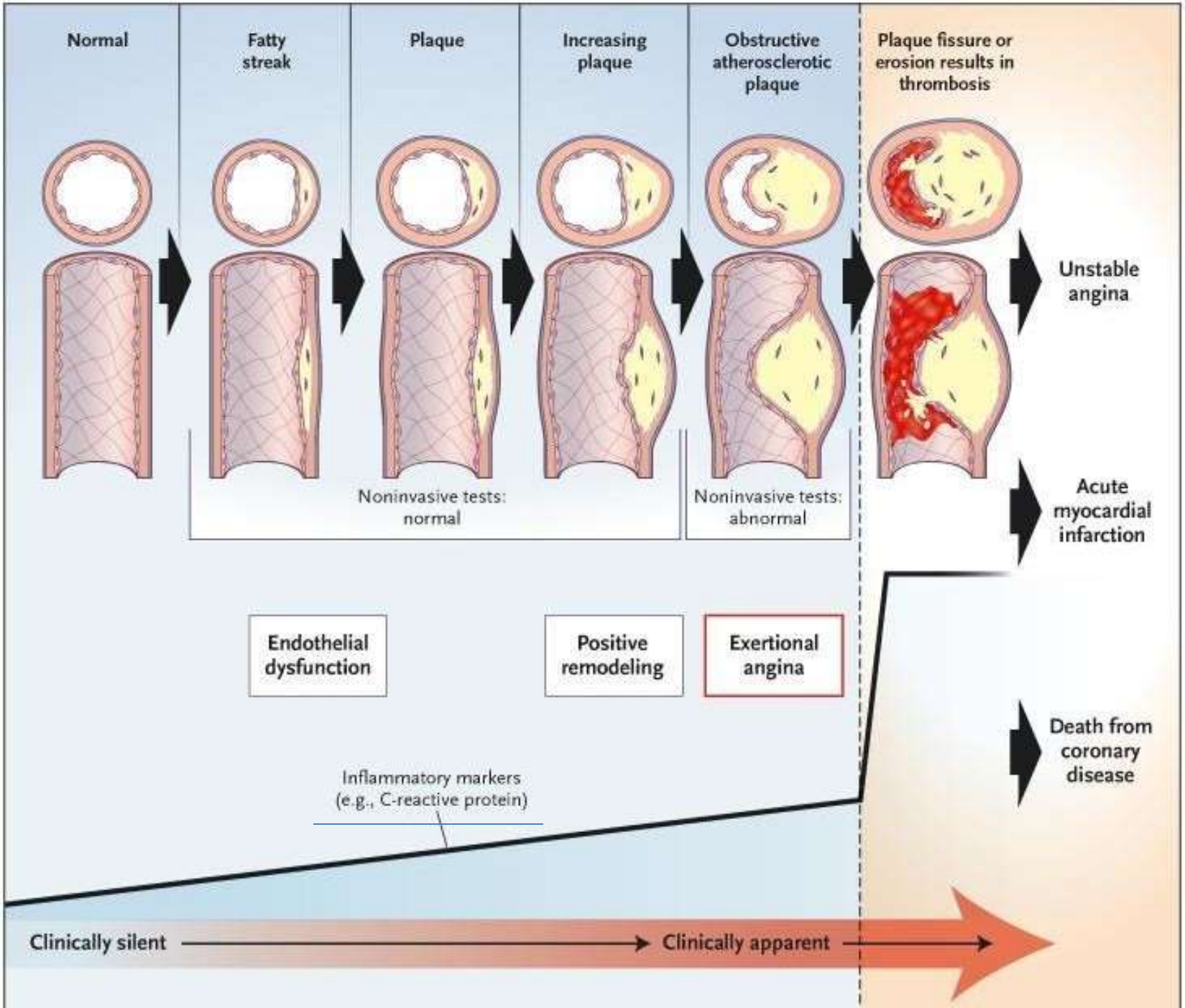
- **Ischemic Heart Disease (IHD)** may present as:
  - **Myocardial ischemia** without clinical symptoms,
  - **Chronic stable exertional angina pectoris (SA)**,
  -
  - **An acute coronary syndrome (ACS)**
    - **Unstable angina (USA)**
    - **Non–ST-segment elevation myocardial infarction (NSTEMI)**
    - **ST-segment elevation myocardial infarction (STEMI)**
  - Coronary artery vasospasm (**variant or Prinzmetal angina**) produces similar symptoms but is **not caused by atherosclerosis**.

Pathophysiology of chronic stable angina:



Panel A depicts the cross-section of a normal coronary artery.
Panel B depicts the cross-section of a coronary artery with a stable atherosclerotic plaque.
Note that the lipid core is relatively small in size and the fibrous cap is made up of several layers of smooth muscle cells.


Acute coronary syndrome
D
Smooth muscle cells
Coronary artery lumen
Platelet adhesion
Platelet
Intima
Media
Lipid core
Adventitia
C
Plaque fissure/rupture
Smooth muscle cells
Coronary artery lumen
Intima
Media
Lipid core
Adventitia
Platelet adhesion in response to the fissured plaque
Unstable atherosclerotic plaque
E
Smooth muscle cells
Platelet aggregation
Fibrinogen
Intima
Media
Lipid core
Adventitia
F
Smooth muscle cells
Thrombus formation
Intima
Media
Lipid core
Adventitia
Meshlike occlusion in the coronary lumen
Occlusive thrombus


Normal
Fatty streak
Plaque
Increasing plaque
Obstructive atherosclerotic plaque
Plaque fissure or erosion results in thrombosis
Unstable angina
Acute myocardial infarction
Death from coronary disease
Noninvasive tests: normal
Noninvasive tests: abnormal
Endothelial dysfunction
Positive remodeling
Exertional angina
Inflammatory markers (e.g., C-reactive protein)
Clinically silent
Clinically apparent

Types of Angina

1. Stable Angina

   exertional angina, **typical** or **classic** angina, angina **of effort**, **atherosclerotic angina**

2. Unstable Angina

   Pre-infarction angina**, crescendo** angina, angina **at rest**

3. **Prinzmetal's** Angina

   vasospastic angina**, variant** angina

4. Silent Ischemia

1- Stable Angina

- The patient has occasional periods of anginal symptoms, which are usually **predictable and related to the amount of work the heart is doing (MVO_2).**

- Underlying pathology is **usually atherosclerosis**

- Anginal episodes can be precipitated by **exercise, cold, stress, emotion, or eating**

- Often a **chronic condition**
  - Characterized by the need for **chronic and/or prophylaxis medication to** prevent **chest pain/discomfort**

2- Unstable Angina

- Caused by recurrent episodes of small platelet clots at the site of a ruptured atherosclerotic plaque which can also precipitate local vasospasm

- Associated with **a change** in the **character, frequency, and duration of angina** in patients with **stable angina** and when there are **prolonged episodes of angina at rest**

- **Urgent medical** condition
  - Requires **aggressive medical management** to **prevent MI**

- **part of the clinical spectrum of** acute **coronary syndrome**

3- Prinzmetal's Angina

- Results from **transient vasospasm of the coronary vessels**
- **May be associated** with **underlying atheromas**
- **Patients with this angina** may be **relatively young** and **have few or even no cardiac risk factors**
- **The chest pain** is **often unpredictable** and cyclical in nature, sometimes **reverting spontaneously into remission**.
  - More likely to experience **pain at rest** and in **the early morning** hours. **Pain is not usually brought on by exertion** or e**motional stress nor relieved by rest**; the **ECG pattern** is that of current injury **with ST-segment elevation rather than depression.**

4- Silent Ischemia

- **Transient episodes** of **myocardial ischemia** not associated **with angina** or other symptoms **despite ECG changes consistent with ischemic heart disease**

- Silent ischemia is very common
  - As demonstrated by continuous Holter monitor recordings

Clinical presentation

- **CSA** should be distinguished from **UA** since the latter is **associated** with **a greater risk for MI and death** and requires **more aggressive treatment**.

- Because the pathophysiology of CSA is due primarily to increases in **oxygen demand**→ symptoms are **typically reproducible.**
  - patient will generally experience a **similar pattern of discomfort** (i.e., same quality, location, and accompanying symptoms) with **a similar level of exertion with** each **angina attack.**

- The **exception** maybe a patient with **coronary artery vasospas**m, in whom symptoms **maybe more variable and unpredictable.**

Clinical presentation

- Patients with **CSA** will generally be in **no acute distress**. In patients presenting in **acute distress**, the clinician should be **suspicious of ACS.**

- The **five components** commonly used to characterize chest pain are quality, location, and duration of pain; factors that provoke pain; and factors that relieve pain:

  - **Typical pain:** sensation of **pressure**, **heaviness**, or **squeezing** in the **anterior chest area**. **Sharp pain is not a typical symptom of IHD**.
  - may radiate to the **neck, jaw, shoulder, back, or arm.**
  - may be accompanied by **dyspnea, nausea, vomiting, or diaphoresis.**

Clinical presentation

- Symptoms are often provoked by **exertion** (e.g., walking, climbing stairs, and doing yard-or housework) or emotional **stress** and relieved within **minutes by rest or sublingual nitroglycerin.**

- Other precipitating factors include exposure to **cold temperatures** and **heavy meals**. **Pain that occurs at rest (without provocation) or that is prolonged and unrelieved by sublingual nitroglycerin is indicative of an ACS**.
- Some patients, most commonly **women** and patients with **diabetes**, may present with ***atypical symptoms*** including indigestion, gastric fullness, and shortness of breath.

- Patients with **diabetes** may experience associated symptoms, such as **dyspnea and diaphoresis**, without having any of the classic chest pain symptom!!
- **In some cases**, **ischemia may not produce any symptoms** and is termed **"silent ischemia."**

Conditions Provoking or Exacerbating Ischemia

Increased Oxygen Demand

Non-Cardiac

- Hyperthermia
- Hyperthyroidism
- Sympathomimetic toxicity (cocaine use)
- Hypertension
- Anxiety
- Arteriovenous fistula

Cardiac

- Hypertrophic cardiomyopathy
- Aortic stenosis
- Dilated cardiomyopathy
- Tachycardia
  - ventricular supraventricular

Decreased Oxygen Supply

Non-Cardiac

- Anemia
- Hypoxemia
  - pneumonia, asthma, COPD, pulmonary hypertension, interstitial pulmonary fibrosis, obstructive sleep apnea
- Sickle-cell disease
- Sympathomimetic toxicity (cocaine use)
- Hyperviscosity
  - polycythemia, leukemia, thrombocytosis, hypergammaglobulinemia

Cardiac

- Aortic stenosis
- Hypertrophic cardiomyopathy

Symptoms

Sensation of pressure or heavy weight on chest alone or with pain

Pain described variably as feeling of tightness, burning, crushing, squeezing, vicelike, aching, or "deep"

Gradual increase in intensity followed by gradual fading away (distinguished from esophageal spasm)a

SOB with feeling constriction about the larynx of upper trachea

Location of Pain or Discomfort

Over the sternum or very near to it

Anywhere between epigastrium and pharynx

Occasionally limited to left shoulder and left arm

Rarely limited to right arm

Lower cervical or upper thoracic spine

Left interscapular or suprascapular area

Radiation of Pain

Medial aspect of left arm

Left shoulder

Jaw

Occasionally, right arm

Duration of Symptoms

0.5–30 min

Electrocardiogram

ST-segment depression >2 mm

T-wave inversion

Precipitating Factors

Mild, moderate, or heavy exercise, depending on patient

Effort that involves use of arms above the head

Cold environment

Walking against the wind

Walking after a large meal

Emotions: fright, anger, or anxiety

Coitus

Nitroglycerin Relief

Relief of pain occurring within 45 sec to 5 min of taking nitroglycerin

Symptoms

- The **severity of symptoms** does **not correlate** with the **severity of CAD**, but should be assessed to facilitate diagnosis and treatment decisions

- **The Canadian Cardiovascular Society (CCS) classification of angina** is a widely used mechanism for characterizing angina based on an assessment of **disability resulting** from **the anginal symptoms.**

- **Statistically significant correlation between** the **CCS angina class** and the **severity of CAD** as determined by **coronary angiography.**

The Canadian Cardiovascular Society (CCS) classification of angina

Angina Classification	Accompanying Symptoms
Class I	**Normal physical activity (e.g., climbing stairs or walking) does not cause anginal symptoms**; angina occurs primarily with **strenuous, extended, or rapid physical a**ctivity or recreation
Class II	**Angina poses a slight limitation on ordinary activity** and typically occurs with the following types of activities: •**Quickly walking or climbing** stairs •**Uphill walking** •**Walking/stair climbing after meals** •**Windy or cold weather** •**Emotional stress** •Within the first few hours after waking •**Walking more than two blocks** or **climbing more than one flight** of stairs at a **normal pace (under** normal conditions)
Class III	**Anginal symptoms impose marked limitation on physical activity**; angina occurs upon walking one to two blocks or climbing one flight of stairs at a normal pace (under normal conditions)
Class IV	**Symptoms of angina may be present at rest**; physical activity cannot be carried out without discomfort

Diagnosis and evaluation

- A **thorough medical history, physical exam, and laboratory** analysis are necessary to ascertain cardiovascular risk factors and to **exclude nonischemic** and **noncardiac** conditions that could cause **angina-like symptoms.**

- Laboratory analyses should assess **for glycemic control** (i.e., fasting glucose, glycosylated hemoglobin), **fasting lipids, hemoglobin, and organ function** (i.e., blood urea nitrogen, creatinine, liver function tests, thyroid function tests). Additionally, serial measurements of **cardiac enzymes** (usually three measurements within 24 hours) are used to *exclude the diagnosis of MI*. (CK, CK-MB, Troponin I and II usually normal in CSA and UA and elevated in MI)

Assessment of Risk Factors

- Age / gender
  - M > 45yrs, F > 55yrs*
- Family history of premature IHD
  - M < 55yrs, F < 65yrs
- Hypertension
  - BP > 140/90 or on anti- hypertensive therapy
- Smoking
- Hyperlipidemia

* or post-menopausal, whichever occurs first

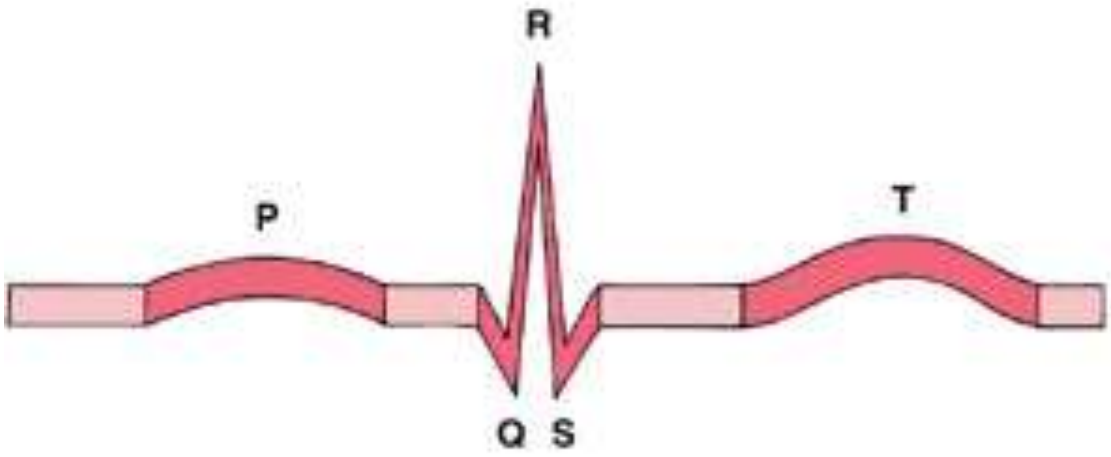
- HDL < 40 mg/dL
  - > 60 (subtract one risk factor)
- Diabetes
- Obesity
  - BMI >30 kg/m^2
- Sedentary lifestyle
- CVD
- PVD

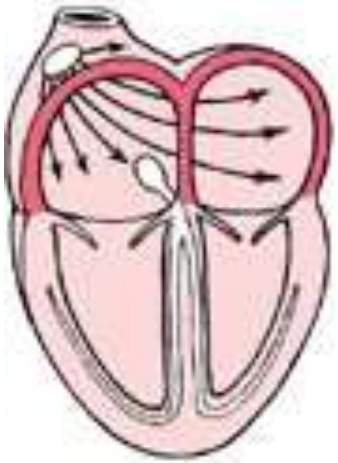
Diagnosis and Evaluation

- **Objective**
  - Physical examination
  - Electrocardiogram (ECG)
  - Laboratory data
  - Radiographic evaluation
    - Echocardiogram
    - Radionuclide scanning
    - Coronary angiography
  - Cardiac stress testing (functional testing)
    - Exercise
    - Pharmacologic : either to **increase myocardial work and oxygen demand (dobutamine)** or to **induce vasodilation-elicited heterogeneity in induced coronary flow (vasodilators)**

Diagnostic tests

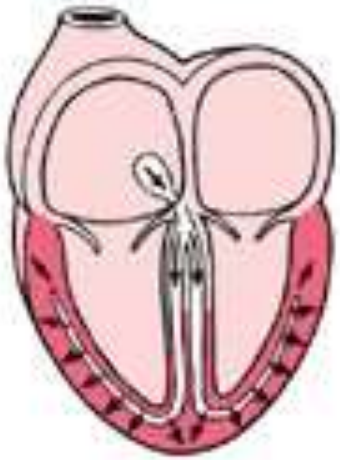
- **A 12-lead ECG recorded during rest** is often normal in patients with **chronic stable angina** in the **absence of active** ischemia.
  - should **be done within 10 minutes** of presentation to the emergency department in patients with **symptoms of ischemia.**
- **Cardiac stress test**
  - **Physical exercise (treadmill),**
  - **Pharmacologic stress** :**Dobutamine is commonly used with stress echocardiography**, whereas **adenosine or dipyridamole are used for nuclear imaging studies**
- **Treadmill or bicycle exercise ECG,** commonly referred to as **a "stress test,"** is considered **positive for IHD** if the ECG shows **at least a 1 mm** deviation of the ST-segment (depression or elevation).
- **Pharmacologic stress test: Dobutamine** (beta1 agonist) is a pharmacologic stressor used in patients who are unable to exercise and is **commonly used with echo**cardiography→ to identify stress-induced wall motion abnormalities indicative of coronary disease.





