

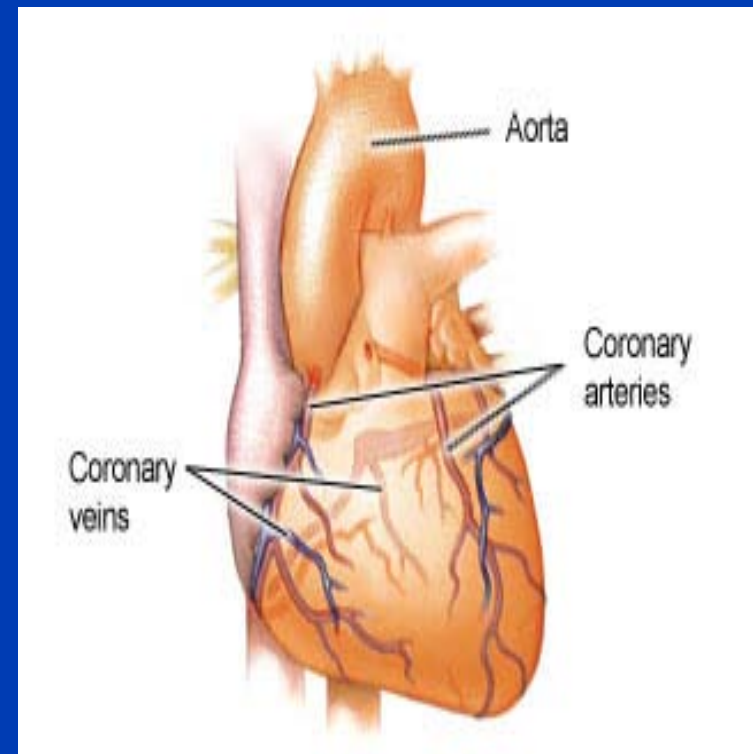
Internal Medicine

Lecture 2. Atherosclerosis

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Blood Supply To The Heart

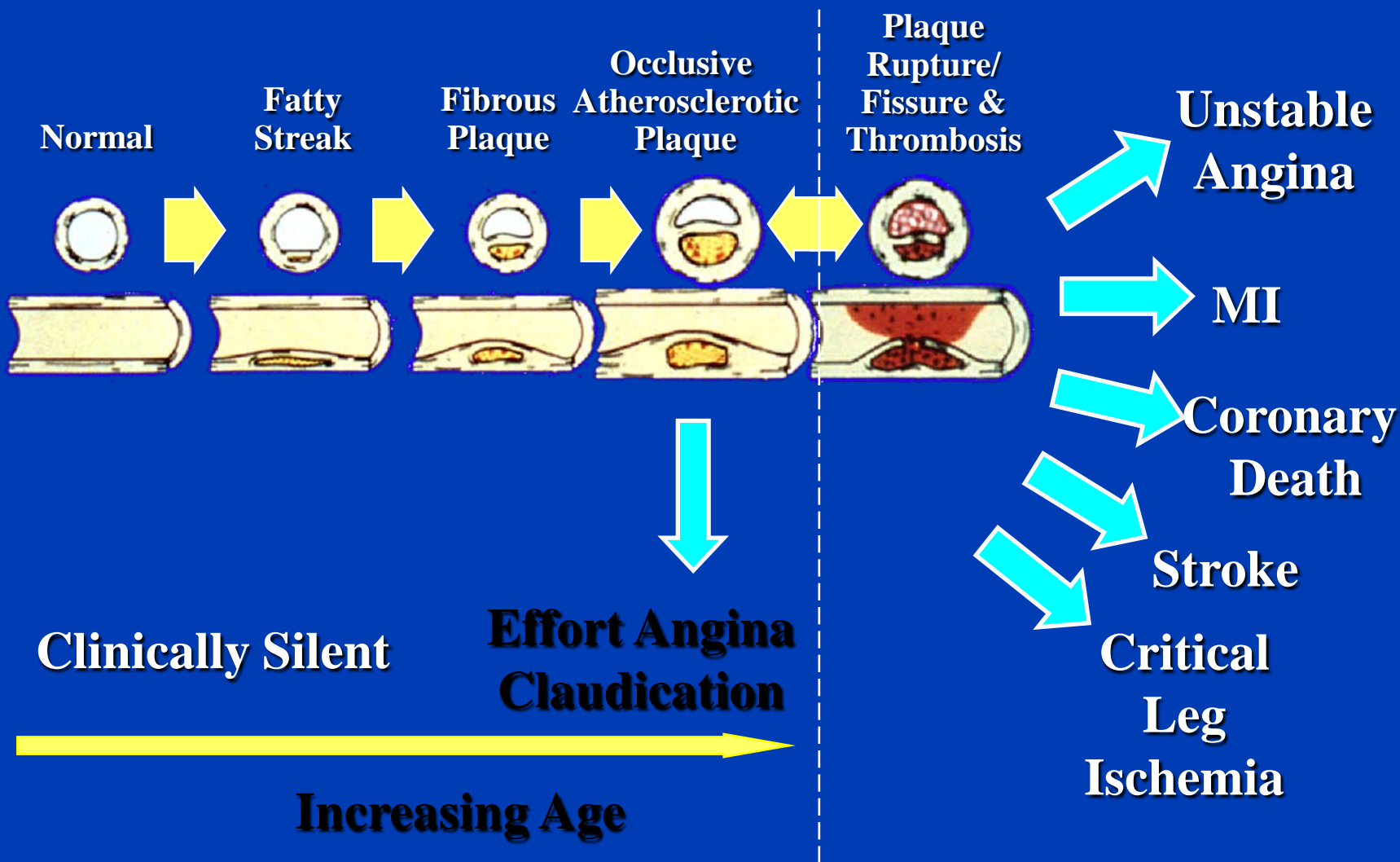
2 coronary arteries branch from the main aorta just above the aortic valve. "No larger than drinking straws, they divide and encircle the heart to cover its surface with a lacy network that reminded physicians of a slightly crooked crown (*coronary* comes from the Latin *coronarius*, belonging to a crown or wreath). They carry out about 130 gallons of blood through the heart muscle daily." (Clark, 119)



Atherosclerosis

can, and does, occur in almost any artery in the body. But in the heart it's effects can be crucial. "The body depends on a strong pumping heart to circulate life-giving blood, and this includes to the heart muscle itself. If the coronary arteries become blocked, the cardiac muscle begins to fail, and so the blood circulation decreases, which includes the circulation to the heart muscle itself." (Thibodeau, 494)

