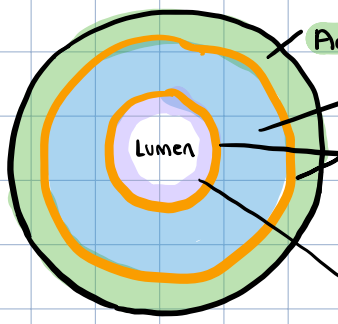
ATHEROSCLEROSIS



Adventitia - contains nerves, lymphatics, and blood vessels

Media - thickest layer. Smooth muscle cells.

Elastic lamina

- elastic component of media more prominent in large arteries
- muscular compartment of media more prominent in smaller arteries.

Intima - endothelial cells. Metabolically active. Contains blood and controls passage of molecules.

Pathophysiology: disruption of homeostasis due to activation of endothelial and smooth muscle cells.

Key components:

1. endothelial dysfunction
2. lipid accumulation in intima

→ leukocyte recruitment

Fatty streaks: earliest visible lesions of atherosclerosis. Does **NOT** impede bloodflow.

Endothelial damage →

- ↑ permeability - entry of LDL → "trapped"
- ↑ inflammatory cytokines - release promotes plaque progression
- ↑ leukocyte adhesion - key step in atherogenesis
- ↓ vasodilatory molecules
- ↓ antithrombotic molecules

- hydrodynamic stress at branch points
- toxins (ex. tobacco)

Foam cell maturation - macrophages inject lipoproteins → release of pro-inflammatory cytokines → plaque progression → accumulation of debris → Necrotic core

Plaque Progression - smooth muscle cells in the intima trap lipoproteins.

Early Plaque → **Progression** → **vulnerable plaque**

- Early Plaque: compensatory remodeling of arterial wall without limiting blood flow
- Progression: Restriction of vessel lumen, impeding blood flow and perfusion
- vulnerable plaque: thin cap with many inflammatory cells

↓ **Stable plaque**: Thick cap with preserved vessel lumen

↓ **Plaque Rupture**

RISK FACTORS

Non-modifiable: advanced age, male, heredity

Modifiable

① Tobacco - hypoxia leads to:
- ↑ increased endothelial damage
- ↑ oxidative modification of LDL
- ↓ circulating HDL
- ↑ platelet adhesion

② Hypertension - accelerates atherosclerosis
- ↑ endothelial injury
- ↑ permeability and retention of LDL
- manage w/ DASH, exercise, meds

③ Diabetes - accompanying dyslipidemia, glycation of lipoproteins, prothrombotic state, impaired baseline endothelial function.

④ Metabolic Syndrome - obesity, hypertriglyceridemia, dyslipidemia, hyperglycemia, hypertension

⑤ Sedentary Lifestyle - physical activity ↓ bp, ↑ HDL, ↑ insulin sensitivity, ↑ NO

⑥ Dylipidemia - major risk factor for atherosclerosis

DYSLIPIDEMIA

Abnormal circulating lipid levels are a major risk factor for atherosclerosis.

5 Major Lipoproteins
- Chylomicrons: very large. carry dietary lipid.
- Very low density lipoprotein: carry endogenous triglycerides and some cholesterol
- Intermediate density lipoprotein: carry cholesterol esters and triglycerides

LDL = "bad cholesterol"
- penetrates endothelium → accumulate in foam cells of plaques
- proinflammatory and immune changes via cytokines and antibodies
- ↑ platelet aggregation and thromboxane release

HDL = "good cholesterol"
- antiatherogenic - removal of cholesterol from macrophages
- returns cholesterol to liver → synthesis of bile
- Protects against thrombosis

Lowering LDL is effective at reducing cardiovascular disease events

HYPERTRIGLYCERIDEMIA

Epidemiology: acquired or hereditary

Etiology: lipoproteins rich with triglycerides → ↑endothelial activation → monocyte infiltration → penetrate arterial wall → atherosclerosis

Clinical Manifestations: asymptomatic. ± xanthomas.
- Pancreatitis if >800

Diagnosis: fasting triglycerides >200 mg/dl without elevation in LDL.
- BMP, urinalysis, TSH

Treatment: prevent pancreatitis and ↓risk of adverse cardiac events.

Lifestyle modifications – first line

Medical - fenofibrate, gemfibrozil, ± statin

PRIMARY PREVENTION

- LDL-C ≥190
  - high intensity statin
- Diabetes and 40-75 yo
  - moderate-intensity statin
  - consider high intensity
- Age >75
  - Clinical assessment
  - risk discussion

Age

- 0-19 yo
  - Lifestyle
  - Fam History → Statin
- 20-39 yo
  - Lifestyle
  - Statin if fam history, premature ASCVD and LDL-C ≥160
- 40-75 yo, 190 > LDL-C > 70, without diabetes
  - <5% Low risk
    - risk discussion
  - 5-7.5% Borderline
    - consider statin
  - 7.5-20% Intermediate
    - moderate intensity statin
  - >20% High risk
    - initiate statin to ↓LDL-C ≥50%.

SECONDARY PREVENTION

- Not very high risk
  - ≤75 → High intensity statin ± ezetimibe
  - >75 → Moderate-high intensity statin
- Very high risk
  - High or max intensity statin ± ezetimibe
  - not controlled
    - ± PCSK-9 inhibitor

MEDICATIONS

1. **STATINS** - HMG CoA Reductase Inhibitors. ↑HDL, ↓LDL, ↓TG
   - Moderate intensity: Simvastatin, pravastatin
   - High intensity: atorvostatin, rosuvastatin
   - MOA: inhibits rate-limiting step in hepatic cholesterol synthesis
     - Removes LDL from blood
   - Indications: Primary prevention and elevated LDL.
2. **EZETIMIBE** - inhibits intestinal cholesterol absorption, decreasing LDL
   - Indications: second line therapy with statin
3. **PCSK-9 INHIBITORS** - inhibit enzyme involved in LDL receptor degradation
   - Alirocumab and Evolocumab
   - Indications: add to high-intensity statin if history of ASCVD events and high risk for future events
4. **NIACIN** - delays HDL clearance and decreases hepatic production of LDL
   - toxicities: flushing, headaches, hyperuricemia, hyperglycemia, hepatotoxicity
   - one of best meds at ↓TG and ↑HDL
5. **FIBRATES** - best drug to ↓TG. Reduces hepatic triglyceride synthesis. ↑HDL synthesis
   - Gemfibrozil and Fenofibrate
   - Indications: hypertriglyceridemia
   - Toxicities - myalgias. ↑risk of gallstones
6. **BILE ACID SEQUESTRANTS** - binds bile acids in intestine, blocking reabsorption
   - Cholestyramine, Colestipol
   - Only lipid-lowering agent safe for pregnancy
   - effective when used w/ statins
   - causes ↑TG levels

CURRENT GUIDELINES

Statin + ezetimibe ± PCSK-9 inhibitor for high-risk