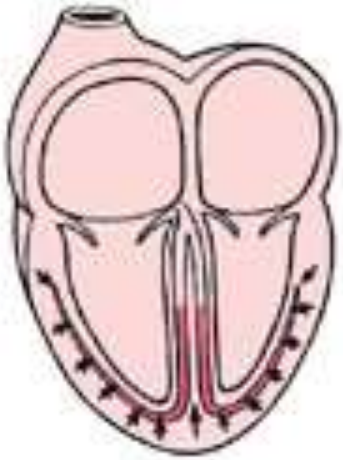
P Wave

Activation of the atria



QRS Complex

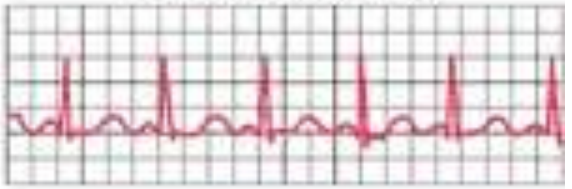
Activation of the ventricles



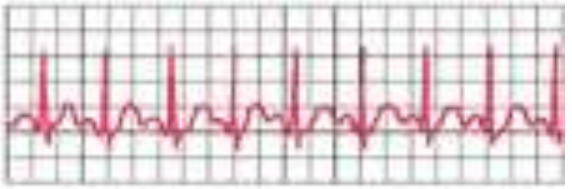
T Wave

Recovery wave

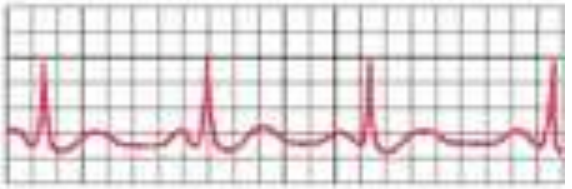
Normal Heartbeat



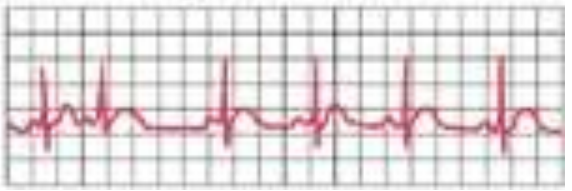
Fast Heartbeat



Slow Heartbeat



Irregular Heartbeat



Diagnosis (cont'd)

- **Radionuclides myocardial perfusion imaging (rMPI)** with the gamma-emitting **radionuclides technetium-99m sestamibi** or **thallium-201** allows for the identification of **multivessel disease** and assessment of **myocardial viability**. (exercise, pharmacological (vasodilator or dobutamine)
  - An IV radioactive tracer is used to detect areas of the heart that receive less blood after adenosine or dipyridamole infusion, indicating a **myocardial perfusion defect and coronary disease**

  - **Coronary artery calcium scoring via CT**, also known as electron beam CT (**EBCT) or "ultra-fast CT**," may be performed as a **noninvasive means to assess for IH**D.
    - **Calcium deposits** within the coronary arteries which are indicative **of IHD** are detected **on CT**. A **calcium score is calculated**, and the **risk for IHD-related events** is estimated.

Diagnostic tests (cont'd)

- **Coronary angiography (invasive)** detects the **location and degree of coronary atherosclerosis** and is used to evaluate the potential benefit from **revascularization procedures**.
  - **Stenosis o**f at **least 70%** of the diameter of **at least one of the major epicardial arteries** on coronary angiography is indicative of **significant IHD**

- **Is considered the gold standard for the diagnosis of IHD when**:
  - **stress testing** results **are abnormal**
  - or symptoms of angina are **poorly controlled.**

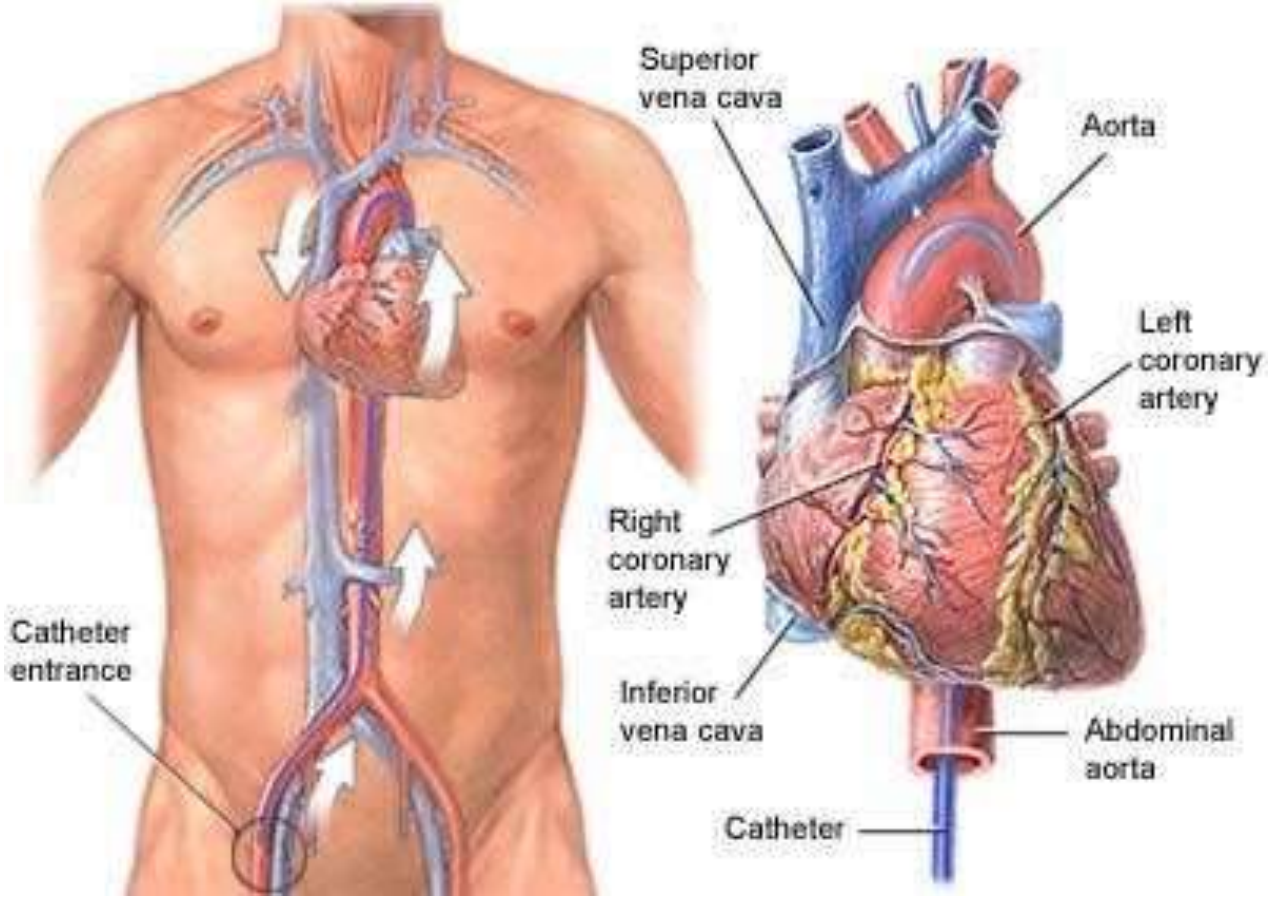
  - **Contrast medium** must be used cautiously **with adequate hydration** in patients with **pre-existing renal disease** (especially in **those with diabetes**) to **avoid contrast-induced nephropathy**

Diagnosis and Evaluation

- **Cardiac catheterization and coronary angiography** used in patients with suspected CAD to document the presence and severity of disease as well as for prognostic purposes.

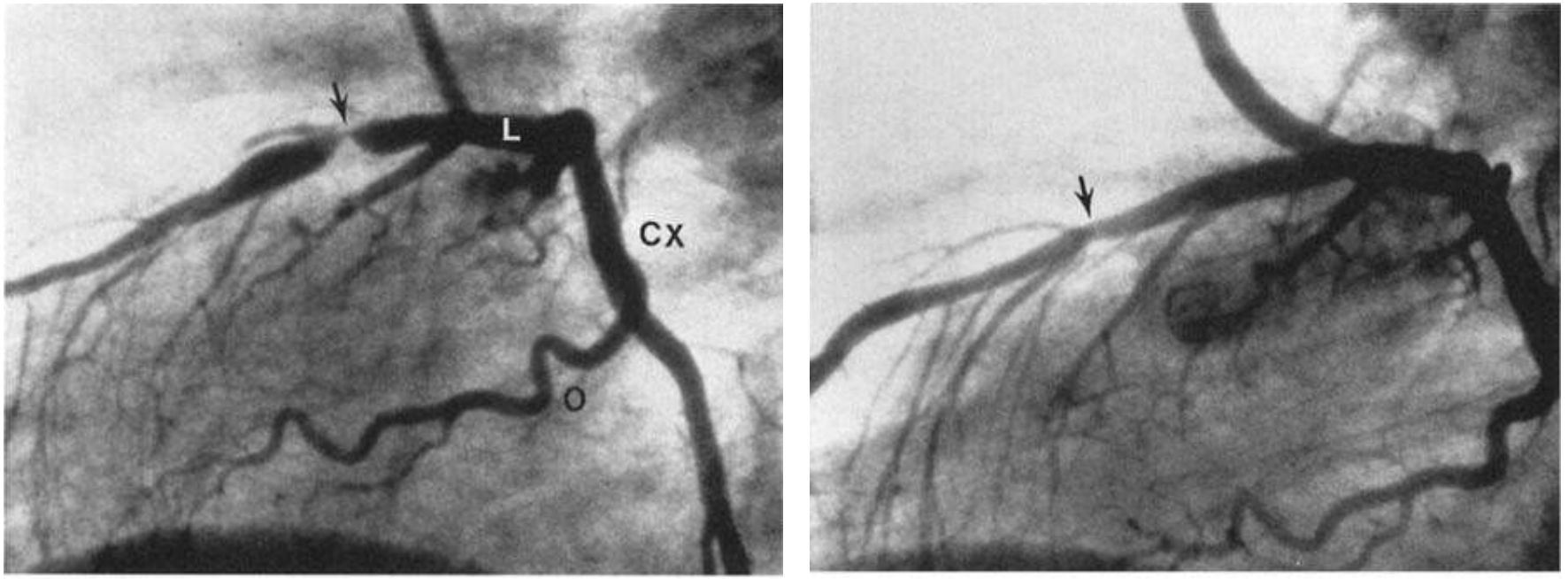
- **Interventional catheterization** used for **thrombolytic therapy** in patients with **acute MI** and for managing patients **with significant CAD to relieve obstruction** through **percutaneous transluminal coronary angioplasty** (PTCA), **atherectomy**, laser **treatment, or stent placement.**

Cardiac Catheterization



Cardiac catheterization is used to study the various functions of the heart. Using different techniques, the **coronary arteries can be viewed by injecting dye or opened using balloon angioplasty.** The oxygen concentration can be measured across the valves and walls (septa) of the heart and pressures within each chamber of the heart and across the valves can be measured. The technique can even be performed in small, newborn infants.

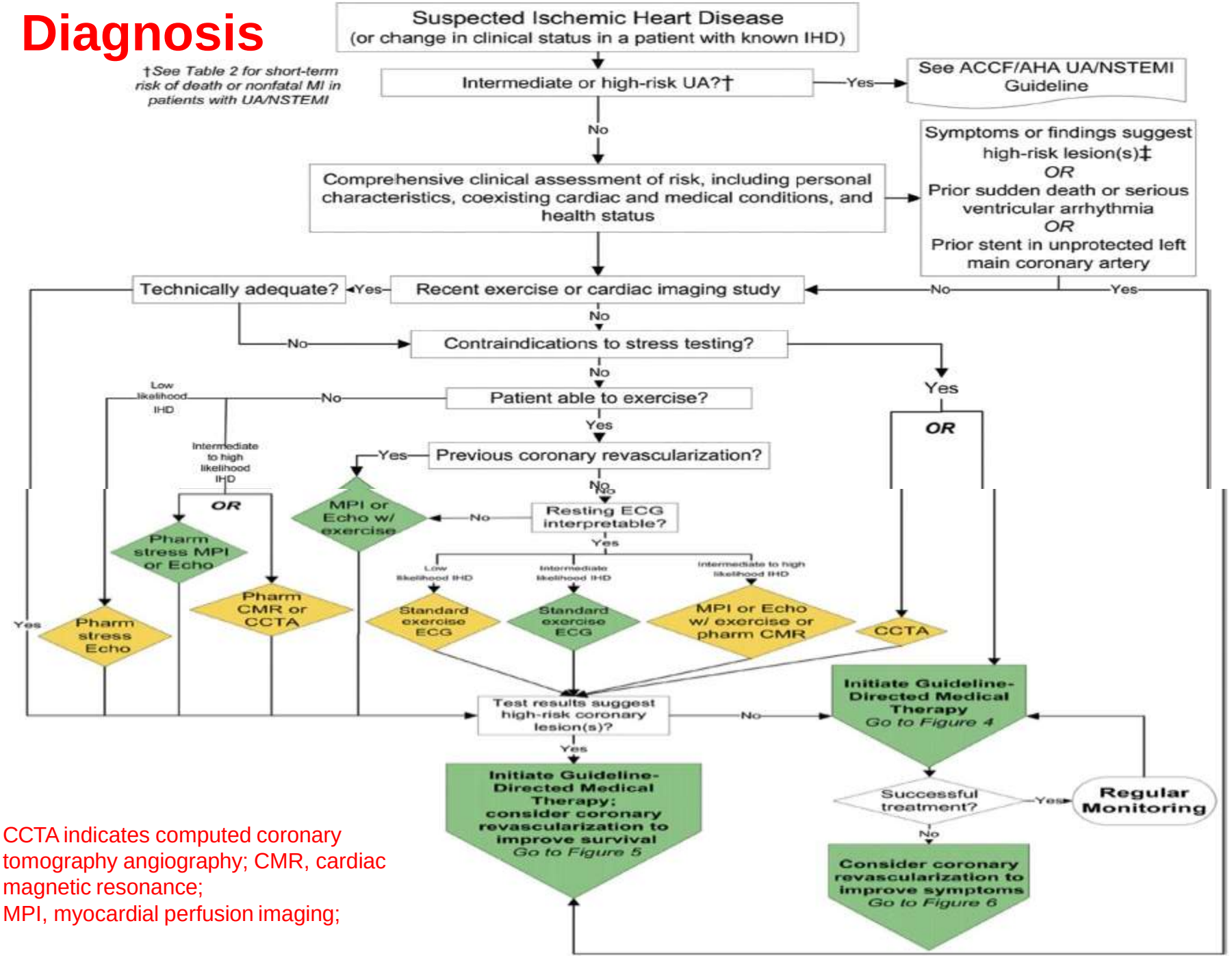
Coronary Angiography



A.Coronary arteriogram. Images were obtained from the left lateral projection with contrast injection into the left main coronary artery. The left anterior descending (L), left circumflex (CX), and first obtuse marginal (O) branches are visualized. Severe stenosis is seen in the midportion of the left anterior descending artery (*arrow*) in this patient, who had unstable angina pectoris.

B.Coronary arteriogram, same projection and patient as in *A*, obtained 1 day later. The stenosis in the left anterior descending coronary artery (*arrow*) has been reduced after percutaneous balloon angioplasty.