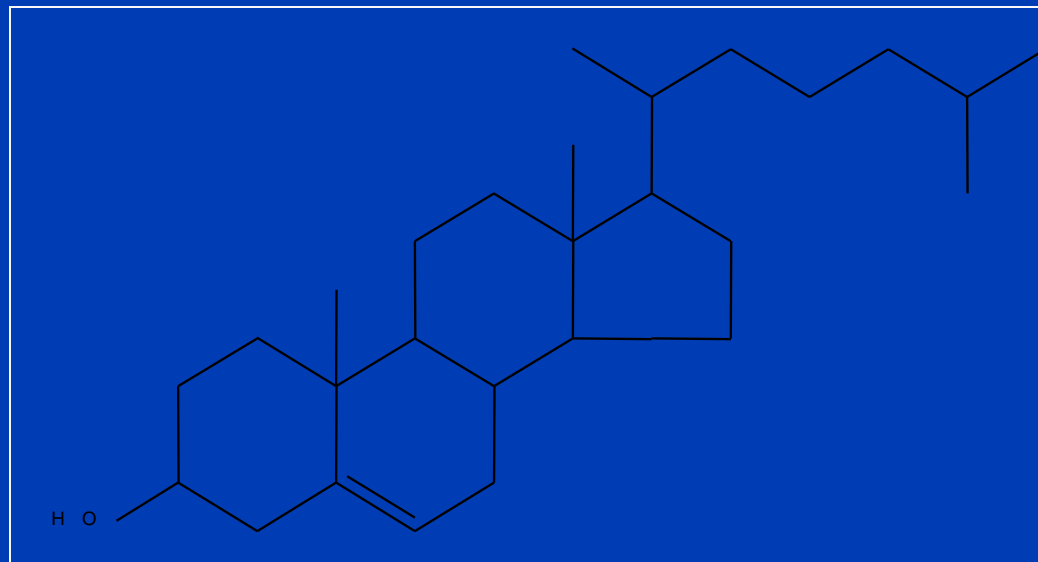
Atherosclerosis: A Progressive Process



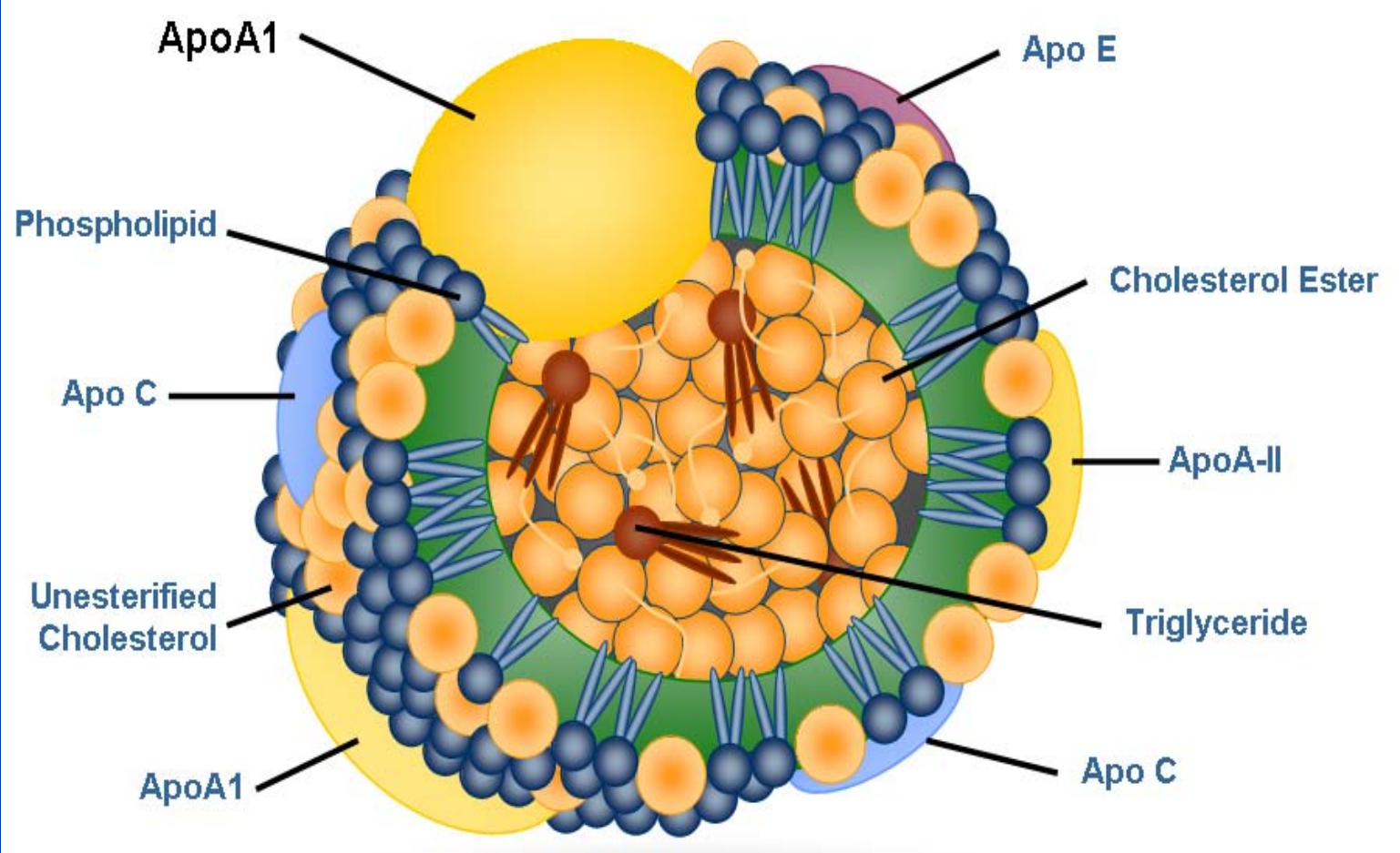
Cholesterol: What is it?¹

Cholesterol is a fatty steroid made primarily in the liver of most animals and humans. It is an integral component in the synthesis of hormones, can also be found in cell walls of animals and humans.

Isolated cholesterol is a white, flaky solid that is insoluble in aqueous environments.



Cholesterol



Two types of transportation for cholesterol

In order to transport the steroid through blood, cholesterol is attached to a set of proteins called lipoproteins. There are two types of lipoproteins: high density and low density lipoproteins.

HDL: High-density lipoproteins – collect cholesterol particles as they travel through blood vessels and deposits them in the liver where they are transferred to bile acids and disposed off.

LDL: Low-density lipoproteins –deposits on the walls of blood vessels, and over time, builds up into cholesterol plaque and blocks blood vessels, especially arteries that feed blood to the heart.

1. The liver manufactures, secretes and removes LDL cholesterol from the body. To remove LDL cholesterol from the blood, there are special LDL receptors on the surface of liver cells.

2. LDL receptors remove LDL cholesterol particles from the blood and transport them inside the liver. A high number of active LDL receptors on the liver surfaces is necessary for the rapid removal of LDL cholesterol from the blood and low blood LDL cholesterol levels.

A deficiency of LDL receptors is associated with high LDL cholesterol blood levels.

Diets that are high in cholesterol diminish the activity of LDL receptors!!!!

Biological Role:

- It is an important component of cell linings
- It helps in the digestion of lipids
- It is a key component in the building of hormones

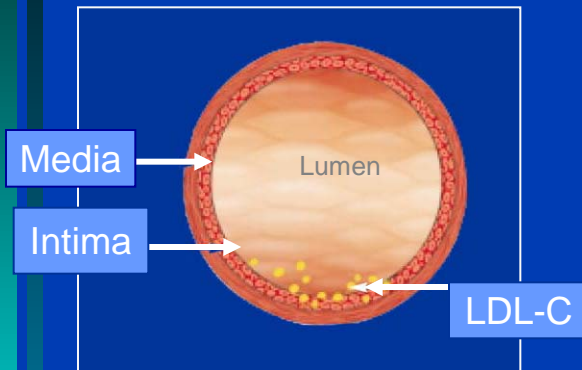
Hypercholestraemia: High blood cholesterol

- Usually a result of high LDL/low HDL cholesterol levels
- Leads to
 - narrowing of artery walls (atherosclerosis)
 - decreased blood and oxygen supply to heart
 - heart attack
 - death
- **Coronary heart disease:** Leading cause of death in western countries.