Diagnosis



CCTA indicates computed coronary tomography angiography; CMR, cardiac magnetic resonance;
MPI, myocardial perfusion imaging;

Test	Recommended	Not Recommended
Exercise ECG testing (using the Bruce protocol and Duke treadmill score)	Symptomatic patients with intermediate-to-high probability of CAD who are able to exercise and not taking digoxin (LOE: B) After significant change in anginal pattern (LOE: C)	Baseline ECG abnormalities (Wolff-Parkinson-White syndrome, electronically paced ventricular rhythm, > 1 mm ST depression at rest, LVH, or complete LBBB) (LOE: B) Established diagnosis of CAD (prior MI, angiography) (LOE: B)
Cardiac stress imaging (able to exercise) -- exercise MPI or exercise echocardiography	Patients with intermediate pretest probability of CAD with abnormal results on resting ECG or are using digoxin (LOE: B)	Patients with LBBB or cardiac pacing device (LOE: B)
Cardiac stress imaging (unable to exercise) -- adenosine or dipyridamole MPI or dobutamine echocardiography	Patients with an intermediate pretest probability of CAD (LOE: B) or in patients with prior revascularization (LOE: B), but do not have LBBB or a cardiac pacing device	Dobutamine echocardiography not recommended in patients with LBBB or cardiac pacing device (LOE: B)
Cardiac **stress imaging -- adenosine or dipyridamole** MPI	**Patients with LBBB or with cardiac pacing device (regardless of ability to exercise**) (LOE: B)	

CAD = coronary artery disease; ECG = electrocardiographic; LBBB = left bundle branch block; LOE = level of evidence; LVH = left ventricular hypertrophy; MPI = myocardial perfusion imaging

Risk Stratification

Low Risk	High Risk
✓ Stable angina	✓ Unstable angina
✓ Absence of CHF symptoms	✓ CHF symptoms
✓ Normal resting ECG	✓ Resting ECG with Q-waves or ST-T wave changes
✓ Normal LVF	✓ Markedly depressed LVF

Treatment of Ischemic Heart Disease

Treatment of Ischemic Heart Disease

- Establish Goals of Therapy
- **Risk Factor Modification**
- Lifestyle Modification
- Pharmacotherapy
  - **antianginal/anti-ischemic therapies** (i.e., **beta-blocker**s, **calcium channel antagonists**, **and nitrates**)
  - **vasculoprotective agents** (i.e., **lipid-lowering** therapies and **antiplatelet agents**)
  - **ranolazine** was approved in **January 2006** by the **FDA** as a **novel treatment option for CS**A in patients who **have not achieved adequate** control **of angina symptoms with standard therapies.**
- **Interventional therapies**

Goals of Therapy

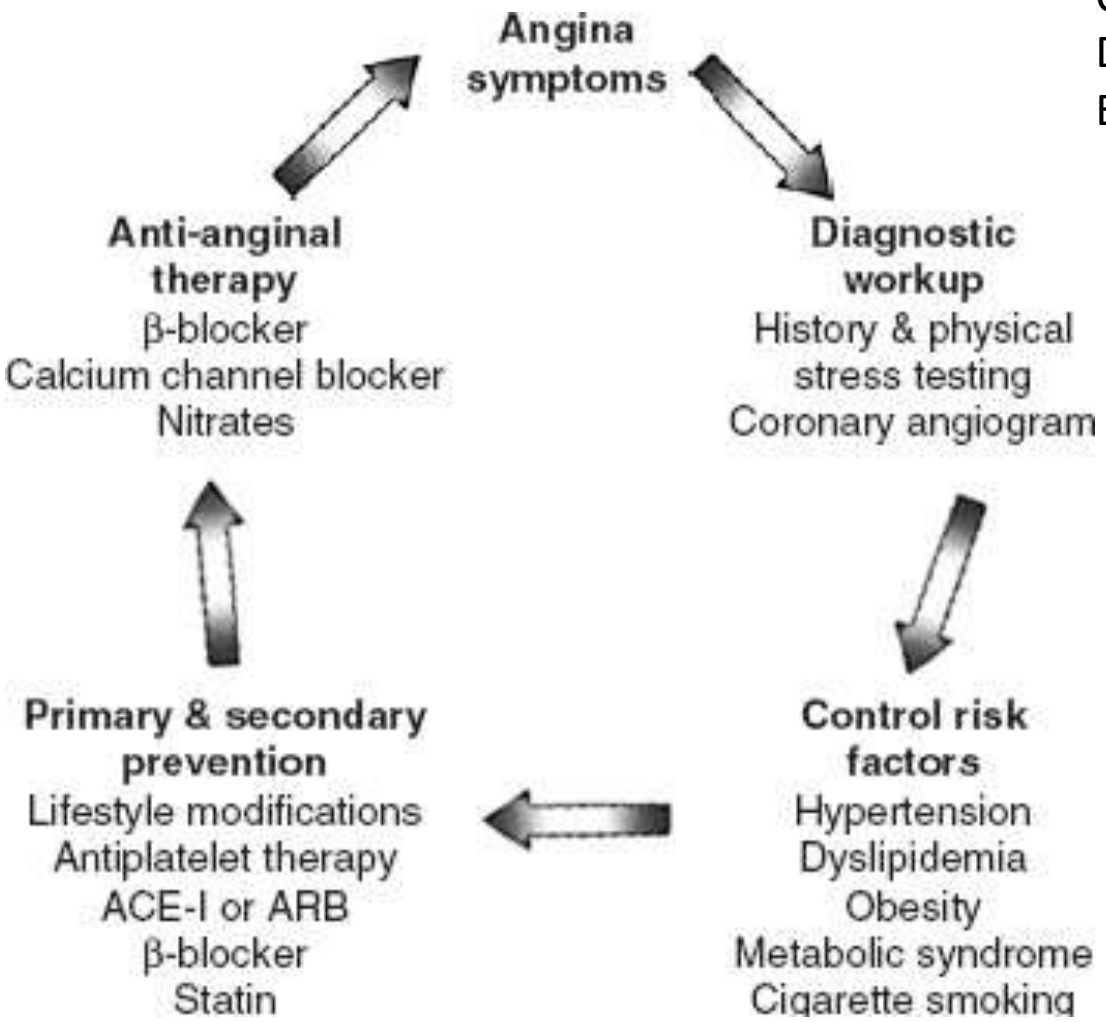
- **Short-Term**
  - **Stabilize chest pain/discomfort** and reduce or prevent anginal symptoms
  - **Prevent ischemia and subsequent infarction**
  - Improve **exercise tolerance** and quality of life

- **Long-Term**
  - **Alter or modify underlying process of ischemia**
    - Risk factor modification and optimization of medical management
  - **Prevent primary or secondary CV** events **MI, HF, ARR**
  - **Stabilize the pattern** of **chest pain**
  - **Decrease overall CV mortality and morbidity**

General treatment strategies

Angina Treatment Mnemonic

A – aspirin, anti-anginals
B – β-blockers and blood pressure
C – cholesterol and cigarettes
D – diet and diabetes
E – education and exercise



ACC/AHA Guideline Recommendations for CV Risk Reduction in Patients With Stable CAD

Risk Factor	Recommendations
Smoking	Complete cessation; no exposure to environmental tobacco smoke
Blood pressure control	< 140/90 mm Hg ***or < 130/80 mm Hg if patient has diabetes or chronic kidney disease??JNC8***
Lipid management **2013 AHA/ACC dyslipidemia***	**There is no evidence to support continued use of specific LDL-C and/or non–high-density lipoprotein cholesterol (non–HDL-C) treatment targets** **The appropriate intensity of statin therapy should be used to reduce risk in those most likely to benefit. (4 groups)** **High-intensity statin therapy is defined as a daily dose that lowers LDL-C by ≥50%** and moderate-intensity by 30% to <50%. All patients with ASCVD (including stable angina) who are age ≤75 years, as well as patients >75 years, should **receive high-intensity statin** therapy; or **if not a candidate** for high-intensity, should receive **moderate-intensity statin therapy.**

Risk Factor	Recommendations
Physical activity	- **30-60 m**in, 7 **days/wk (minimum, 5 days/wk)** - **Moderate-intensity aerobic activity** should be **encouraged on all days of the** week, supplemented by an increase in daily activities
Weight management	Body mass **index: 18.5-24.9 kg/m^2** **Waist circumference:** - Men: < 40 in (102 cm) - Women: < 35 in (88 cm)
Diabetes management	HbA1c < 7% (rosiglitazone???)
Antiplatelet agents*	Aspirin should be started **at 75-162 mg/day** and continued **indefinitely in all** patients unless contraindicated *Adding warfarin and/or clopidogrel increase the risk of bleeding→ monitor closely (Harm)

ACE inhibitors	**ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction ≤ 40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated**
ARBs	Use in patients who **are intolerant of ACE inhibitors** and **have heart failure** or have had a **myocardial infarction with left ventricular ejection fraction ≤ 40%**
Aldosterone blockade	Use in patients post MI, without significant renal dysfunction or hyperkalemia, who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker, have a left ventricular ejection fraction ≤ 40%, and have either diabetes or heart failure
Beta Blockers	They should be started and continued for 3 years in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction (EF ≤40%) with or without heart failure symptoms (prior MI), unless contraindicated (2012 guidelines for SIHD)
Influenza vaccination	An annual influenza vaccination is recommended for patients with cardiovascular disease

Risk Factor Modification

- **Primary prevention** through **early recognition** and **modification of risk factors** is considered "optimal management"

- **Secondary prevention** is more prevalent and is an important and effective means **of reducing subsequent morbidity and mortality**

- Risk factors are **considered additive** and are classified as either **alterable or unalterable**

Risk Factor Modification

- **Alterable (Modifiable)**
  - Smoking (A, P)
  - Hypertension
  - Hyperlipidemia
  - Obesity
  - Diabetes
  - Sedentary lifestyle
  - Excessive alcohol use
  - Psychosocial factors
  - -- Type A personality(?)
  - Others

- **Unalterable (Non-modifiable)**
  - Gender

    Male > Female
  - Age

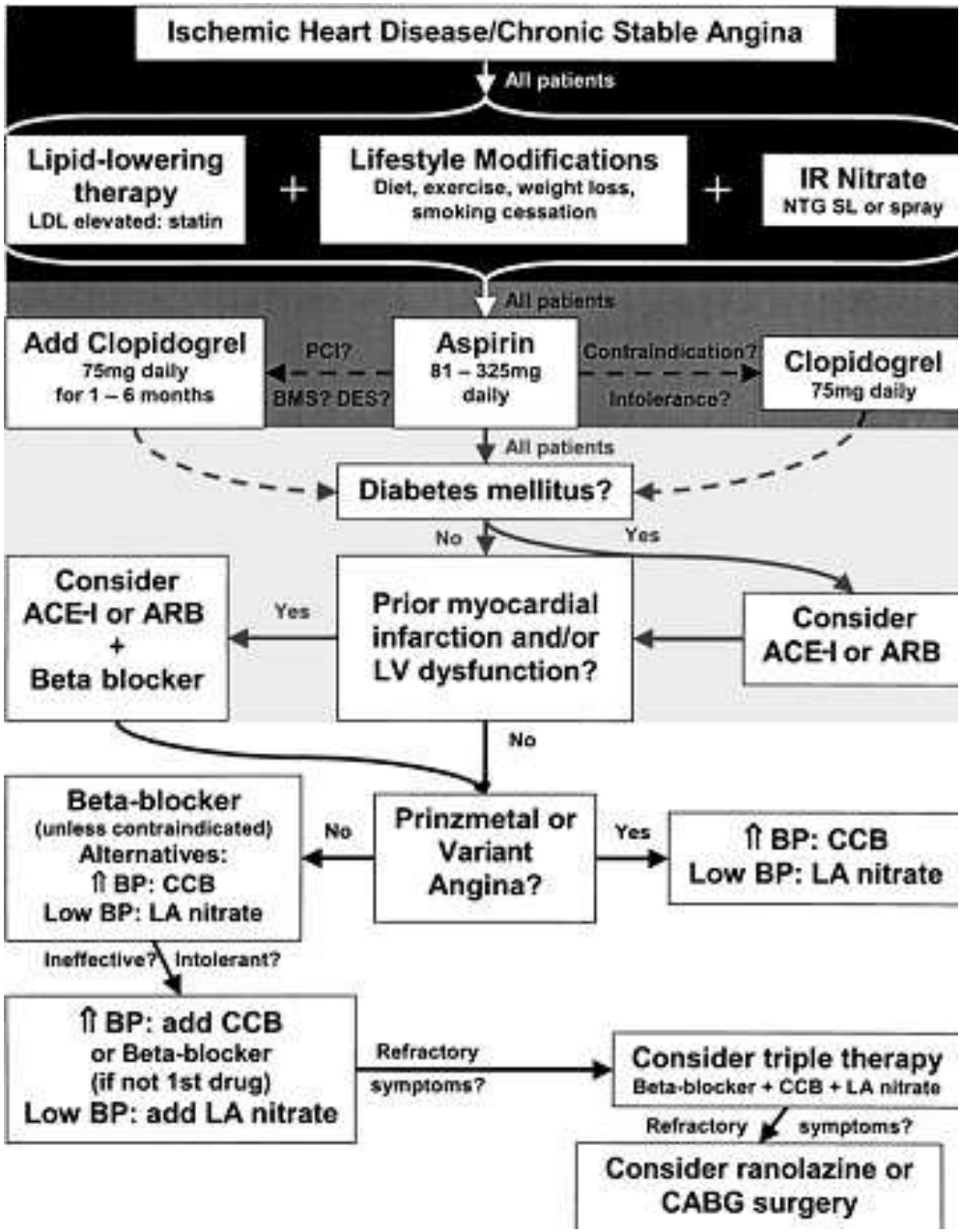
    Male > 45yrs

    Female > 55yrs
  - Family History

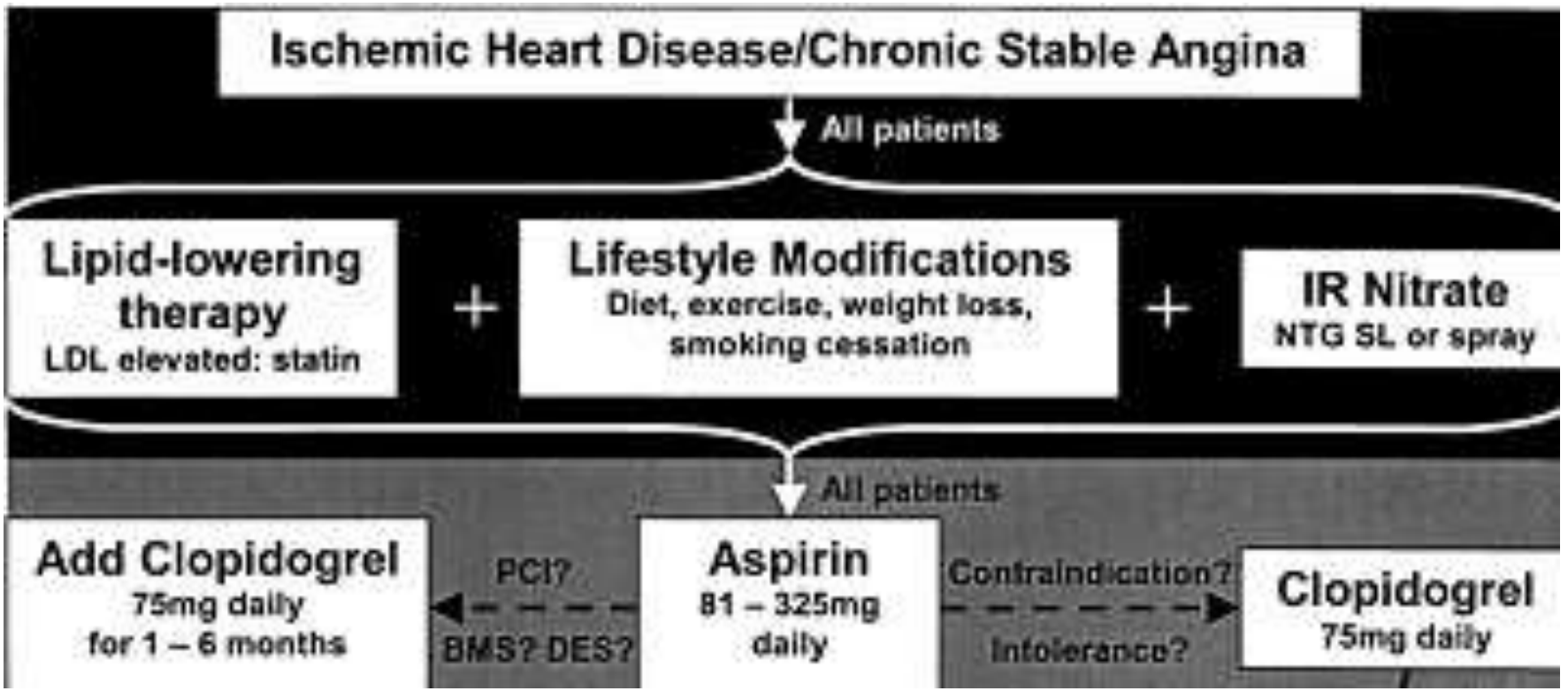
    Male < 55yrs

    Female < 65yrs
  - Genetic composition
  - Environmental factors
  - Diabetes (to some extent)

The treatment algorithm for ischemic heart disease



Treatment (cont'd)

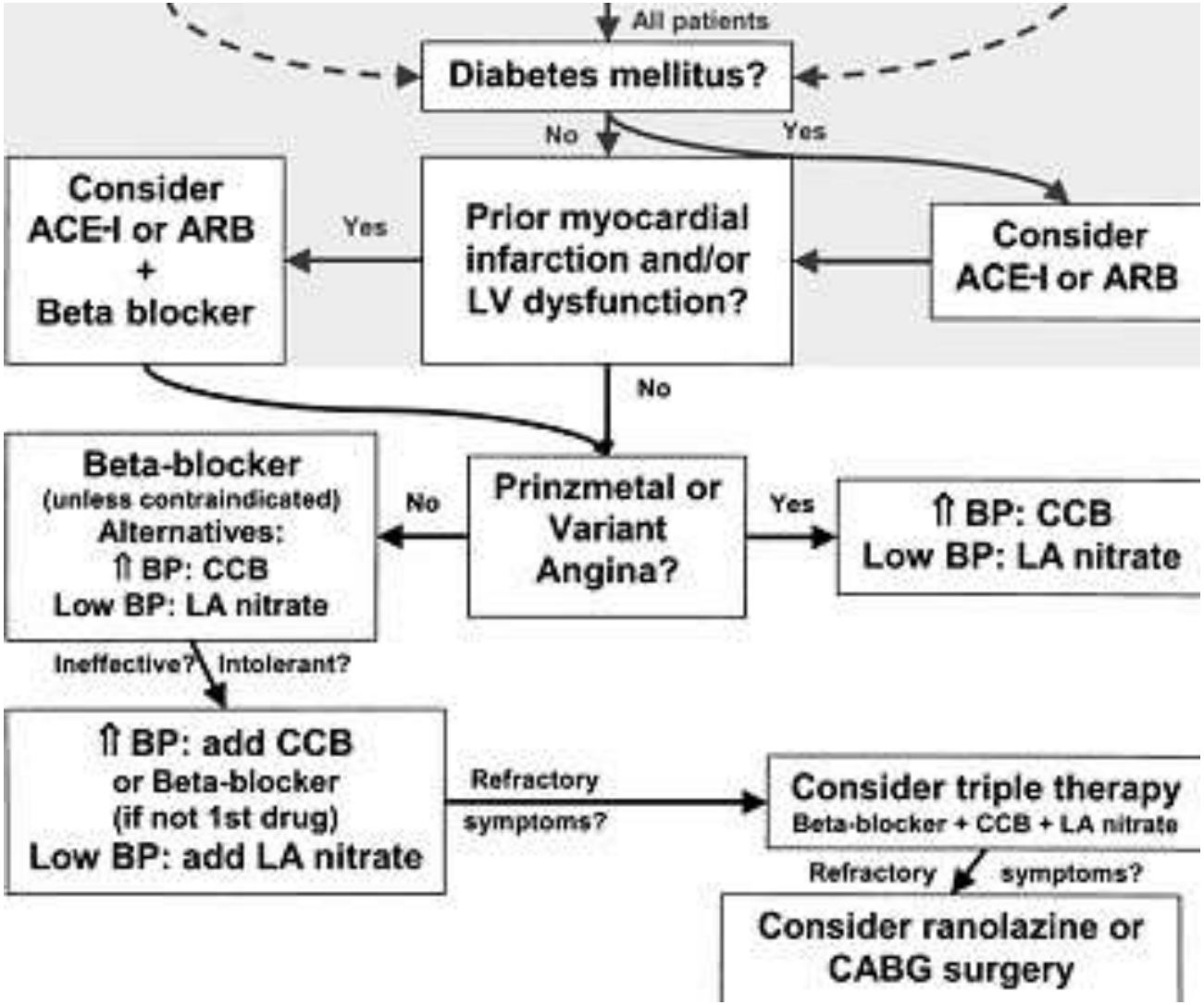


It begins at the top (**black section**), which suggests risk factor modifications as the first treatment modality.

Moving down to the **dark gray section**, **appropriate antiplatelet** therapy is selected.

BMS, bare metal stent; **DES**, drug-eluting stent; **PCI**, percutaneous coronary intervention;

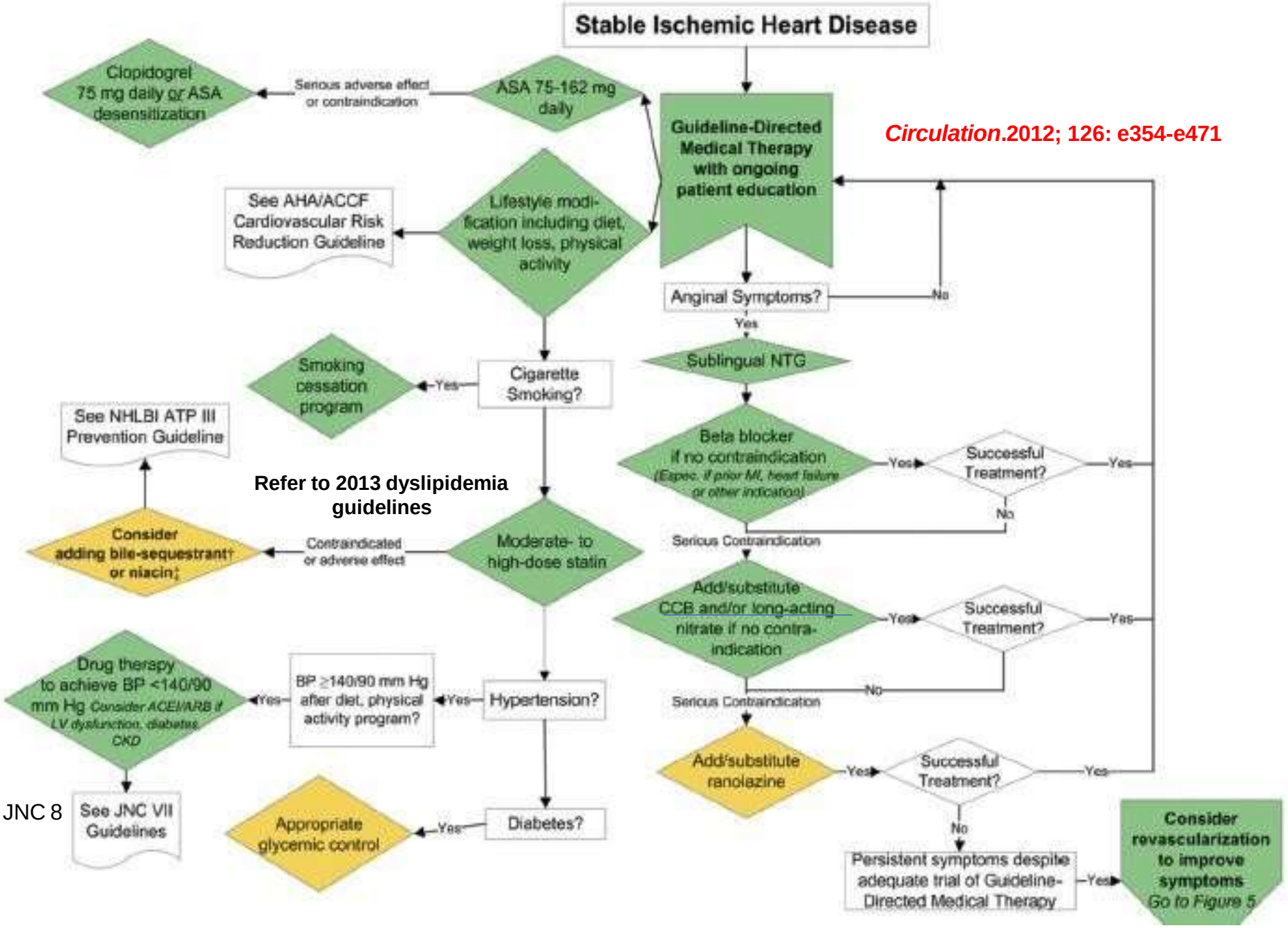
Treatment (cont'd)



The **light gray section** identifies patients at high-risk for major adverse cardiac events and <u>suggests appropriate drug therapy to decrease cardiovascular risk.</u>

The **white section** recommends appropriate anti-anginal therapy.

CABG, coronary artery bypass graft;


Stable Ischemic Heart Disease
Guideline-Directed Medical Therapy with ongoing patient education
Circulation.2012; 126: e354-e471
ASA 75-162 mg daily
Serious adverse effect or contraindication
Clopidogrel 75 mg daily or ASA desensitization
Lifestyle modification including diet, weight loss, physical activity
See AHA/ACCF Cardiovascular Risk Reduction Guideline
Anginal Symptoms?
No
Yes
Sublingual NTG
Beta blocker if no contraindication (Especially if prior MI, heart failure or other indication)
Yes
Successful Treatment?
Yes
No
Serious Contraindication
Add/substitute CCB and/or long-acting nitrate if no contraindication
Yes
Successful Treatment?
Yes
No
Serious Contraindication
Add/substitute ranolazine
Yes
Successful Treatment?
Yes
No
Persistent symptoms despite adequate trial of Guideline-Directed Medical Therapy
Yes
Consider revascularization to improve symptoms
Go to Figure 5
Cigarette Smoking?
Yes
Smoking cessation program
Moderate- to high-dose statin
Contraindicated or adverse effect
Consider adding bile-sequestrant† or niacin‡
See NHLBI ATP III Prevention Guideline
Refer to 2013 dyslipidemia guidelines
Hypertension?
Yes
BP ≥140/90 mm Hg after diet, physical activity program?
Yes
Drug therapy to achieve BP <140/90 mm Hg Consider ACEI/ARB if LV dysfunction, diabetes, CKD
Yes
See JNC VII Guidelines
JNC 8
Diabetes?
Yes
Appropriate glycemic control

Lifestyle Modification

- **Diet**
  - **No large clinical** data available in stable angina
  - **Lyon Heart Study**
    - Patients with **h/o MI** were randomly assigned to **Mediterranean-style diet** or "prudent" Western-type diet
      - Mediterranean diet –high in polyunsaturated omega-3 FA
    - Patients following **Mediterranean-style diet had a 50-70% lower risk** of recurrent heart disease
      - Benefit was determined early and remainder continuous throughout 46 months of follow up
  - **Specific dietary recommendations for patients with IHD should include the following:**
    - Limit **fat** intake to less than 30% of total caloric consumption.
    - Limit **cholesterol** intake to less than 200 mg per day.
    - Limit consumption of **saturated fat** found in fatty meats, full-fat dairy products, and hydrogenated vegetable oils to less than 7% of total calories.
    - Consume at least two servings of **fish** per week.
    - Consume at least six servings of **grains**, five servings of **fruits and vegetables**, and two servings of **non-fat or low-fat dairy products** per day.
    - Limit **daily sodium intake** to 2.4 grams (6 grams of salt) for blood pressure control.

Lifestyle Modification

- **Weight Reduction**
  - Obesity is associated with and contributes to other coronary disease risk factors

- **Exercise**
  - ↓ **frequency of anginal symptoms,** functional capacity, and **improves endothelial function**
  - Initiate at low-levels for 20-30 minutes, and as tolerated
  - **Compared** to **revascularization at one-year**, daily exercise resulted in fewer CV major events and **improved exercise tolerance.**

- **Smoking**
  - **No randomized trials** in **chronic stable angina**
  - Smoking CV disease mortality by 50%
  - **Incidence of coronary** events **↓ by 15-25% within 2 years** of smoking cessation
  - **Primary prevention studies** – **smoking cessation** resulted in a **7 to 47% reduction CV events**

Pharmacotherapy

- **Nitroglycerin to relieve acute symptoms**
- **Pharmacotherapy to prevent recurrent ischemic symptoms**
  - *Beta-blockers*
  - *Calcium channel blockers*
  - *Long-acting nitrates*
  - *Ranolazine*
- **Pharmacotherapy to prevent acute coronary syndromes and death (vasoprotective agents)**
  - *Antiplatelet agents*
  - *Statins*
  - *ACE inhibitors and angiotensin receptor blockers*
  - *Control of risk factors*
- **Pharmacotherapy with no benefit or potentially harmful effects**
  - *Hormone replacement therapy*
  - *Antioxidants*
  - *Folic acid*
  - *Herbal supplements*

Pharmacotherapy to prevent recurrent ischemic symptoms (anti-ischemic medications)

ß-blockers, calcium channel blockers, and nitrates:

•exert their anti-anginal effects by improving the balance between myocardial oxygen supply and demand, with specific effects listed in the table below.

• **reduce from the frequency of angina and delay the onset of angina during exercise.**

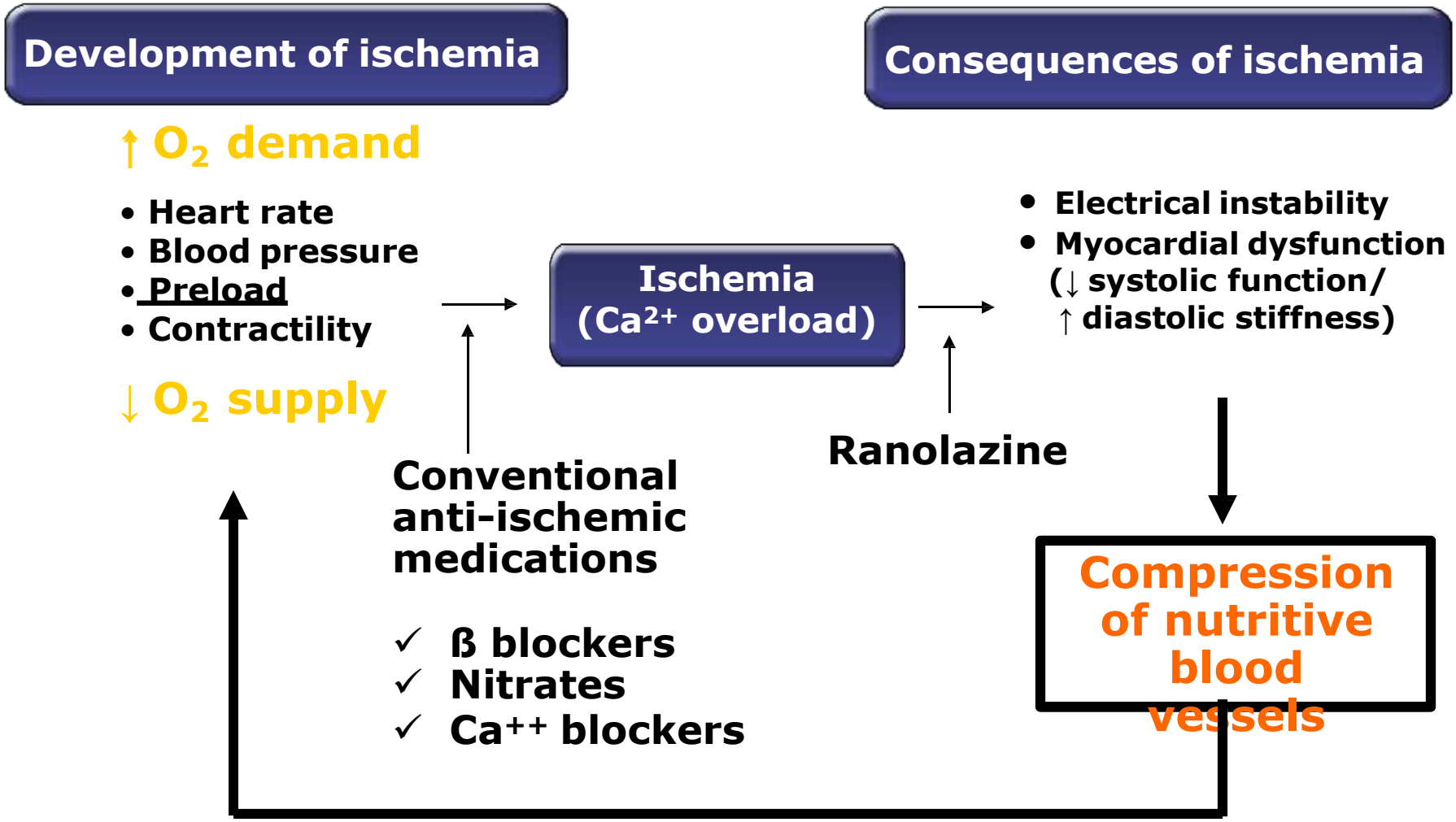
•there is **no** evidence that any of these agents prevent ACS or improve survival in patients with chronic stable angina.

Ranolazine: newly approved for the treatment of chronic stable angina in patients **unresponsive to traditional anti-anginal medications. Combination therapy with two or three anti-anginal drugs is often needed.**

	Oxygen Demand			
Anti-anginal Agent	Heart Rate	Wall Tension	Cardiac Contractility	Oxygen Supply
β-Blockers	↓	↔ or ↑	↓	↔
Calcium channel blockers				
Verapamil, diltiazem	↓	↓	↓	↑
Dihydropyridines	↔ or ↑	↓	↓	↑
Nitrates	↑	↓	↔	↑

↓, decreases; ↔, no change; ↑, increases.

Sites of action of anti-ischemia medication

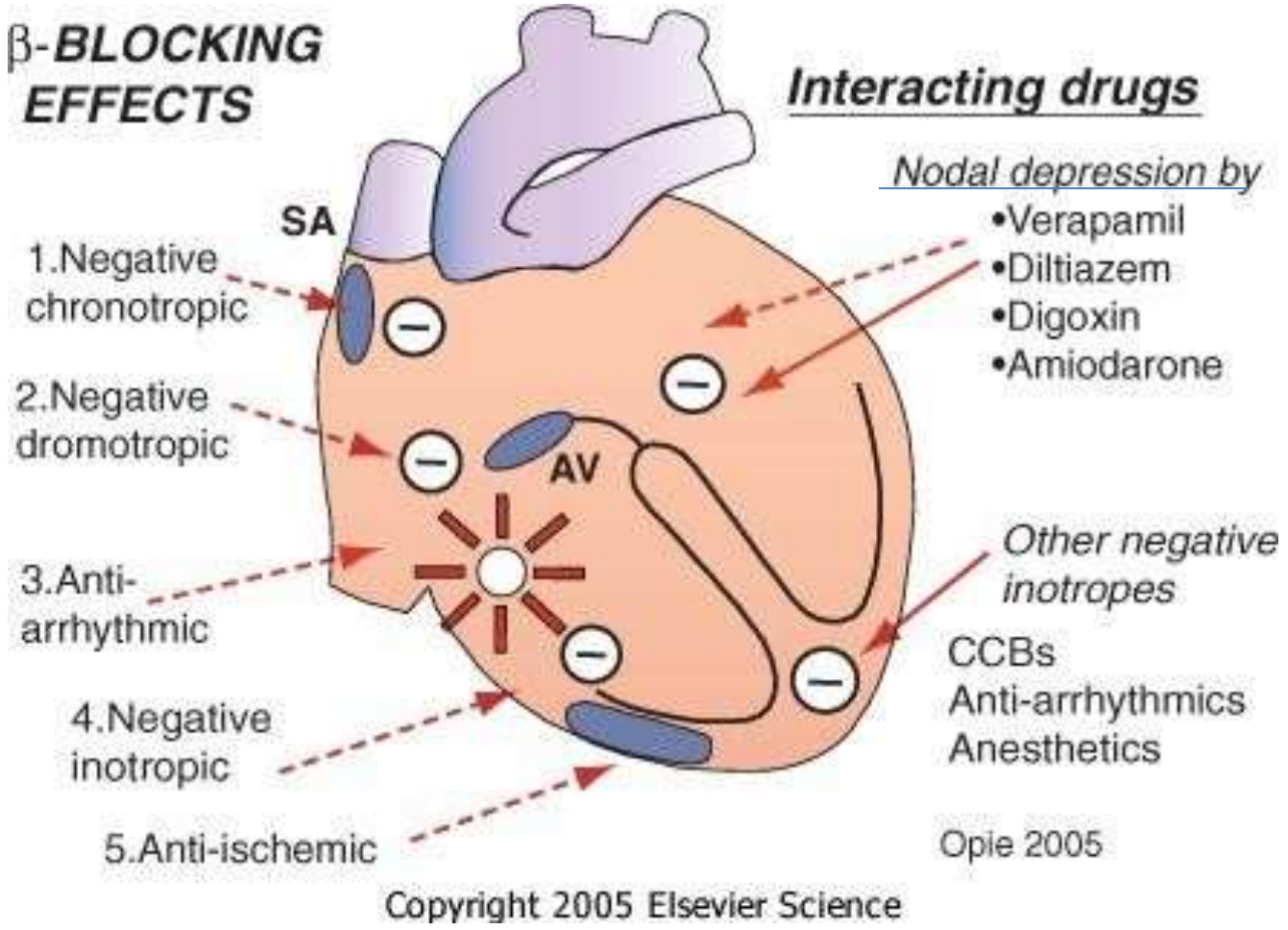


Antianginal agents - BBs

Drug Class	Beta-blockers
Mechanism of Action	Decreased myocardial oxygen demand, resulting from a reduction in heart rate, myocardial contractility, and blood pressure
Place in Therapy	**First-line in all patients without contraindications**
Specific Agents (Dosing)	Atenolol: 25-200 mg qd; Metoprolol tartrate: 100-450 mg/day in 2 to 3 divided doses; Propranolol: 80-320 mg/day in divided doses (2 to 4 times/day); Long-acting formulation: 80-320 mg qd
Side Effects	Bradycardia, hypotension, glucose intolerance, fatigue, exercise intolerance, worsening claudication
Contraindications	**Absolute**: severe bradycardia, sick sinus syndrome, AV block, unstable heart failure **Relative:** asthma, depression, peripheral vascular disease