Genetic Causes of Dyslipidemia

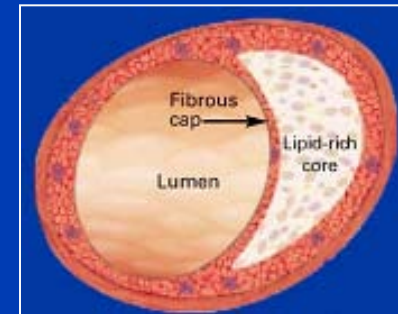
- **Familial Combined Hyperlipidemia**
 - Increased TC, LDL and/or triglycerides; decreased HDL
 - Most common genetic dyslipidemia: prevalence 1:50
 - Heterogenous inheritance
 - Accounts for 10-20% of patients with premature CAD
- **Defects in HDL Metabolism**
 - Most often low HDL is secondary to other dyslipidemia
 - Not all associated with increased CAD risk (e.g. apo A_I_{Milano})
 - Tangier's Disease
 - CETP defects result in increased HDL

Atherosclerosis Timeline

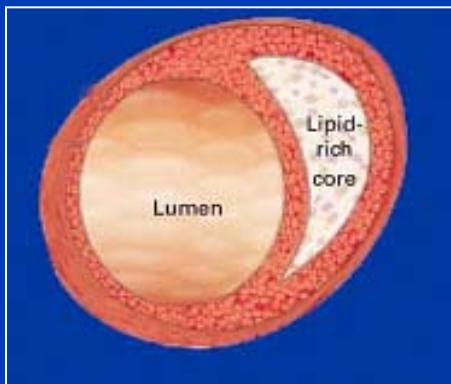


Phase I: Initiation

LDL-C plays a major role in initiating the development of atherosclerotic plaque.

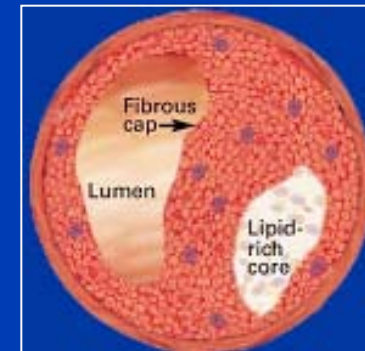


Unstable



Phase II: Progression

Disease progression results in the remodeling of the vascular wall so that the size of the lumen does not change significantly.



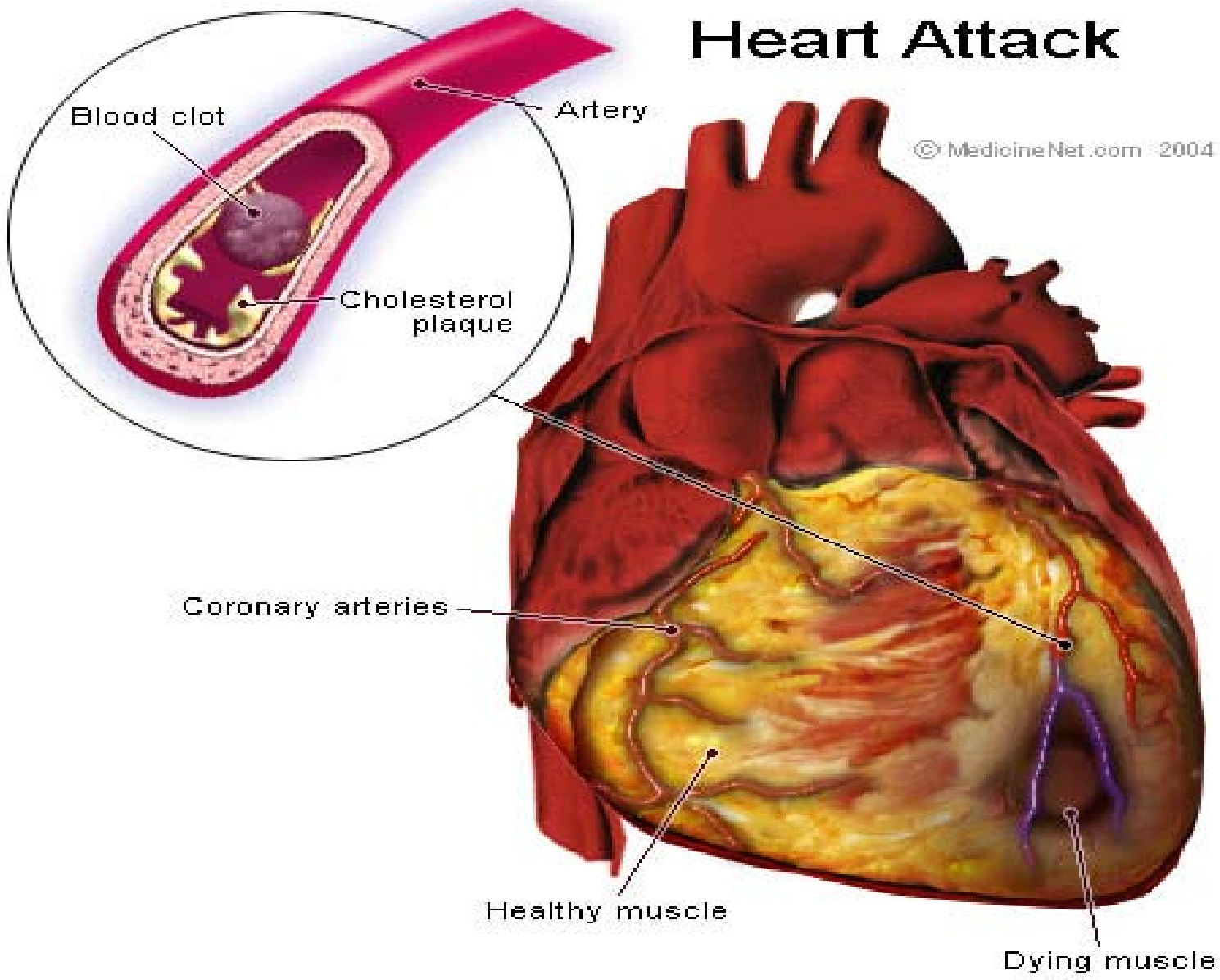
Stable

Phase III: Complication

Extensive lipid accumulation and a greater inflammatory component can pose the threat of plaque rupture.

Heart Attack

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Coronary Artery Disease

- Coronary artery disease is one of the most common and serious effects of aging. Fatty deposits build up in blood vessel walls and narrow the passageway for the movement of blood. The resulting condition, called atherosclerosis often leads to eventual blockage of the coronary arteries and a "heart attack".



Lipoprotein Profile Classification

- LDL Cholesterol

- < 70 Optimal in HRP
- < 100 Optimal
- 100-129 Near Optimal
- 130-159 Borderline High
- 160-189 High
- 190+ Very High

- HDL Cholesterol

- < 40 Low
- 60+ High

- Total Cholesterol

- < 200 Desirable
- 200-239 Borderline High
- 240+ High

- Triglycerides

- < 150 normal
- 150-199 Borderline High
- 200-499 High
- 500+ Very High

CHD and CHD Risk Equivalents

- CHD
- CHD Risk Equivalents
 - Peripheral Vascular Disease
 - Abdominal Aortic Aneurysm
 - Symptomatic Carotid Arterial Disease
 - Diabetes
 - Framingham 10-year risk 20+%

Major Risk Factors

ATP III

- Cigarette Smoking
- Hypertension (140+/90+ or on meds)
- Low HDL Cholesterol (< 40 mg/dL)
- FH of Premature CAD
 - Male 1st degree relative < 55
 - Female 1st degree relative < 65
- Personal Age
 - Male 45+
 - Female 55+

The Metabolic Syndrome

Any 3 of the following

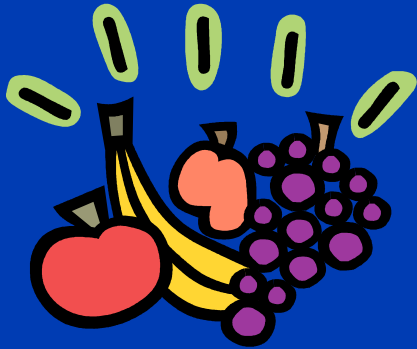
- Abdominal Obesity (waist circumference)
 - Men > 40 inches
 - Women > 35 inches
- Triglycerides 150+ mg/dL
- HDL
 - Men < 40 mg/dL
 - Women < 50 mg/dL
- Blood Pressure 130+/85+ mm Hg
- Fasting Glucose 110+ mg/dL

Treatment

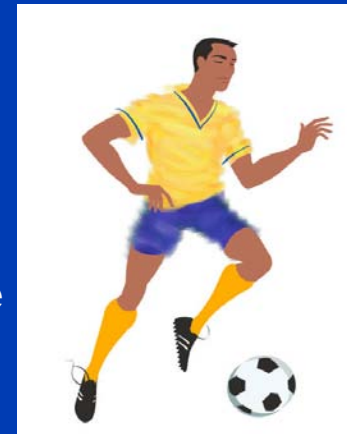
ATP III Treatment Priorities

- Reduce LDL-C to goal (new goals)
- Correct residual lipid/lipoprotein abnormalities(non-HDL-cholesterol)
- Address the metabolic syndrome

Initial treatment of hypercholesterolemia was directed toward limiting LDL-cholesterol levels through:



Low-cholesterol diet and regular exercise. Exercise burns fat so it is not converted to cholesterol which the Body will have to dispose off.



This approach was not very successful because high blood cholesterol is also hereditary (**Familial Hypercholesterolemia (FH)**) and a chronic condition. People with FH have defective or nonexistent LDL receptors and need rigorous, long-term treatment.

Scientific Approach:

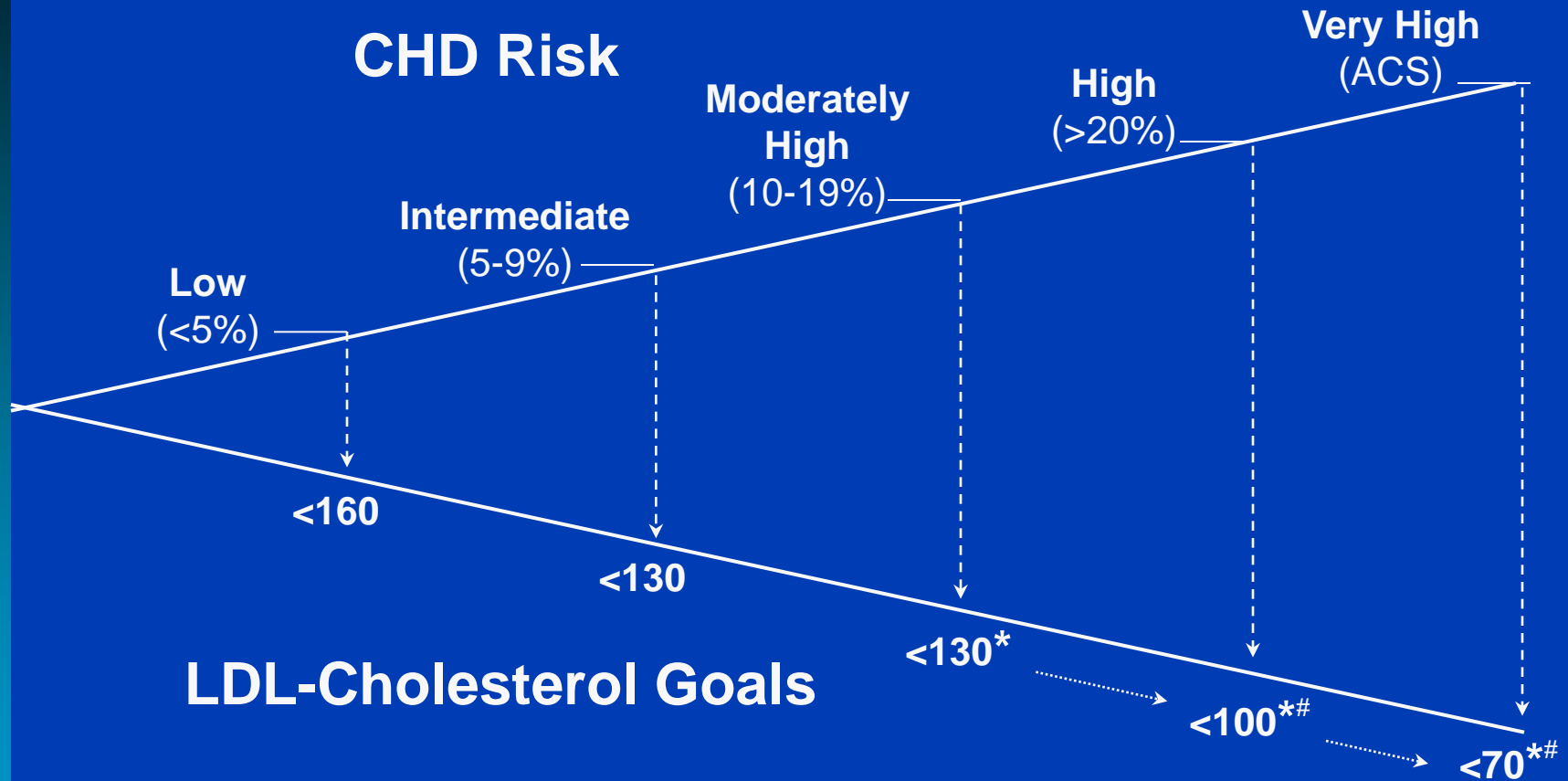
- Know and understand how the body makes cholesterol
- Find a way to effectively control cholesterol levels with minimum adverse effects

Risk Stratification

Update to ATP III

- Very High Risk
 - CHD + multiple risk factors (diabetes)
 - CHD + poorly controlled risk factor (smoking)
 - CHD + metabolic syndrome
 - CHD + ACS
- High Risk
 - CHD
 - CHD Equivalents
- Moderately High Risk
 - 2+ Risk Factors + Framingham Risk of 10-20%
- Intermediate Risk
 - 2+ Risk Factors + Framingham Risk of < 10%
- Low Risk
 - 0-1 Risk Factor