Drug	Receptor Affinity	Intrinsic Sympathomimetic Activity	Usual Dose Range
Acebutolol	β_1-Selective	Yes	100–400 mg twice daily
Atenolol	β_1-Selective	No	25–100 mg once daily
Betaxolol	β_1-Selective	No	5–20 mg once daily
Bisoprolol	β_1-Selective	No	2.5–10 mg once daily
Carvedilol	α_1, β_1, and β_2	No	6.25–25 mg twice daily
Labetalol	α_1, β_1, and β_2	Yes, at β_2-receptors	100–400 mg twice daily
Metoprolol	β_1-Selective	No	50–100 mg twice daily (once daily for extended-release)
Nadolol	β_1 and β_2	No	40–120 mg once daily
Penbutolol	β_1 and β_2	Yes	10–40 mg once daily
Pindolol	β_1 and β_2	Yes	10–40 mg twice daily
Propranolol	β_1 and β_2	No	20–80 mg twice daily (60–180 mg once daily for long-acting formulation)
Timolol	β_1 and β_2	No	10–20 mg twice daily

Cardiac effects of β-adrenergic blocking drugs at the levels of the SA node, AV node, conduction system, and myocardium



Antianginal agents - CCBs

Drug Class	Calcium channel blockers
Mechanism of Action	Dilation of systemic and coronary **arteries**, leading to an increase in coronary blood flow and decreasing myocardial oxygen consumption
Place in Therapy	First-line in patients **with contraindications to beta-blockers** and in patients with **unacceptable adverse events or inadequate symptom control** on monotherapy with beta-blockers
Specific Agents (Dosing)	**Amlodipine**: 5-10 mg**/day** (**5 mg/day** in **elderly** patients) **Diltiazem**: ER capsule: 120-180 mg **qd** (max dose 480 mg/day); ER tablet: 180-360 **mg/day;** IR tablet: 180-360 mg/day in divided doses **Felodipine: 2.5-10 mg qd** **Nifedipine**: IR capsule: 10-30 mg tid; **SR tablet: 30-60 mg qd** V**erapamil**: 240-480 mg/day in 3 to 4 divided doses (**40 mg tid in elderly patients** and **those with small frames**)
Side Effects DD: digoxin	Bradycardia, hypotension, constipation, worsening of heart failure, peripheral edema, agent specific events, prolongation of QT-interval (bepridil), **AV-block (verapamil, diltiazem**), **excessive heart rate elevation (nifedipine)**
Contraindications	DHP: h**ypersensitivit**y. Non-DHP: **acute MI with pulmonary congestion**, **Wolf Parkinson-White syndrome**, **AV block**, hypersensitivity, **symptomatic hypotension**, **sick sinus syndrome**, **cardiogenic shock**, **heart failure (verapamil)**

Antianginal agents - Nitrates

Drug Class	Nitrates
Mechanism of Action	Vasodilation of peripheral veins and arteries, thus decreasing myocardial oxygen demand through a **reduction in preload**
Place in Therapy	**Treatment of angina in patients without compelling indications for other antianginal therapies, or as adjunct therapy**
Specific Agents (Dosing)	***Isosorbide dinitrate*** **Oral (IR)**: 5-40 mg 4 times/day; **Oral (SR)**: 40 mg every 8-12 h; **Sublingual**: **2.5-5 mg every 5-10 min** (max **3 doses in 15-30** min), can also be used as **prophylaxis** 15 min prior to activities that provoke angina **Isosorbide mononitrate**: **Regular tablet**: **5-20 mg bid**, with **at least 12 h separating doses**; **ER tablet**: initiate therapy **at 30-60 mg as a single dose** in the morning, then titrate upward **every 3 days** as needed to **max daily single dose of 240 mg** **Translingual spray**: 0.4 mg/spray, q5 min (max 3 doses in 15 min)
Side Effects	Headache, dizziness, hypotension
Contraindications	Hypersensitivity to nitrates, **concurrent use of PDEs (sildenafil, tadalafil, vardenafil)**, increased intracranial pressure, symptomatic hypotension

TABLE 4–8. Nitrate Formulations and Dosing for Chronic Use

Formulation	Dose
Oral	
Nitroglycerin extended-release capsules	2.5 mg 3 times daily initially, with up-titration according to symptoms and tolerance; allow a 10–12 hour nitrate-free interval
Isosorbide dinitrate tablets	5–20 mg 2–3 times daily, with a daily nitrate-free interval of at least 14 hours
Isosorbide dinitrate slow-release capsules	40 mg 1–2 times daily, with a daily nitrate-free interval of at least 18 hours
Isosorbide mononitrate tablets	20 mg 2 times daily, with doses 7 hours apart
Isosorbide mononitrate extended-release tablets	30–120 mg once daily
Transdermal	
Nitroglycerin extended-release film	0.2–0.8 mg/hour, on for 12–14 hours, off for 10–12 hours

Glyceryl trinitrate

TABLE 6-12 Nitrate Products

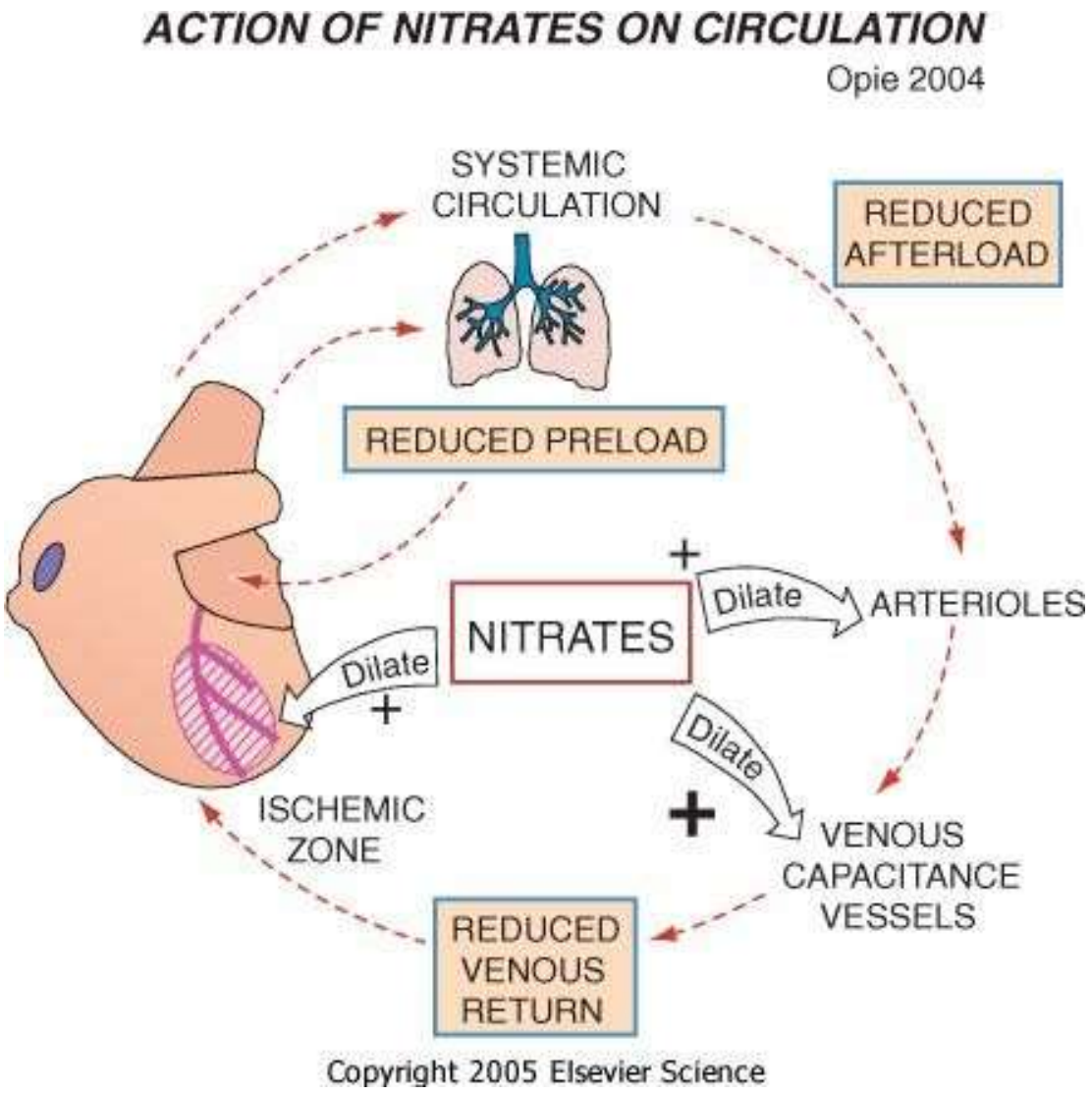
Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 minutes	5 mcg/min
Sublingual/lingual	1–3	30–60 minutes	0.3 mg
Oral	40	3–6 hours	2.5–9 mg three times a day
Ointment	20–60	2–8 hours	0.5–1 in
Patch	40–60	>8 hours	1 patch
Erythritol tetranitrate	5–30	4–6 hours	5–10 mg three times a day
Pentaerythritol tetranitrate	30	4–8 hours	10–20 mg three times a day
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 hours	2.5–5 mg three times a day
Oral	20–40	4–6 hours	5–20 mg three times a day
Isosorbide mononitrate	30–60	6–8 hours	20 mg daily, twice a day[a]

[a]Product dependent.

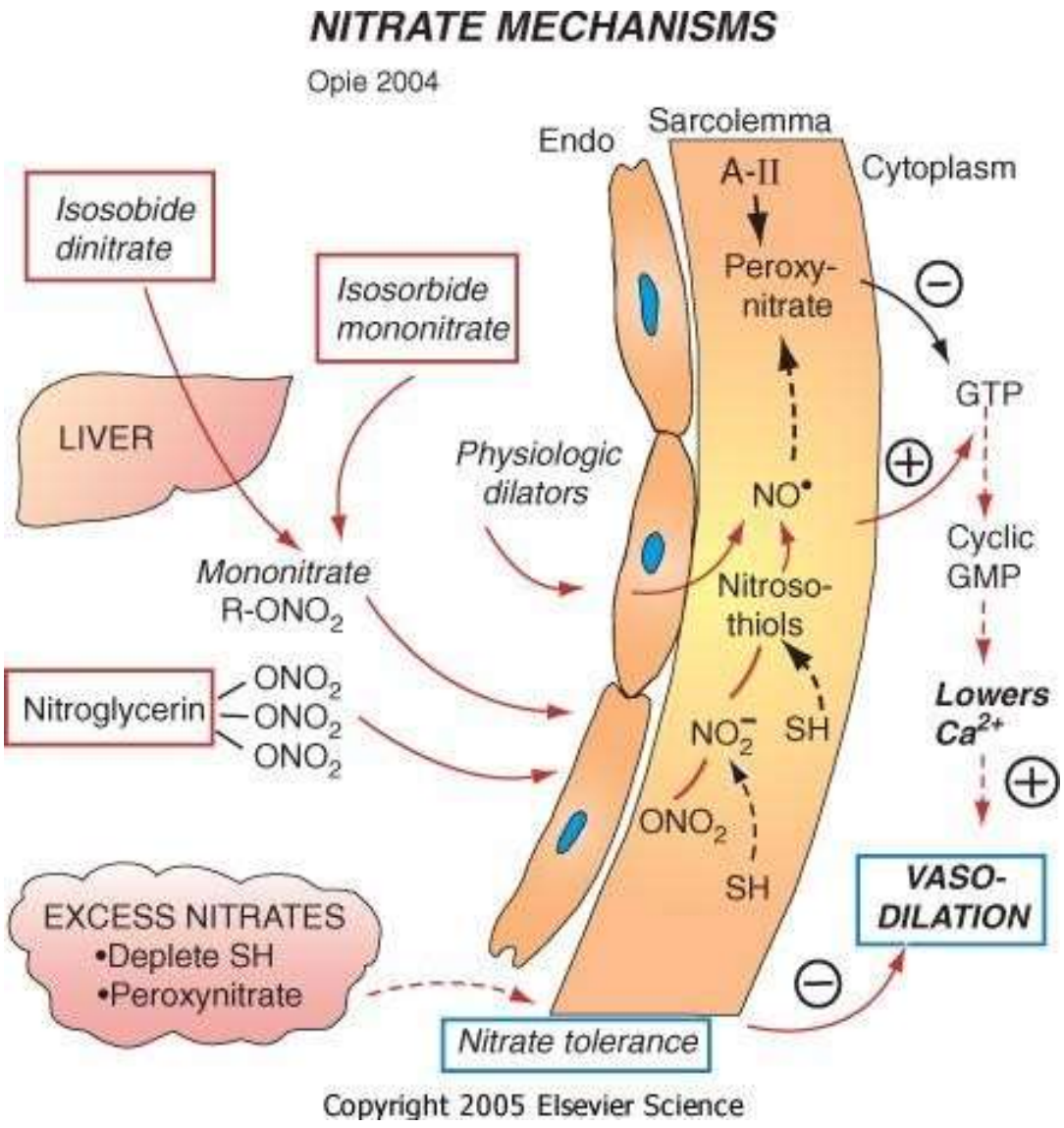
Nitrates

- Nitrate therapy should be the first step in ***managing acute attacks*** for patients with chronic stable angina if the attacks are infrequent (i.e., a few times per month) or for ***prophylaxis of symptoms*** when undertaking activities known to precipitate attacks.
- **Tolerance**
  - "**Monday disease"** – munitions workers
  - **Chronic tolerance** and **withdrawal death**
  - Proposed mechanism(s) for tolerance
    - ↓cGMP production,
    - ↓ cGMP phosphodiesterase, ↓sulfhydrl groups (cysteine) by peroxynitrate
    - Activation of neurohormonal systems
    - intravascular volume (vent. filling pressures)
  - Solution
    - **Avoid Around-the-clock (ATC)** dosing – **need 8 to 12 hr nitrate** free interval
      - Concern **for silent ischemia (rebound ischemia**) in the **nitrate free interval**
    - **acetylcysteine (sulfhydrl donor**) (**NAC has been thought to reverse nitrate tolerance** by replenishing depleted intracellular sulfhydryl groups)
    - Concomitant use of **ACE inhibitors, carvedilol or hydralazine**

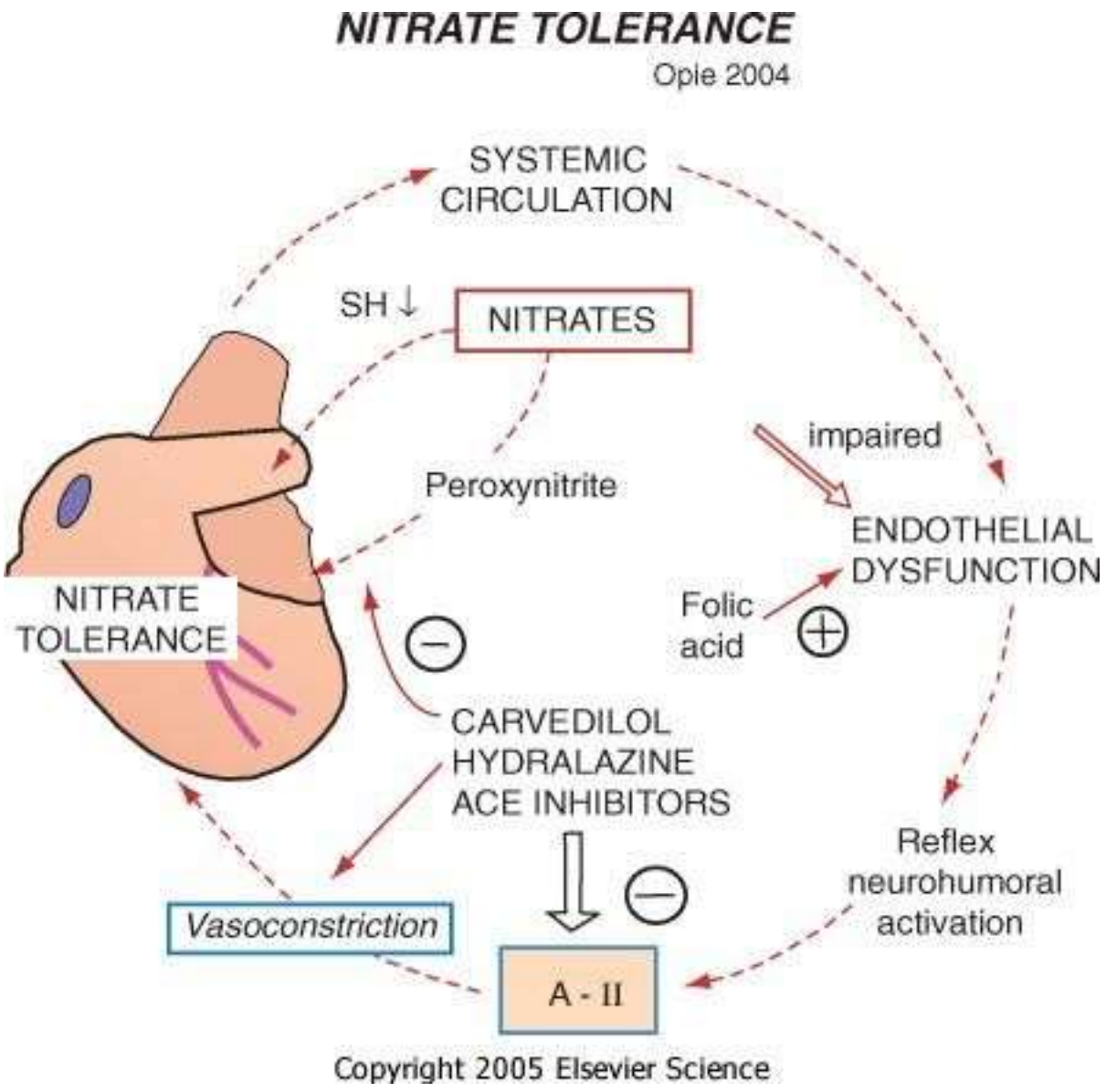
Schematic diagram of effects of nitrate on the circulation