Modified ATP III LDL-C Guidelines



* Treat other lifestyle risk factors, metabolic syndrome

Use non-HDL-C for additional drug treatment

The 2004 NCEP LDL-C goal: lower may be better

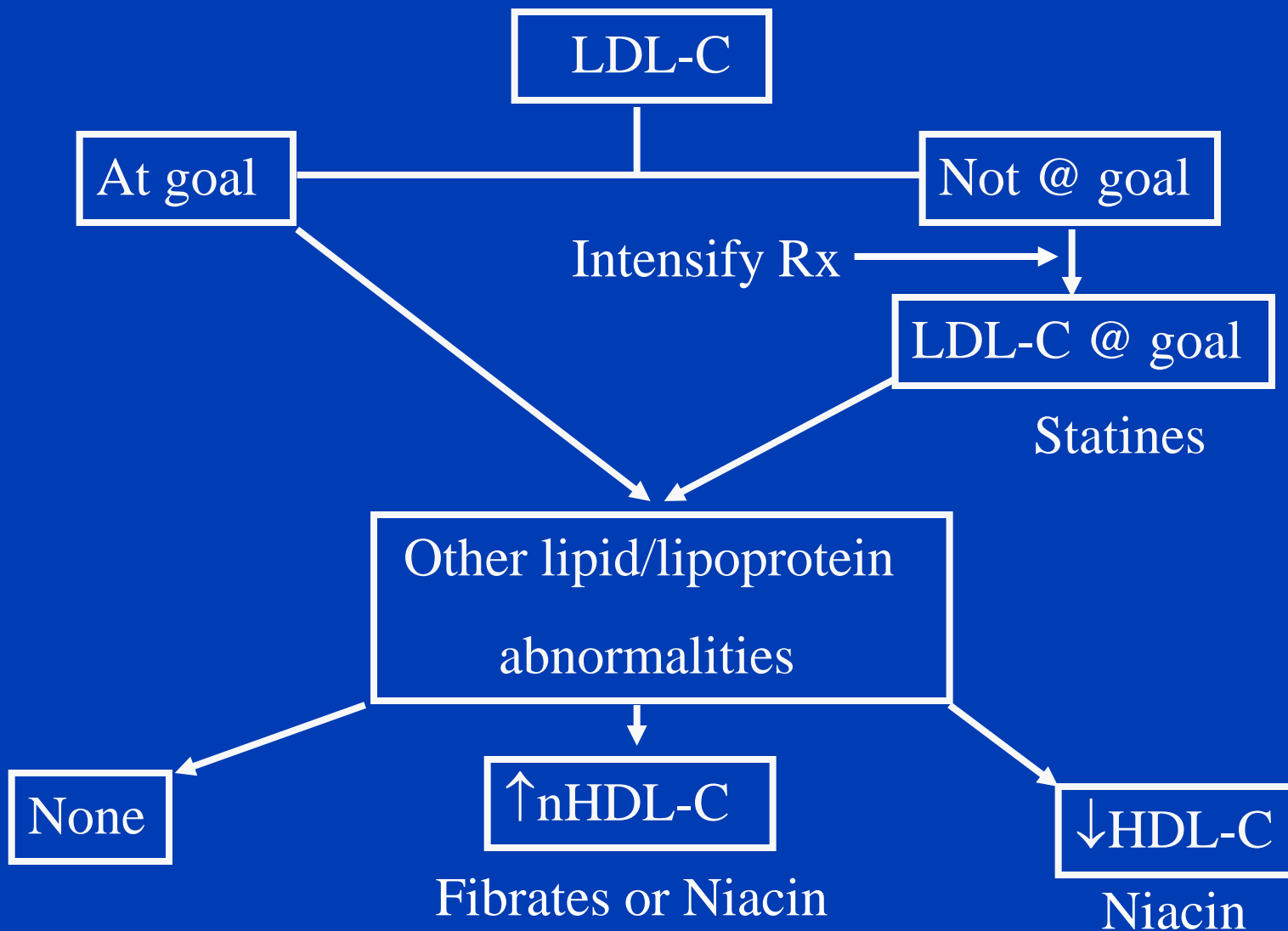
Acute Coronary Syndromes

- MIRACL: LDL-C, 125 → 72 mg/dl
- PROVE-IT: LDL-C, 106 → 62 mg/dl

Stable CHD

- HPS: benefit if basal LDL-C < 100 mg/dl
- ALLIANCE: 111 → 95 mg/dl
- REVERSAL: 150 → 79 mg/dl

Lipid Management Strategy



All patients should receive TLC advise. Simultaneous drug therapy should be started in:

- Patients with symptomatic CHD
- All high risk patients
- Intermediate risk
 - men@40-45 yrs
 - women@50-55 yrs

Lipid Lowering Drugs and the Data

- HMG Co-A Reductase Inhibitors
- Niacin
- Fibrates
- Ezetimibe
- Others

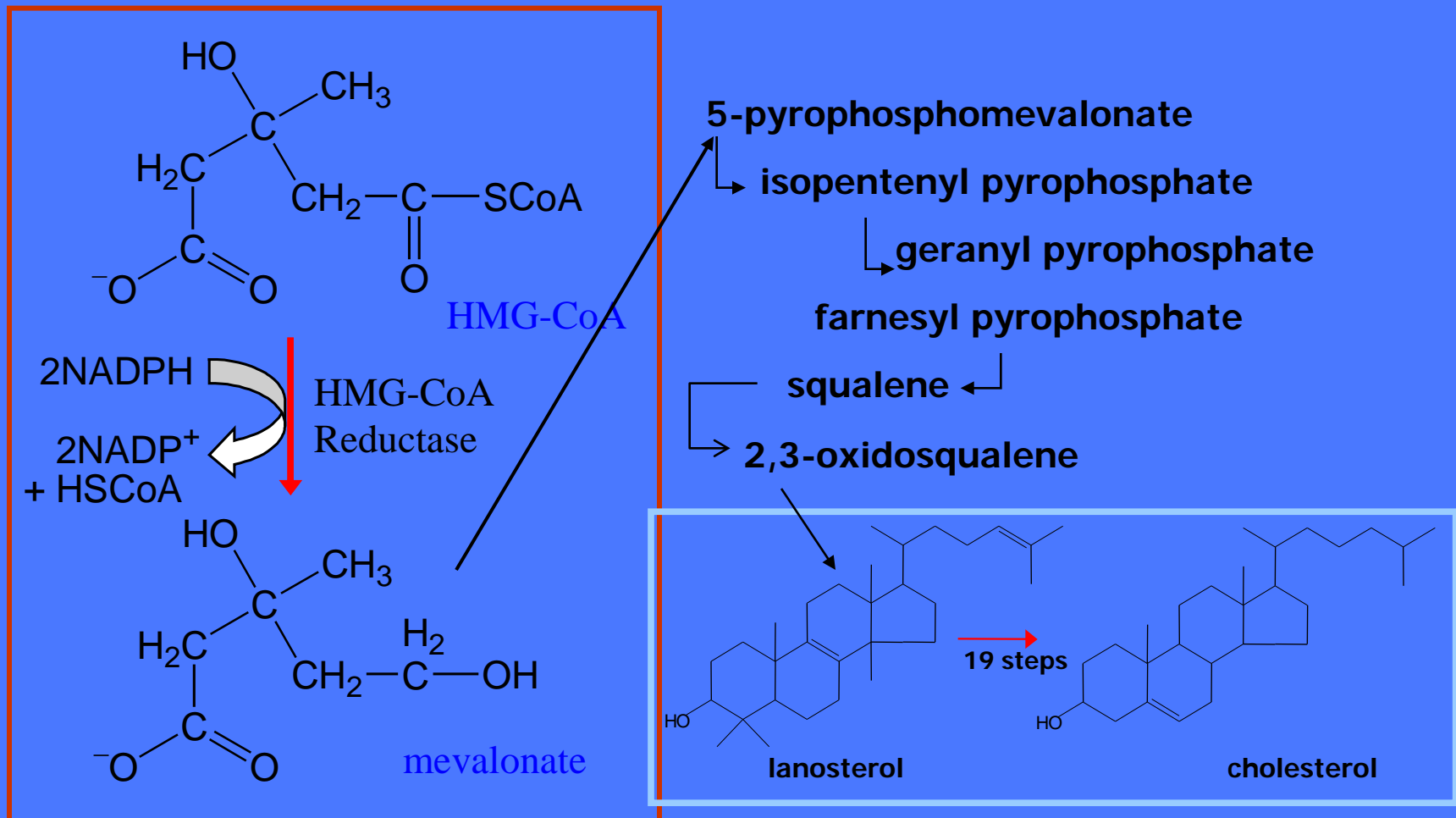
HMG Co-A Reductase Inhibitors

"Statins"

- Drugs structurally similar to HMG-CoA
 - precursor of cholesterol
- Competitive inhibitors of HMG-CoA reductase
 - last step in cholesterol synthesis
- Lower serum LDL concentrations by:
 - Upregulating LDL receptor activity
 - Reducing LDL entry into the circulation
- Most effective agents for lowering LDL
- Impressive body of evidence for CHD treatment

The Mevanolate Pathway

The biosynthesis of cholesterol and isoprenoids (a group of compounds responsible for cell fluidity and cell proliferation)