Effects of nitrates in generating NO• and stimulating guanylate cyclase to cause vasodilation



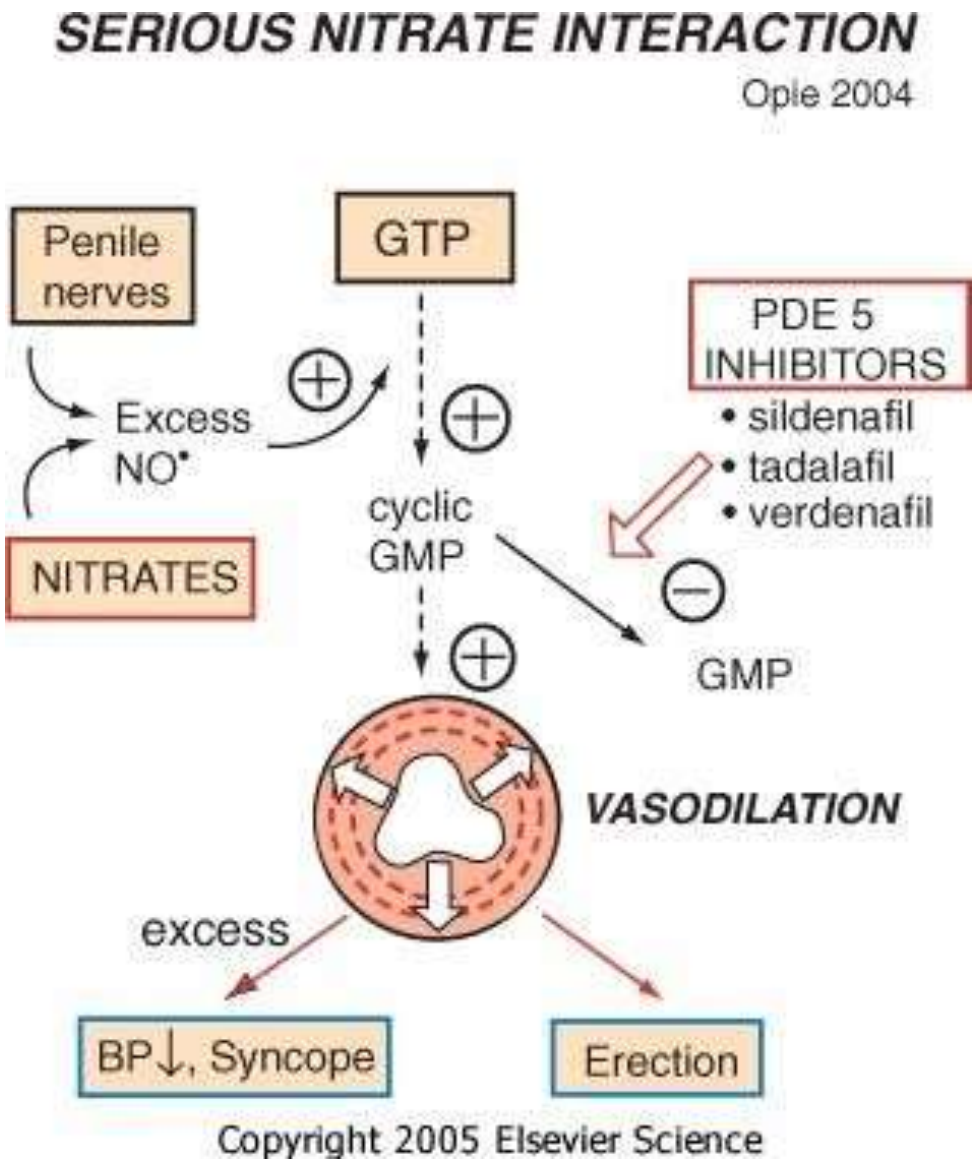
Current proposals for therapy of nitrate tolerance.



Nitrates

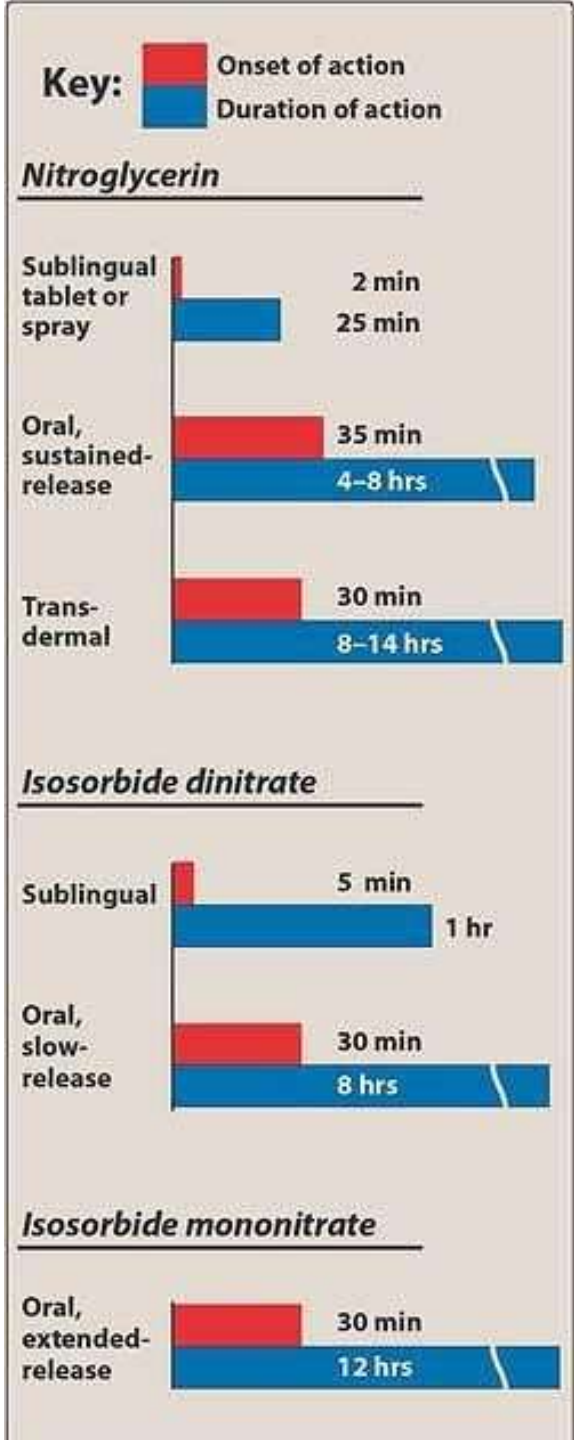
- **Patient related variables**
  - SBP < 90mmHg, HR < 50 bpm–use caution
- **Toxicity**
  - **Headache, flushing, hypotension, reflex tachycardia** and **syncope**
  - Rare: m**ethemoglobinemi**a-Due to **ability of nitrate ions to oxidize hemoglobin**
- **Patient information**
  - Concept of tolerance, side-effects, proper storage
- **Significant Drug Interactions**
  - Phosphodiesterase-5 inhibitors
    - Sildenafil, vardenafil, tadalafil – prevent breakdown of cGMP
      - Sildenafil and vardenafil (24hr washout)
      - Tadalafil (48 hr washout)
  - Heparin
    - Heparin resistance at NTG IV doses >350 mcg/min

A serious nitrate drug interaction



Nitrate preparations

- **Three groups of nitrates:**
  - Glyceryl trinitrate
  - Isosorbide dinitrate (metabolized to the mononitrate)
  - Isosorbide mononitrate



Nitrate preparations

- **IV infusions**
- **Slow-release tablets and capsules** (for majority of pts with stable angina) - cheap, administered 2-3 times D, permits nitrate free period. **Extensive first pass metabolic effect.**
- **Transdermal patches** - expensive, no flexible dosing rate and may not permit a nitrate free period.
- **Ointments** - messy!
- **Adhesive buccal tablets** - expensive, no real therapeutic advantage in regular therapy.
- **Sublingual tablets and sprays** - **rapid onset of action**, and **bypasses the live**r. For the prevention or relieve of acute attacks of pain.

Nitrate preparations

- **Main side effects**
  - Hypotension with dizziness and fainting
  - Throbbing headache

- **Advice patient to**
  - **Sit down (rather than lie or stand)**
  - For **short-acting nitrates - Spit out** or **swallow** the **tablet once angina** is **relieved**
  - **Sublingual glyceryl trinitrate** have very s**hort shelf life - s**tore **carefully and replace frequently.**

Treatment of Angina – acute attack

- All patients with a history of angina should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms.

- **During an Acute Angina attack –**
  - ***GNT Sublingual tablet*,**

    300–600 micrograms (half to 1 tablet) repeated every 3–4 minutes until pain is resolved, to a ***maximum of 2 or 3 tablets over 15 minutes.***

  - ***Sublingual spray*,**

    400–800 micrograms (1–2 sprays).

- **Sublingual nitroglycerin** can also be used **to prevent effort-induced angina** (i.e., angina that occurs **with exertion).** In this case, the patient should use sublingual nitroglycerin **2 to 5 minutes** prior to an **activity known to cause** angina, with the effects **persisting for approximately 30 minutes**.

- **Isosorbide dinitrate**, also available in a sublingual form, has **a longer half-life** with anti-anginal effects lasting **up to 2 hours.**

Counseling pts on sublingual tablets

- **Advice pt to:**
  - **Sit or lie down before use** as it may cause dizziness.
  - Place half to one tablet **under your tongue; do not swallow it;** after the pain has been relieved, you may spit out or swallow what is left of the tablet to avoid adverse effects such as headache.
  - **Call an ambulance if 2 or 3 tablets over 15 minutes do not relieve pain.**
  - It is important **to store these tablets properly** or they may not work as well. Keep them in the original glass bottle away from moisture, heat and light. Do not carry them close to your body. **Write the date** on the bottle when you open it and discard any unused **tablets 3 months later.**
  - **Never to take sildenafil, tadalafil or vardenafil** (contraindicated)
  - **Common adverse effects** include headache, flushing, palpitations, orthostatic hypotension, fainting, peripheral edema

Counseling pts on Sublingual spray

- **Advice pt to :**
  - **Prime the spray before using it** for the first time by pressing the nozzle 5 times, spraying it into the air. Prime it with 1 spray if it hasn't been used for 7 days. Prime it with 5 sprays if it hasn't been used for more than 4 months.
  - When ready to use, **aim the spray under the tongue** and press the nozzle once; do not inhale the spray.
  - **Call an ambulance** if **2 sprays over 15 minutes** do **not relieve pain.**

Case study

- DD came back to your pharmacy later on with a script for *Imtrate SR* (Isosorbide Mononitrate).

- **What would you counsel the patient on?**

Counseling on Isosorbide Mononitrate

- Initially 30–60 mg **once daily**, increased up to 120 mg once daily if necessary.
  - **twice daily dosing with isosorbide mononitrate is *not* recommended**, as there will be no nitrate-free interval and tolerance will be more likely to develop

- Swallow whole; do not crush or chew the tablet.

- **Take at the time of day when angina is most frequent**, e.g. at night for nocturnal angina or in the morning for daytime angina.

- **Isosorbide mononitrate** is ***not*** **recommended for treatment of acute episodes of angina** because of **its slow onset of action**

- Do not cut Imtrate® in half (there is insufficient evidence to show that a halved tablet delivers half the dose of one full tablet (the other products can be halved)

Antianginal agents - Ranolazine

Drug Class	Ranolazine
Mechanism of Action	Mechanism of action not clear; possible **shift in the production of ATP away from oxidation of fatty acids**, thus favoring the **more oxygen-efficient oxidation** of carbohydrates.* **Altering the trans-cellular late sodium current**
Place in Therapy	**Combination therapy** with amlodipine, nitrates, or beta-blockers in patients **not well controlled with monotherapy on these agents**
Specific Agents (Dosing)	Initiate at **500 mg bid**; titrate up to **max dose of 1,000 mg bid**
Side Effects	Dizziness, headache, constipation, nausea, Torsades de pointes
Contraindications	Dizziness, headache, constipation, nausea. **Severe hepatic dysfunction**, **concurrent use of QT-interval-prolonging agents or preexisting QT interval prolongation at baseline, concurrent therapy with CYP3A inhibitors**

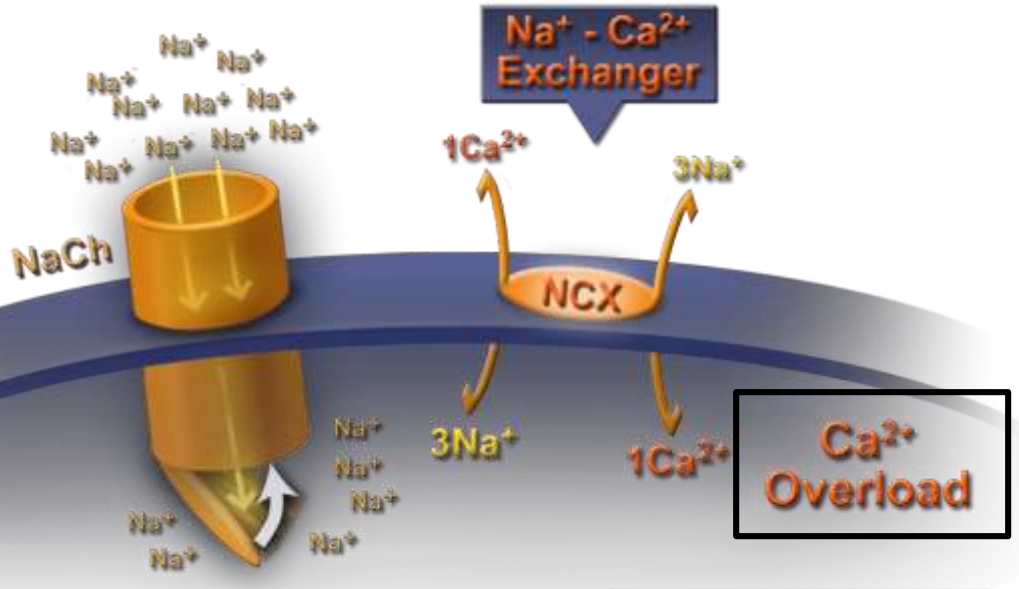
*trimetazidine

Consequences associated with dysfunction of late sodium current

- **Diseases** (eg, ischemia, heart failure)
- **Pathological milieu** (reactive O_2 species, ischemic metabolites)
- **Toxins and drugs** (eg, ATX-II, etc.)