Statins

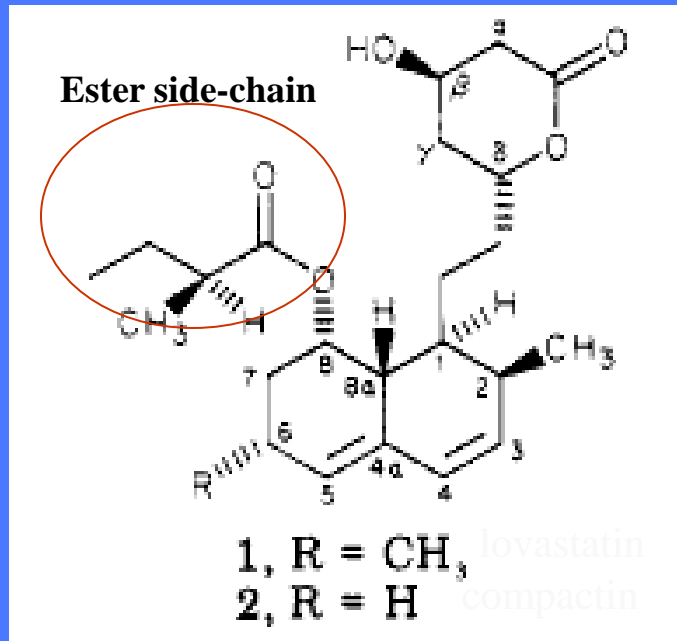
- ML-236B was later called compactin (6-demethylmevinolin or mevastatin). A related fungal metabolite called **lovastatin** (mevinolin) was also found to be another good inhibitor of HMG-CoA reductase. **Lovastatin** was isolated from *Aspergillus terreus*.

Today, there are two classes of statins:

Natural Statins: Lovastatin (mevacor), Compactin, Pravastatin (pravachol), Simvastatin (Zocor).

Synthetic Statins: Atorvastatin (Lipitor), Fluvastatin (Lescol).

Statins are competitive inhibitors of HMG-CoA reductase. They are bulky and literally get “stuck” in the active site. This prevents the enzyme from binding with its substrate, HMG-CoA.



LDL Reduction by Individual Statins

	5 mg	10 mg	20 mg	40 mg	80 mg
Atorvastatin		39%	43%	50%	60%
Fluvastatin			21%	24%	
Lovastatin		21%	24%	30%	40%
Pravastatin		22%	32%	34%	
Rosuvastatin	45%	52%	58%	69%	
Simvastatin	22%	30%	35%	41%	47%

In general, doubling dose = additional 6% reduction in LDL

Source: Gau G, Mayo Clinic Cardiovascular Review

Muscle Adverse Effects

- Myalgia
- Weakness
- Fatigue
- Myopathy without \uparrow CK
- Predisposing factors:
 - Combined hyperlipidemia
 - Subclinical hypothyroidism
 - Suboptimum thyroxine replacement

Ezetimibe (Zetia™)

- Inhibits cholesterol absorption
- Mono or combination therapy
 - MonoRx/added to statin: ~ 20 % ↓ LDL-C
 - VYTORIN (Z+Z); 10mg Z+10mg Z= 80mg Z
 - Lower statin doses: 10mg L+10mg Z = 80mg L
- Minimal effect on TG and HDL-C

What are the options when statin therapy does not get the LDL-C to goal?

- Treatment intensity related to risk
- Increase dose, if therapeutic range permits
- Add Zetia or “resin”
- Add plant stanol/sterol products
- If other lipid abnormalities present add:
 - Fibrates or niacin

Use of statins in patients with hypertriglyceridemia

- TG range in statin trials: 200-450 mg/dl
- Statin, fibrate or niacin?
 - Statin effects best in patients with low HDL-C
- Reduced efficacy of statins in MetS?

Niacin - nicotinic acide

- Cholesterol-lowering effect 1st reported in 1955
- Reduces LDL (5-25%) by decreasing peripheral mobilization of FFAs from adipose tissue
- Most effective drug available clinically for raising HDL (15-35%)
- Also effective for reducing triglycerides (25-50%)
- Reduces Lp(a) by 30%
- Converts small, dense LDL to large, buoyant LDL

Niacin - nicotinic acid

- Pitfalls with niacin therapy
 - Cutaneous flushing, pruritis, nausea, abd pain
 - Hepatotoxicity
 - Glucose intolerance
 - Increase risk of myositis if used with statin
 - Minimal hard endpoint outcome data

Fibrates

- Class of drugs which resemble short chain fatty acids
- Increase oxidation of fatty acids in muscle and liver
- Most effective class of drugs for lowering triglycerides
- Increase size of LDL particles and enhance removal
- May increase HDL-mediated reverse cholesterol transport
- Reduce levels of plasminogen activator inhibitor type I
- Currently available drugs in U.S.
 - Gemfibrozil
 - Fenofibrate (less risk of myopathy when used with a statin)
- ADRs: GI, ED, myopathy (CRF)

Ezetimibe

- 1st in new class of cholesterol absorption inhibitors
- Likely works by binding to and blocking the sterol transporter on the intestinal brush border
- Results in increased LDL-R activity and LDL clearance
- Drug and its metabolites circulate enterohepatically with little systemic penetration
- Potential toxicities essentially limited to liver
- Does not induce or inhibit cytochrome P450 system
- Single dosing option of 10 mg once daily