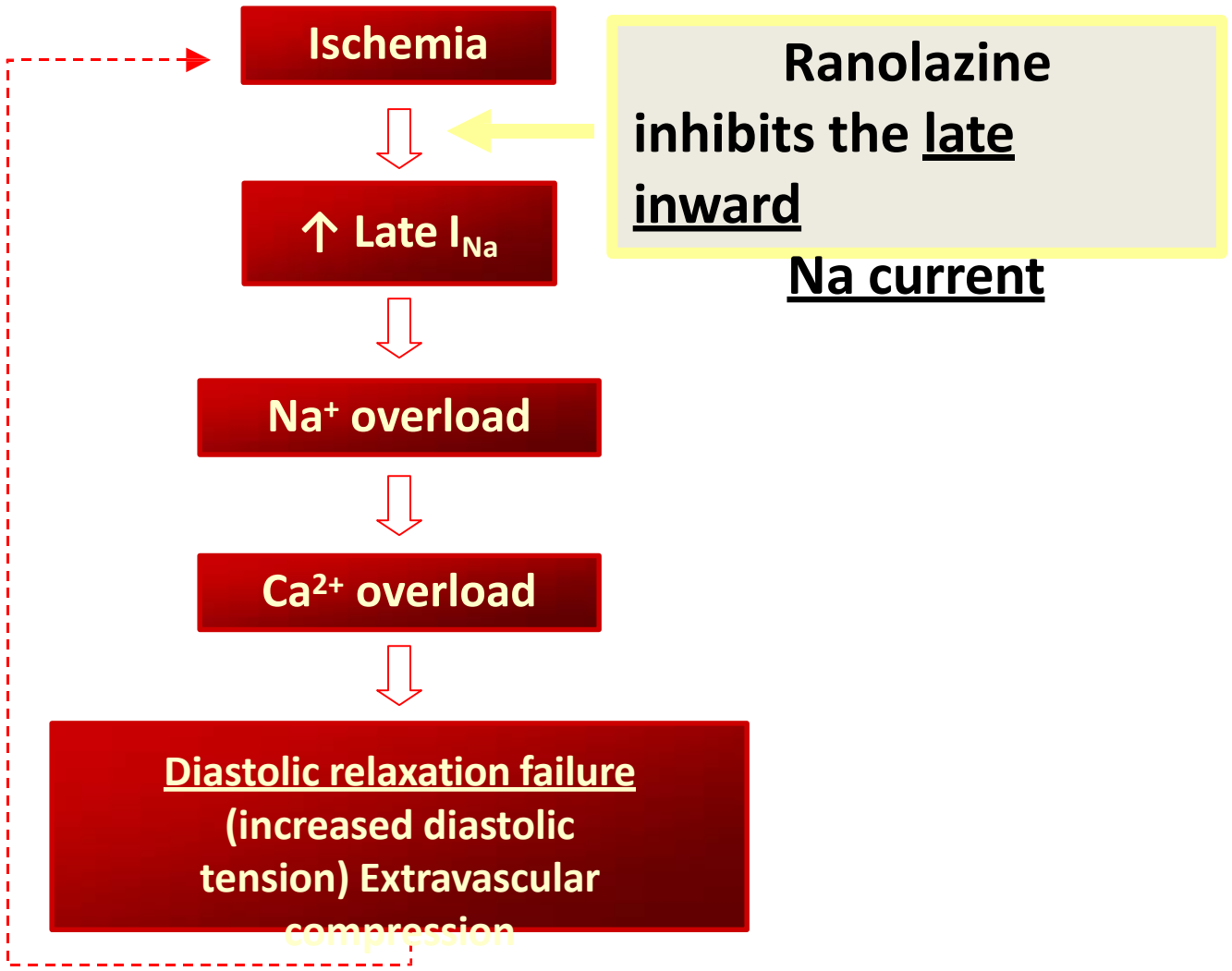
Na^+ channel

(Gating mechanism malfunction)



Mechanical dysfunction	Oxygen supply and demand	Electrical instability
Abnormal contraction and relaxation	Increase ATP consumption	Early after potentials
↑ diastolic tension (↑LV wall stiffness)	Decrease ATP formation	Beat-to-beat ΔAPD
		Arrhythmias (VT)

Ranolazine: Mechanism of action



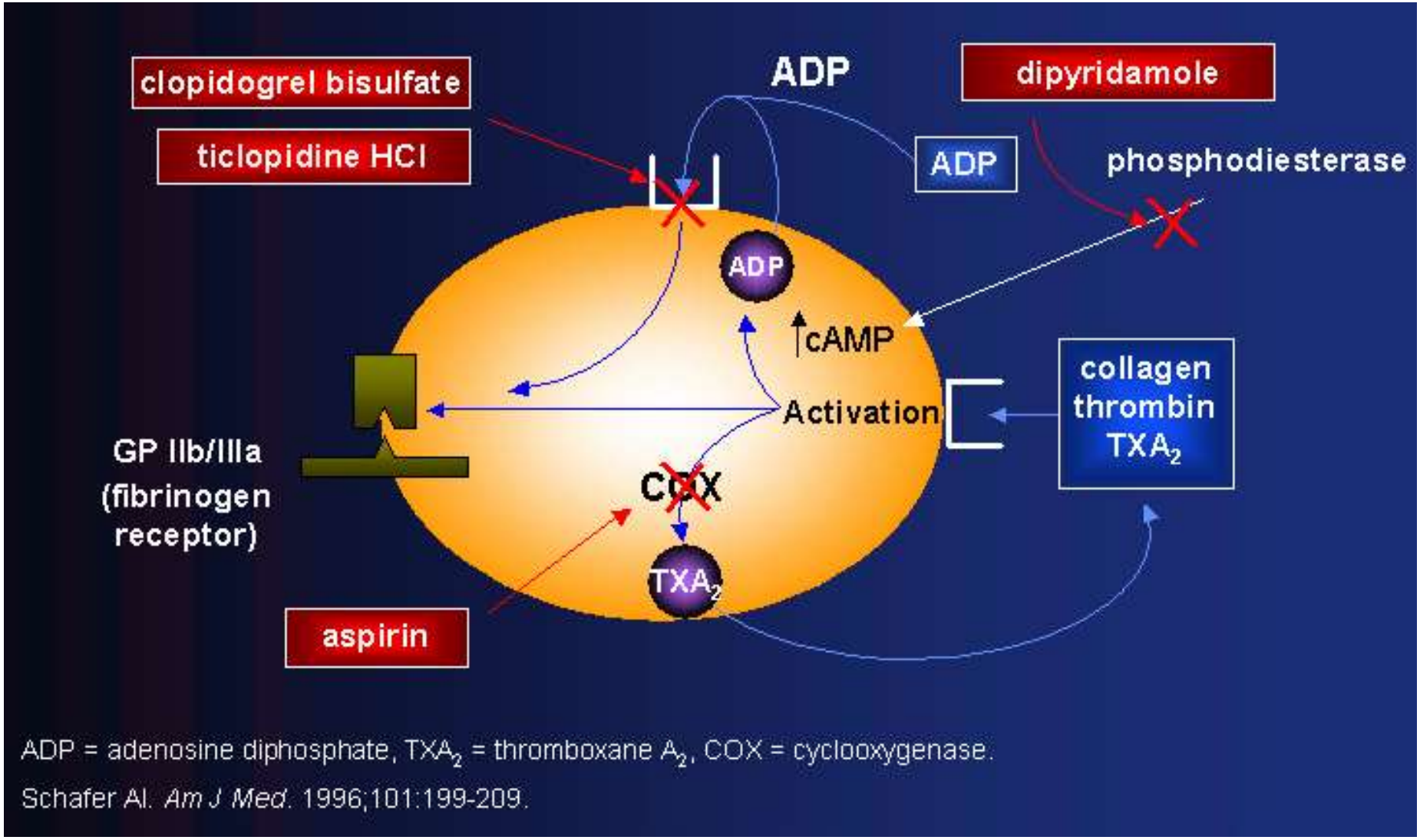
Pharmacotherapy to prevent acute coronary syndromes and death

Antiplatelet Agents

Platelet cascade in thrombus formation:

- **Platelet adhesion**
  - Exposure to subendothelial matrix
- **Platelet activation** and **secretion**
  - changes in the shape of platelets, **activation of the glycoprotein IIb/IIIa receptor**, and induction of platelet coagulant activity
  - **thromboxane A2 (activation)**, thrombin, norepinephrine, collagen, and **adenosine diphosphate (aggregation)**
- Platelet **aggregation--fibrinogen**
  - mediated by the binding of **adhesive proteins** to the **new ligand-receptive** form of the **glycoprotein IIb/IIIa receptor**
- Platelet **integration** with **coagulation factors**

Oral antiplatelet agents



ADP = adenosine diphosphate, TXA_2 = thromboxane A_2, COX = cyclooxygenase.

Schafer AI. *Am J Med*. 1996;101:199-209.

Antiplatelet Agents

- In patients with stable or unstable angina, aspirin has been consistently shown to reduce the risk of major adverse cardiac events, particularly MI.
- Antiplatelet therapy with aspirin should be considered for all patients without contraindications, particularly in patients with a history of myocardial infarction.

- **Aspirin** doses of **75 to 162 mg** daily have been shown to be **cardioprotective.**
- If **aspirin** is contraindicated (e.g., **aspirin allergy**, **active peptic ulcer disease**, or **active internal bleeding**) or is not tolerated by the patient, other antiplatelet agents such as **clopidogrel** should be considered.
- Recent studies have suggested that combination antiplatelet therapy may be synergistic in reducing the risk of IHD-related events.
  - In patients **with ACS**, the **combination of aspirin and clopidogrel 75 mg daily** for up to **9 months** was more effective than aspirin alone in decreasing the risk of death, MI, and stroke.
  - This combination also **prevents complications following PCI**

Statins

- To control risk factors and prevent major adverse cardiac events**, statin therapy should be considered in all patients with ischemic heart disease**, particularly in those with elevated low-density lipoprotein cholesterol.

- Statins are **potent lipid-lowering agents**, possess **non–lipid-lowering effects** that may provide additional benefit to patients with IHD, and have been shown to reduce morbidity and mortality in patients with IHD. Based on these benefits, statins are generally considered the **drugs of choice in patients with dyslipidemias.**

- Moreover, based on evidence that statins improve outcomes in patients with IHD and “normal” LDL cholesterol concentration, statins should be considered in all patients with IHD at high risk of major adverse cardiac events, **regardless of baseline LDL cholesterol.**

ACE-I's and ARB's

- In the absence of contraindications, ACE inhibitors should be considered in ischemic heart disease patients who also have
  - **I. diabetes mellitus,**
  - **II. left ventricular dysfunction,**
  - III. history of **myocardial infarction,**
  - – or any combination of these.

- In addition, they should also be considered in all patients with IHD and in patients at high risk for developing IHD

- **Angiotensin receptor blockers** may be used in patients who cannot tolerate ACE inhibitors due to side effects (e.g., **chronic cough**).

- There are far more data supporting the use of ACE inhibitors in IHD. Therefore, ACE inhibitors should remain first-line in patients with a history of MI, diabetes, or left ventricular dysfunction.

TABLE 4–5. Doses of ACE inhibitors and Angiotensin Receptor Blockers Indicated in Ischemic Heart Disease (IHD).

Drug	Indications	Usual Dosage in IHD
Angiotensin-Converting Enzyme Inhibitors		
Captopril	HTN, HF, post-MI, diabetic nephropathy	6.25–50 mg 3 times daily
Enalapril	HTN, HF	2.5–40 mg daily in 1–2 divided doses
Fosinopril	HTN, HF	10–80 mg daily in 1–2 divided doses
Lisinopril	HTN, HF, post-MI	2.5–40 mg daily
Perindopril	HTN, IHD	4–8 mg daily
Quinapril	HTN, HF, post-MI	5–20 mg twice daily
Ramipril	HTN, high-risk for IHD, HF, post-MI	2.5–10 mg daily in 1–2 divided doses
Trandolapril	HTN, HF, post-MI	1–4 mg daily
Angiotensin Receptor Blockers		
Candesartan	HTN, HF	4–32 mg daily
Valsartan	HTN, HF, post-MI	80–320 mg daily in 1–2 divided doses

HF, heart failure; HTN, hypertension; MI, myocardial infarction.

Alternative Therapies

- Most have **not shown to provide any clinical** benefit in persons with **chronic stable** angina, and in **some cases** may pose **greater CV risk**
  - Fish oils
  - Garlic
  - Folic acid (lower homocysteine levels ?)
  - Antioxidant vitamins (E and C)
  - Hormone/estrogen replacement therapy
  - Chelation therapy

Mechanical Revascularization

- **Many patients** with **chronic stable angina** can be **successfully managed** by **pharmacologic therapy alone**.

- However, for those with **refractory symptoms** or **in certain high-risk subgroups**, revascularization procedures, including **CABG** surgery and percutaneous transluminal coronary angioplasty (**PTCA**), are recommended.

Interventional Therapies

- PCI vs. CABG
  - Decision multifactorial – risk factors, LVF, # of diseased vessels and % of occlusions

- PCI
  - Several catheter-based interventions may be used during PCI, including:
    - Percutaneous transluminal coronary angioplasty (**PTCA)**;
    - Intracoronary **bare metal stent** placement;
    - Intracoronary **drug-eluting stent** placement;
    - Rotational **atherectomy**
  - Tremendous advances over the past 5-10 years, especially in regards to stent technology

- CABG
  - **Left main coronary artery disease** or **severe** **proximal LAD disease**
  - **>3 vessel involvement**

LAD: left anterior descending artery

Coronary Artery Bypass Graft Surgery

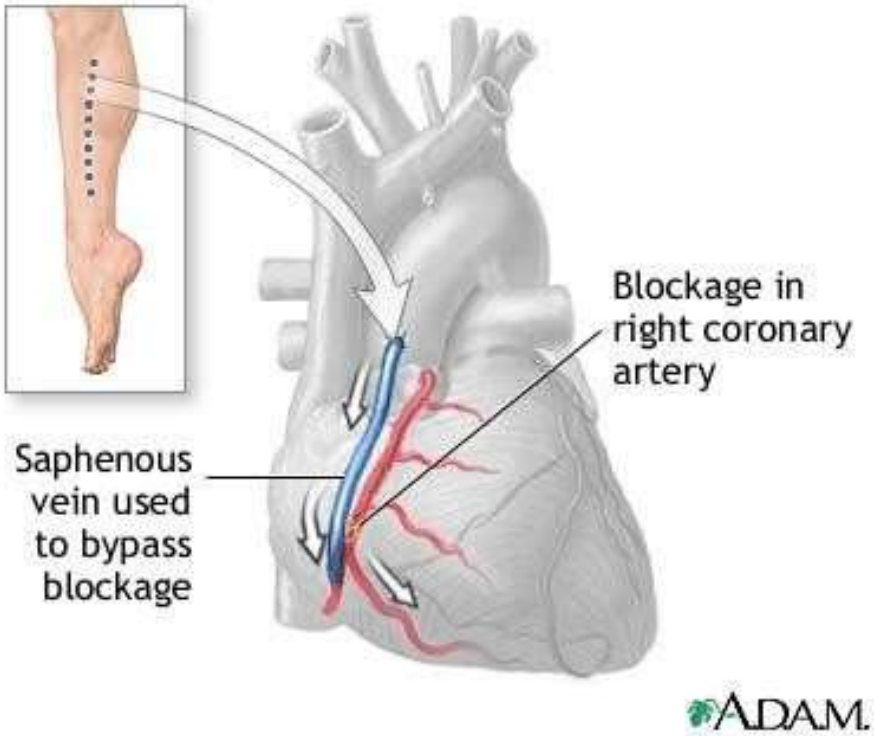
- **Coronary artery bypass surgery involves the placement of grafts to bypass stenosed native coronary arteries**

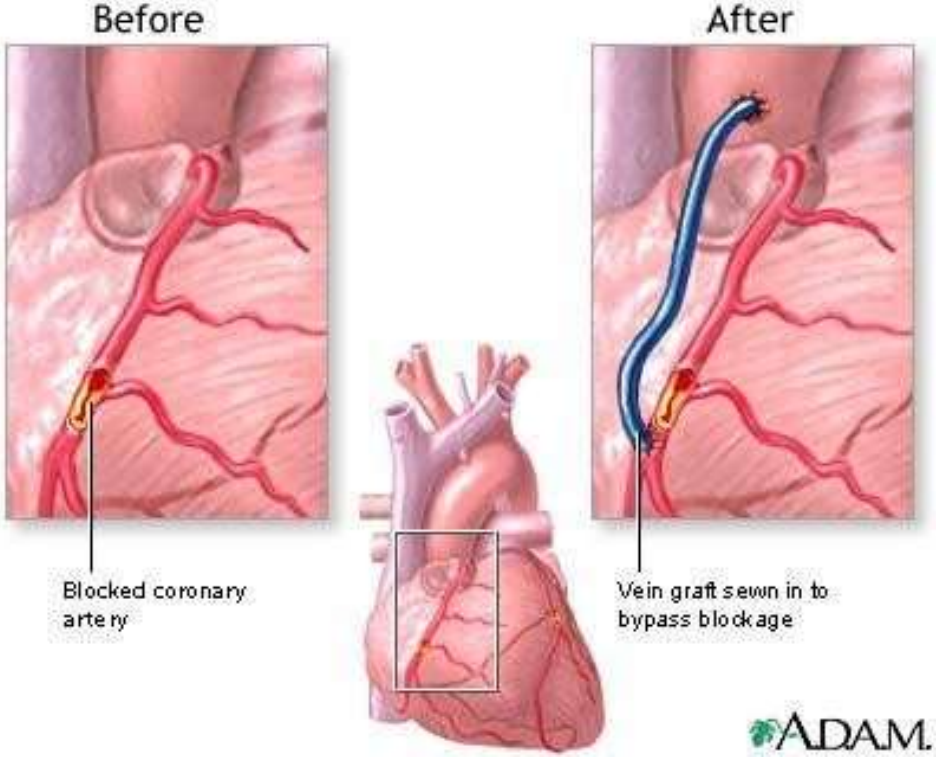
- The grafts are usually **saphenous veins or arteries** (sometimes the left internal mammary artery).

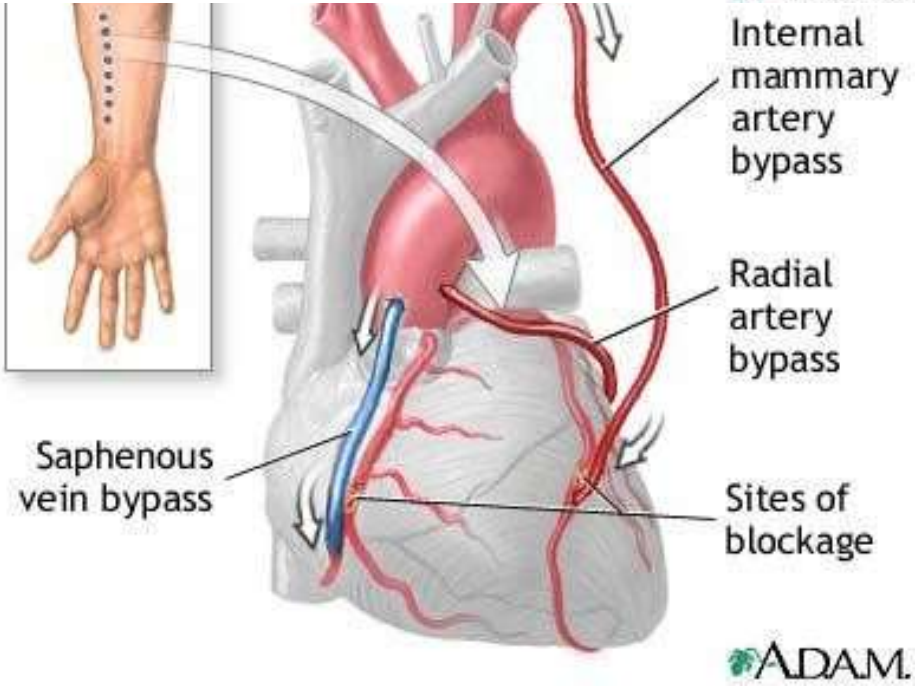
- suturing segments of saphenous vein between the ascending aorta and to the coronary arteries distal to their stenotic narrowings

- Antiplatelet therapy with aspirin has been shown to improve long-term graft patency rates,

- Aggressive lipid-lowering to achieve an LDL cholesterol < 100 mg/dl has been shown to slow the development of atherosclerosis within bypass grafts


Blockage in right coronary artery
Saphenous vein used to bypass blockage
ADAM.


Before
After
Blocked coronary artery
Vein graft sewn in to bypass blockage
ADAM.


Internal mammary artery bypass
Radial artery bypass
Saphenous vein bypass
Sites of blockage
ADAM.

Percutaneous Transluminal Coronary Angioplasty and Intracoronary Stents.

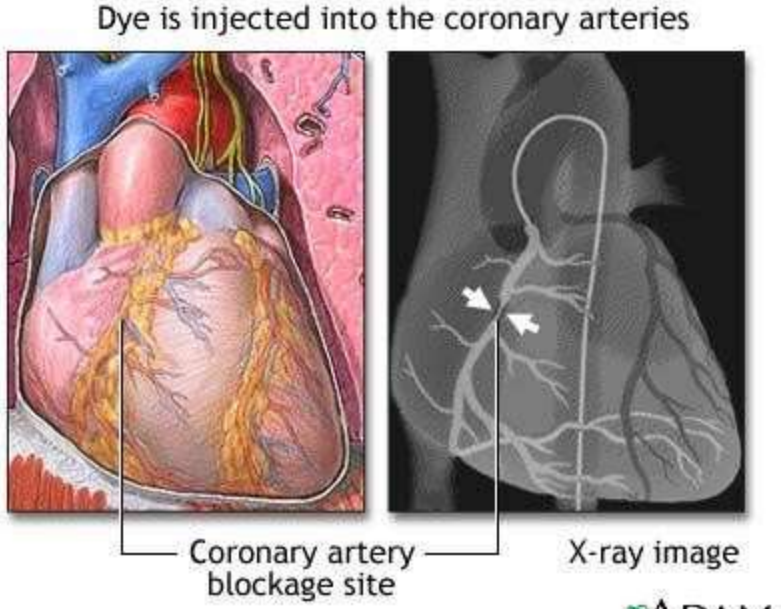
- PTCA is now widely successful in relieving ischemia in patients with one- and two-vessel lesions

- In more than 60% of angioplasty procedures today, metal tubular stents are permanently deployed in the vessel, leaving no, or minimal, residual stenosis and a much improved rate of occlusion or restenosis, **using antiplatelet protocols that include aspirin plus clopidogril.**

- can be easily repeated. The mortality is low (**0.2%**), and the **most serious late complication** is **restenosis.**

- Drug eluting stents are impregnated with low concentrations of **antiproliferative medications**, such as **paclitaxel or sirolimus,** which are slowly released locally within the coronary artery → **inhibit restenosis**

Interventional catheterization



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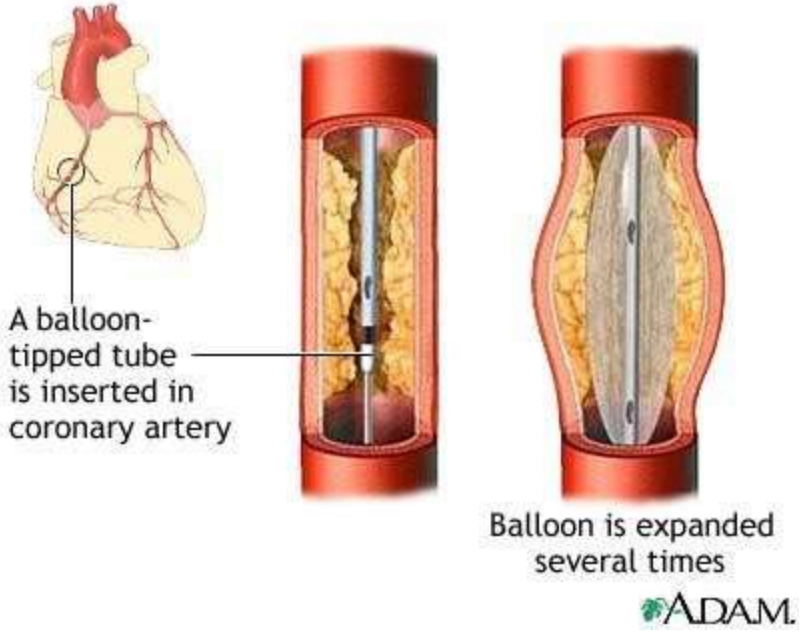

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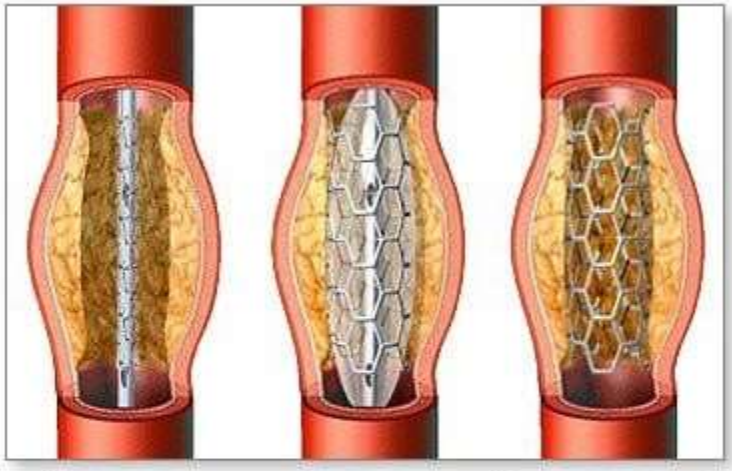

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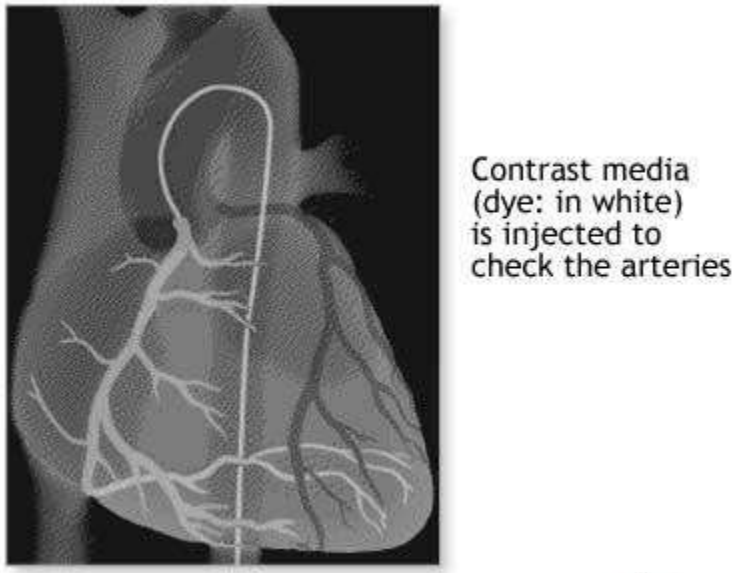
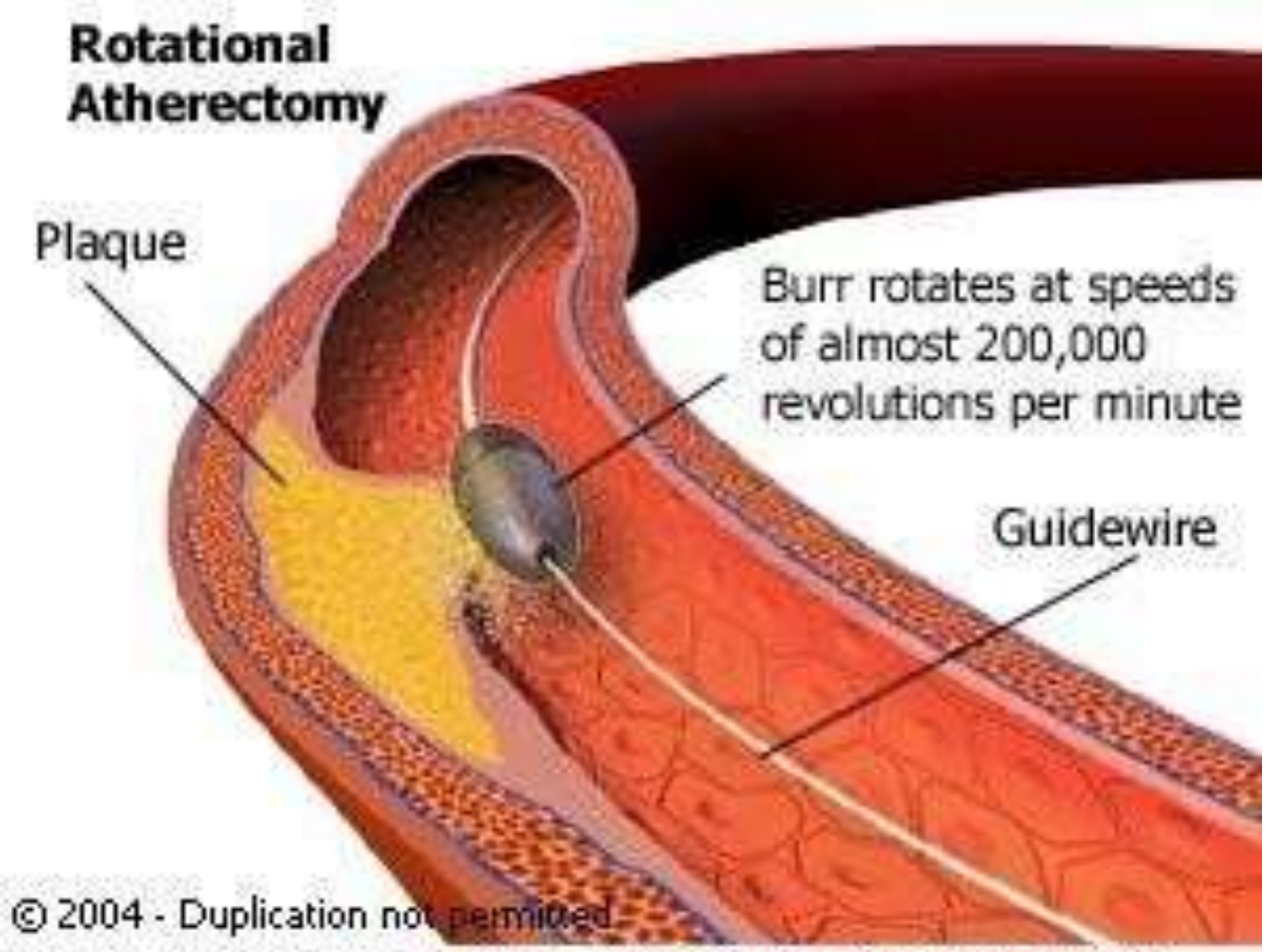


ADAM.

Rotational atherectomy



A catheter equipped with a rotablator is guided to the blockage. Using a diamond-studded tip, the rotablator pulverizes calcified plaque. The small particles can move safely through the circulatory system and out of the body.

Revascularization

Left Main CAD Revascularization

Class I

1. CABG to improve survival is recommended for patients with significant (≥50% diameter stenosis) left main coronary artery stenosis.[328–334] (*Level of Evidence: B*)

Non-Left Main CAD Revascularization

Class I

1. CABG to improve survival is beneficial in patients with significant (≥70% diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery) or in the proximal LAD artery plus 1 other major coronary artery.[125,330,334,358–360] (*Level of Evidence: B*)
2. CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (≥70% diameter) stenosis in a major coronary artery. (*CABG Level of Evidence: B*[122,378,379]; *PCI Level of Evidence: C*[378])

Recommendations for Revascularization With PCI (Percutaneous Coronary Intervention) and CABG in Patients With Stable Angina

1. CABG for patients with significant left main coronary disease. **(>70% stenosis)**
2. CABG for patients with 3-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction less than 50%).
3. CABG for patients with 2-vessel disease with significant proximal left anterior descending CAD **(>70%) and either**

   abnormal LV function (ejection fraction < 50%) ***/or***

   demonstrable ischemia on noninvasive test
4. PCI for patients with 2 or 3-vessel disease with significant proximal LAD CAD, who have anatomy suitable for catheter-based therapy and normal LV function and who do ***not*** have treated diabetes (IB)
5. PCI or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD
6. In patients with prior PCI, CABG or PCI for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing (IB)
7. PCI or CABG for patients who have not been successfully treated by medical therapy and can undergo revascularization with acceptable risk.(IB)

Management of angina

-Stable exertional angina

-Variant angina

-Silent Ischemia

Stable Angina

- All patients should receive the following unless a contraindication is present:
  - Aspirin
  - Beta-blockers
  - ACE inhibitor (if indication present)
  - LDL-lowering therapy
  - SL NTG
  - Calcium channel blockers or nitrates
    - For contraindication or intolerance to β-blockers, lack of efficacy with β-blocker in controlling symptoms.

Treatment Strategies for Chronic Stable Angina

- Angina Treatment Mnemonic
- A– aspirin, anti-anginals
- B – B-blockers and blood pressure
- C – cholesterol and cigarettes
- D– diet and diabetes
- E –education and exercise

Stable Angina

- **β-blocker**s may be **most effective** in those persons who have a **high resting heart rate** and those with a **relatively fixed anginal threshold**

- **Nitrate therapy** for **immediate relief of symptoms** and as **prophylaxis** for symptoms **during exertion**
  - SL taken 5 minutes prior to activity provides for an adequate response in most patients for a duration of ~ 30 minutes
  - Should **not be first-line therapy unless beta-blockers and CCB** are **contraindicated or not tolerated**
  - Tolerance decreases efficacy

- Calcium channel blockers – potential for improving supply and demand, and may be used in place of beta-blockers as initial therapy
  - Useful in **variable threshold** for **exertion angina**

Vasospastic Angina

- Patients are typically younger and have fewer cardiovascular risk factors. Higher rate of smoking
  - Assessment of risk factors and aggressive lifestyle modifications
- Acute attack
  - Nitrates
- Chronic therapy
  - Nitrates and calcium channel blockers
  - Avoid B-blockers

Silent Ischemia

- **Occurrence**
  - As common as 80% with CAD – associated with extent of disease

- **Classification**
  - Class I: Do **not experience angina** at any time
  - Class II: Have **both symptomatic and asymptomatic angina**

- **Treatment**
  - Beta-blockers are first-line
  - CCB are acceptable substitute –but do not confer as great of a benefit with diurnal surge
  - **Combination therapy often provides superior efficacy to monotherapy with any agent**

Coexisting Conditions

Condition	**Use recommended**	**Caution or avoid**
HTN	BB, CCB	
CHF / LVSD	Nitrate, BB*	CCB (nondihydropyridine)
Post-MI	BB (w\o ISA)	CCB (nondihydropyridine)
Hyperlipidemia		BB
SVT, V-arrhythmia	BB CCB (nondihydropyridine)	
COPD / asthma		BB
Raynaud's Disease		BB

* metoprolol SR, carvedilol or bisoprolol

Evaluation of Outcomes

- Symptoms of angina
  - Symptomatic improvement in exercise capacity
  - Fewer symptoms at same level of exertion
  - Questionnaires
  - Effects of optimized therapy
    - Symptom improvement over 2 to 4 weeks and remain stable unless disease progression occurs

- Cardiac performance
  - Assessment only if medical management is failing or in very high risk patients

- Risk factors
  - Assess and reassess

Monitoring Therapy

- **Monitoring Issues (B-blockers, CCBs, Nitrates)**

  (Assess for drug effectiveness and safety)

  – With all agents monitor
    - Blood pressure, clinical signs and symptoms of hypotension (mental status, syncope, etc.)
    - *ECG (*for *HR, intervals, rhythm etc.) -not nitrates*
    - *Edema (CCBs)*

  – **Side effects** which may be important to pursue include: potential **metabolic complications** with **B-blockers (lipids, glucose)**

Major modifications in ACC/AHA guidelines

- For hypertensive patients with well established coronary artery disease, it is useful to add blood pressure medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve target blood pressure.

- Adding **plant stanol/sterols (2 g per day) and/or viscous fiber** (greater than 10 g per day) is **reasonable to lower LDL-C.**

- Reduction of LDL-C to **less than 70 mg/dL** or high-dose statin therapy is **reasonable.**

- Aspirin should be started at 75 to 162 mg per day and continued indefinitely in all patients unless contraindicated.

- ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction less than or equal to 40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated.

Major modifications in ACC/AHA guidelines

- Angiotensin receptor blockers are recommended for patients who have hypertension, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had a myocardial infarction with left ventricular ejection fraction less than or equal to 40%.
- **Angiotensin receptor blockers** may be considered in **combination with ACE inhibitors for heart failure due** to left **ventricular systolic dysfunction.**

- Aldosterone blockade is recommended for use in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a beta blocker, have a left ventricular ejection fraction less than or equal to 40%, and have either diabetes or heart failure.

- It is **beneficial to start and continue beta-blocker** therapy **indefinitely in all patients who have had** MI, **acute coronary syndrome**, **or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.**
- An annual influenza vaccination is recommended for patients with cardiovascular disease.

Distinctive features of ESC guidelines

- **ASA dose** should be **75 mg**
- Statin therapy for all CAD pts
- **High-dose statins** for high risk pts with CAD
- **ACE-I's for all CAD patients**
- **Beta-blockers post MI or in HF**