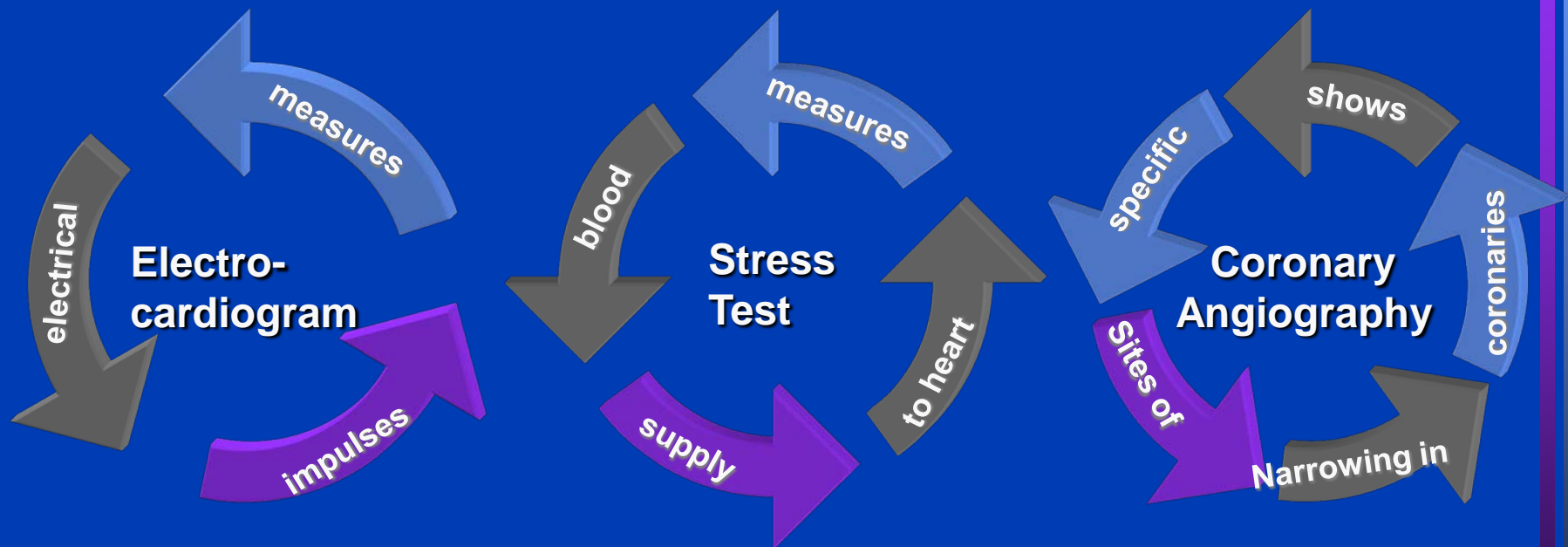
When to Stop Treatment

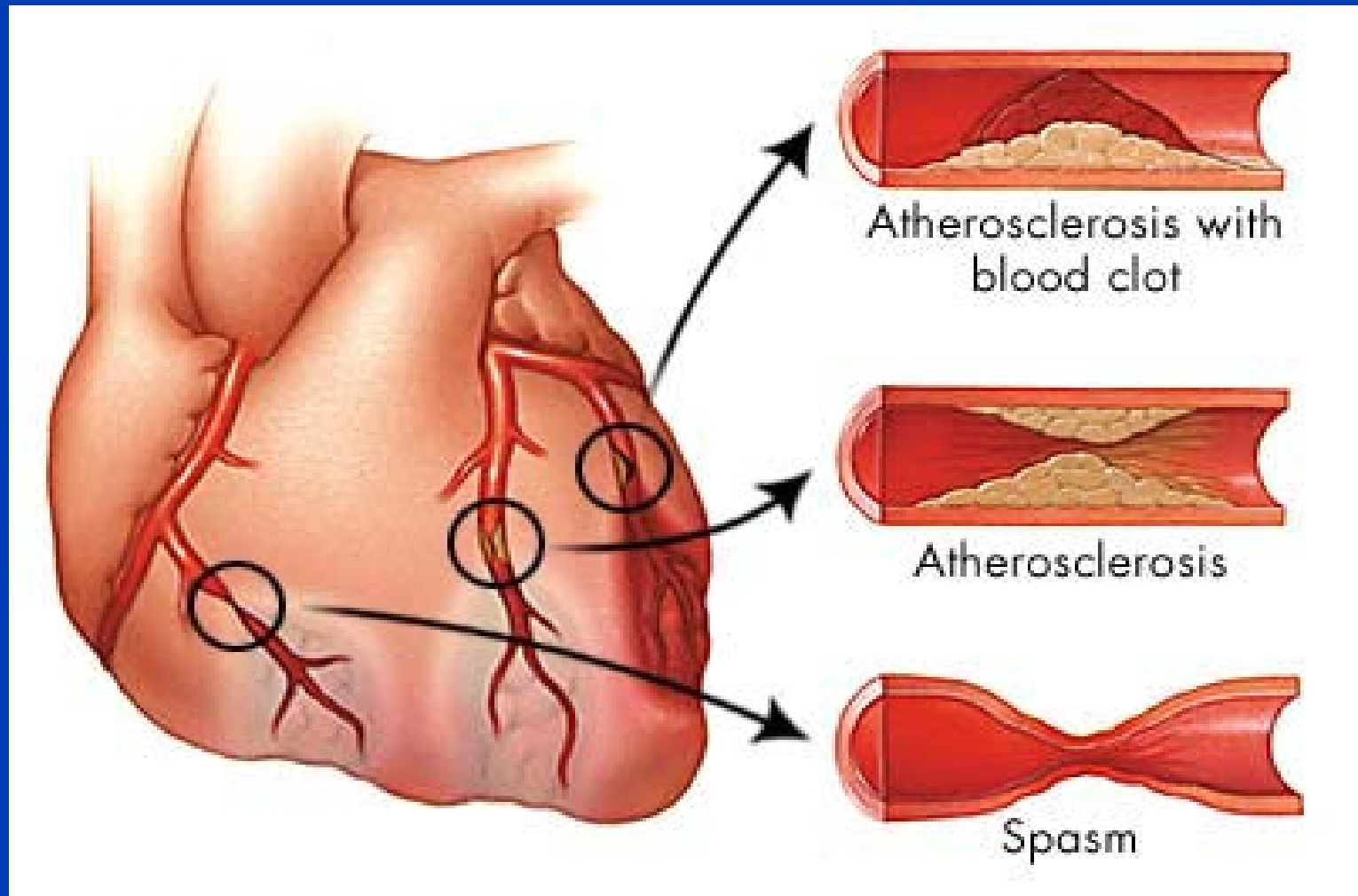
- Statins and Ezetimibe
 - Myopathy - Muscle aches with CK > 10x ULN
 - Abnormal LFTs – 3x ULN
 - Pregnancy and Breast Feeding
- Niacin
 - Abnormal LFTs (3x ULN) or chronic liver disease
 - Gout
 - Poorly controlled diabetes
 - Pregnancy
- Fibrates
 - Chronic liver dysfunction or renal failure
 - Abnormal LFTs or myopathy
 - Pregnancy

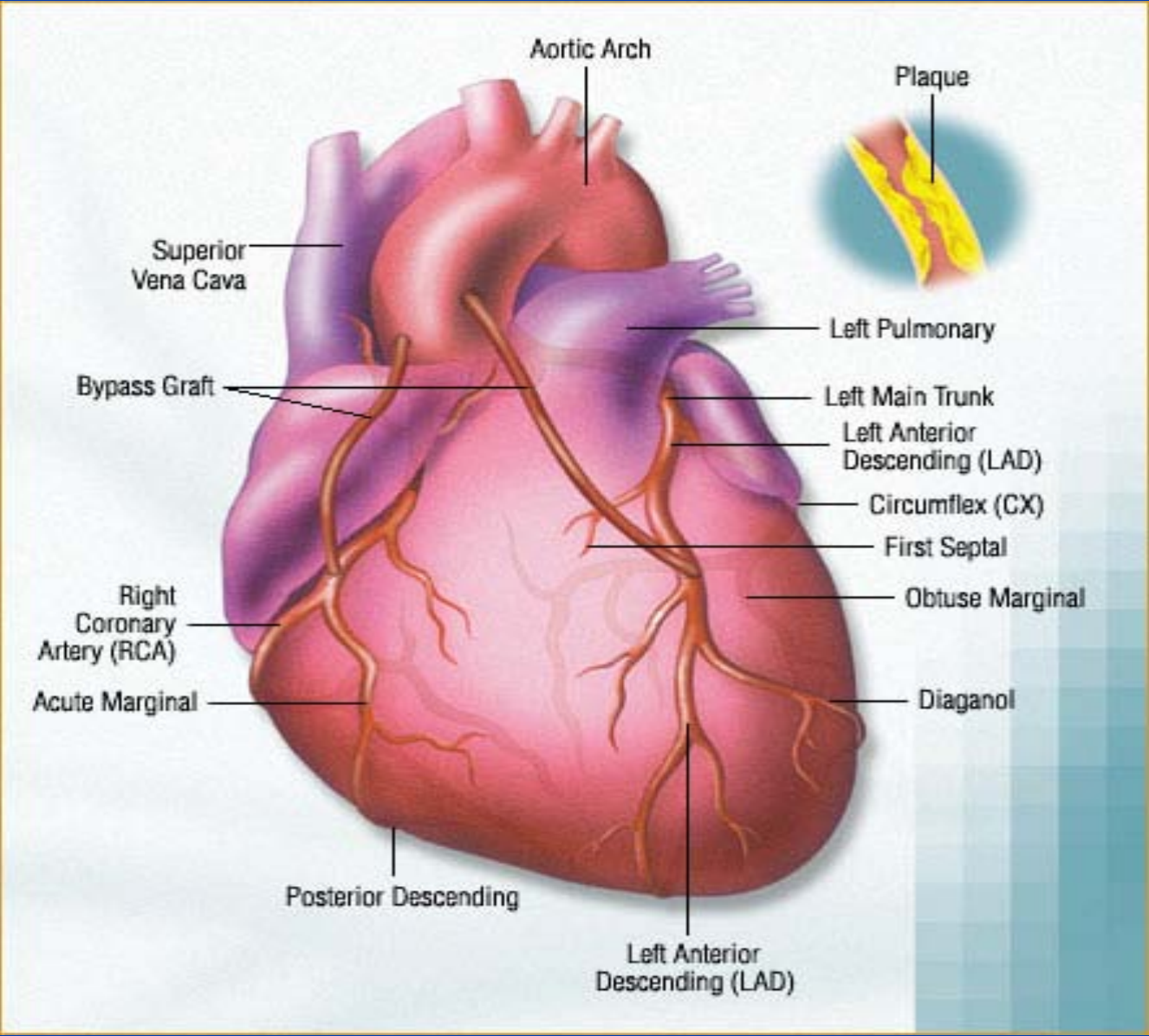
Treatment

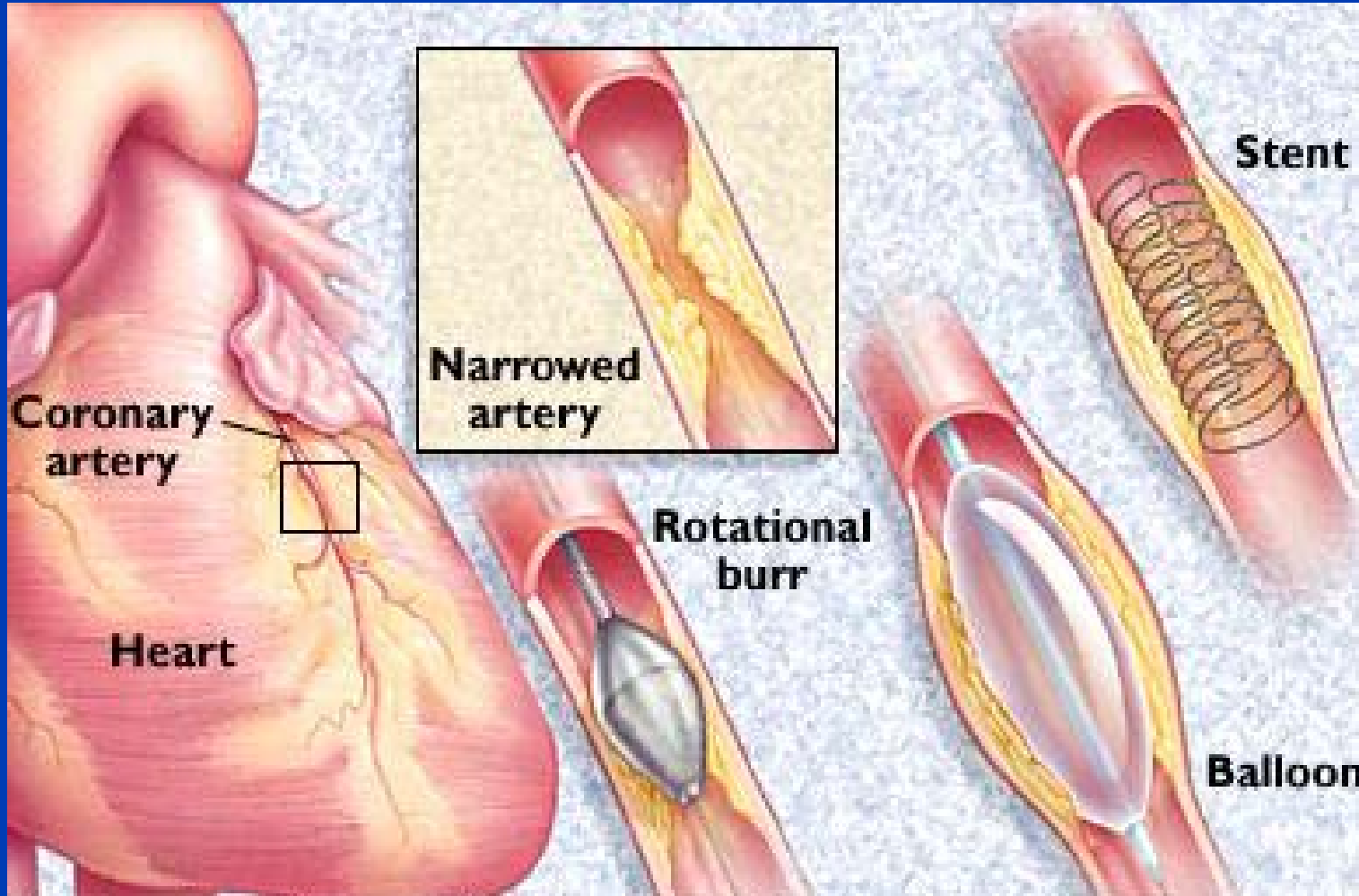
- Many people are able to manage coronary artery disease with lifestyle changes and medications.
- Other people with severe coronary artery disease may need angioplasty or surgery.

Screening and Diagnosis









Treatment (continued)

1) Stenting

- a stent is introduced into a blood vessel on a balloon catheter and advanced into the blocked area of the artery
- the balloon is then inflated and causes the stent to expand until it fits the inner wall of the vessel, conforming to contours as needed
- the balloon is then deflated and drawn back
- The stent stays in place permanently, holding the vessel open and improving the flow of blood.



Treatment (continued)

2) Angioplasty

- a balloon catheter is passed through the guiding catheter to the area near the narrowing. A guide wire inside the balloon catheter is then advanced through the artery until the tip is beyond the narrowing.
- the angioplasty catheter is moved over the guide wire until the balloon is within the narrowed segment.
- balloon is inflated, compressing the plaque against the artery wall
- once plaque has been compressed and the artery has been sufficiently opened, the balloon catheter will be deflated and removed.

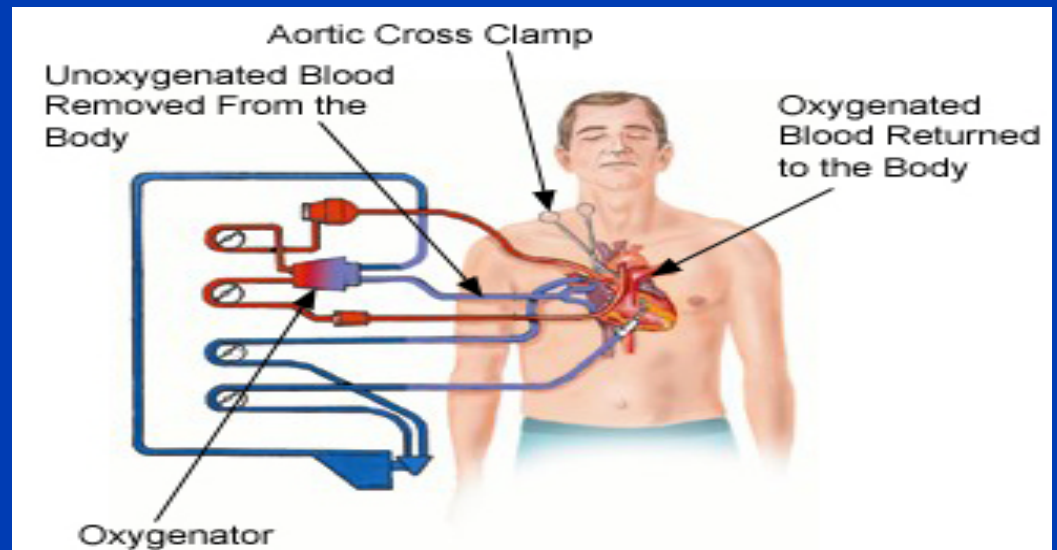


Treatment (continued)

3) Bypass surgery

- healthy blood vessel is removed from leg, arm or chest
- blood vessel is used to create new blood flow path in your heart
- the “bypass graft” enables blood to reach your heart by flowing

around (bypassing) the blocked portion of the diseased artery. The increased blood flow reduces angina and the risk of heart attack.



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- **Get regular medical checkups.**
- **Control your blood pressure.**
- **Check your cholesterol.**
- **Don't smoke.**
- **Exercise regularly.**
- **Maintain a healthy weight.**
- **Eat a heart-healthy diet.**
- **Manage stress.**