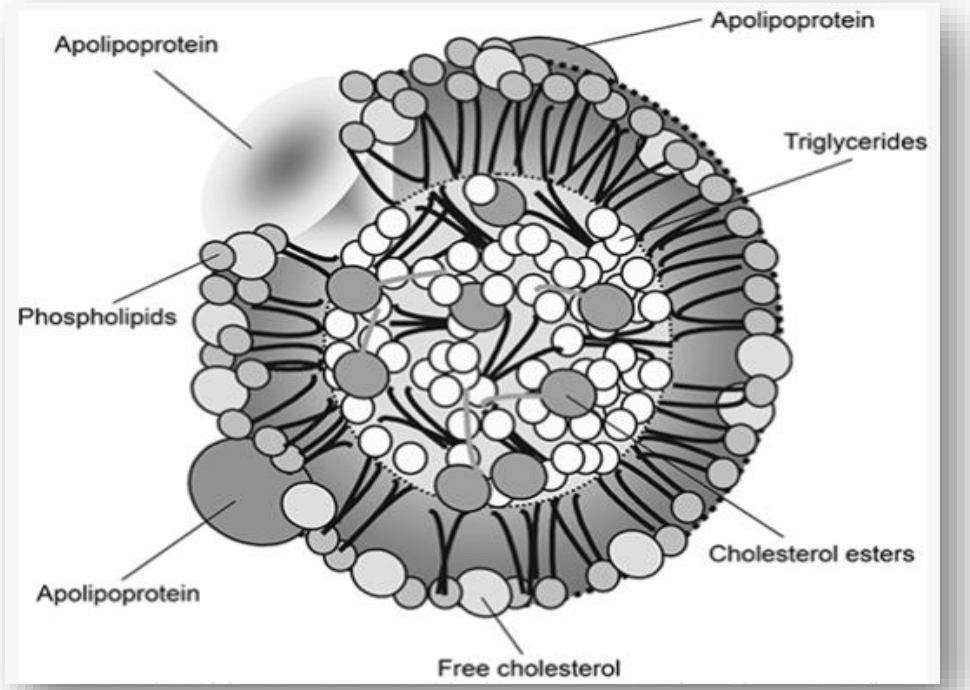

# Dyslipidemia

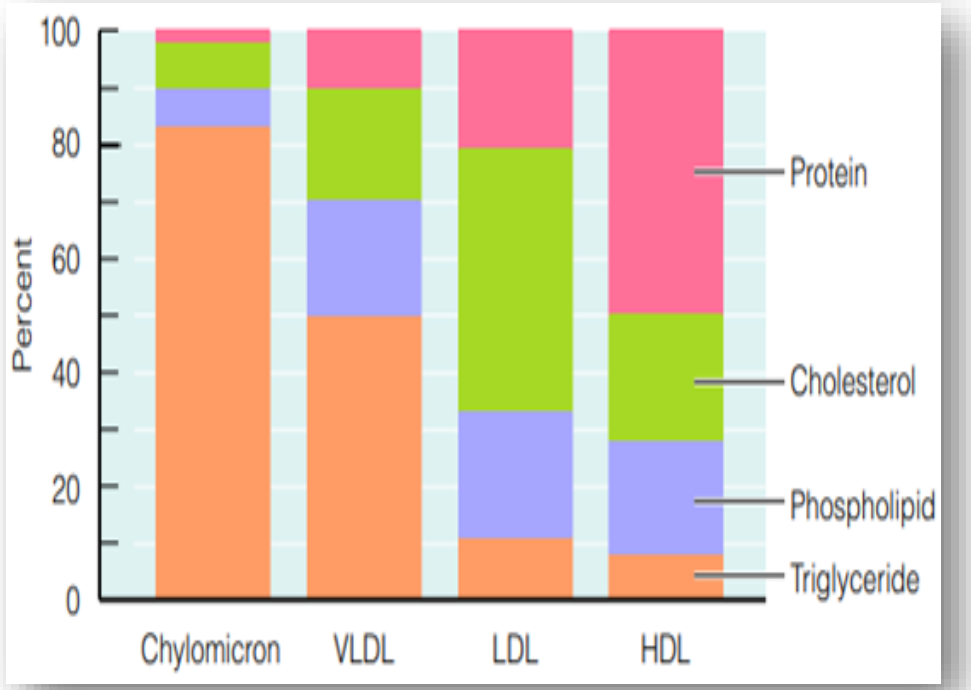
04/03/2025

BADER REMAWI

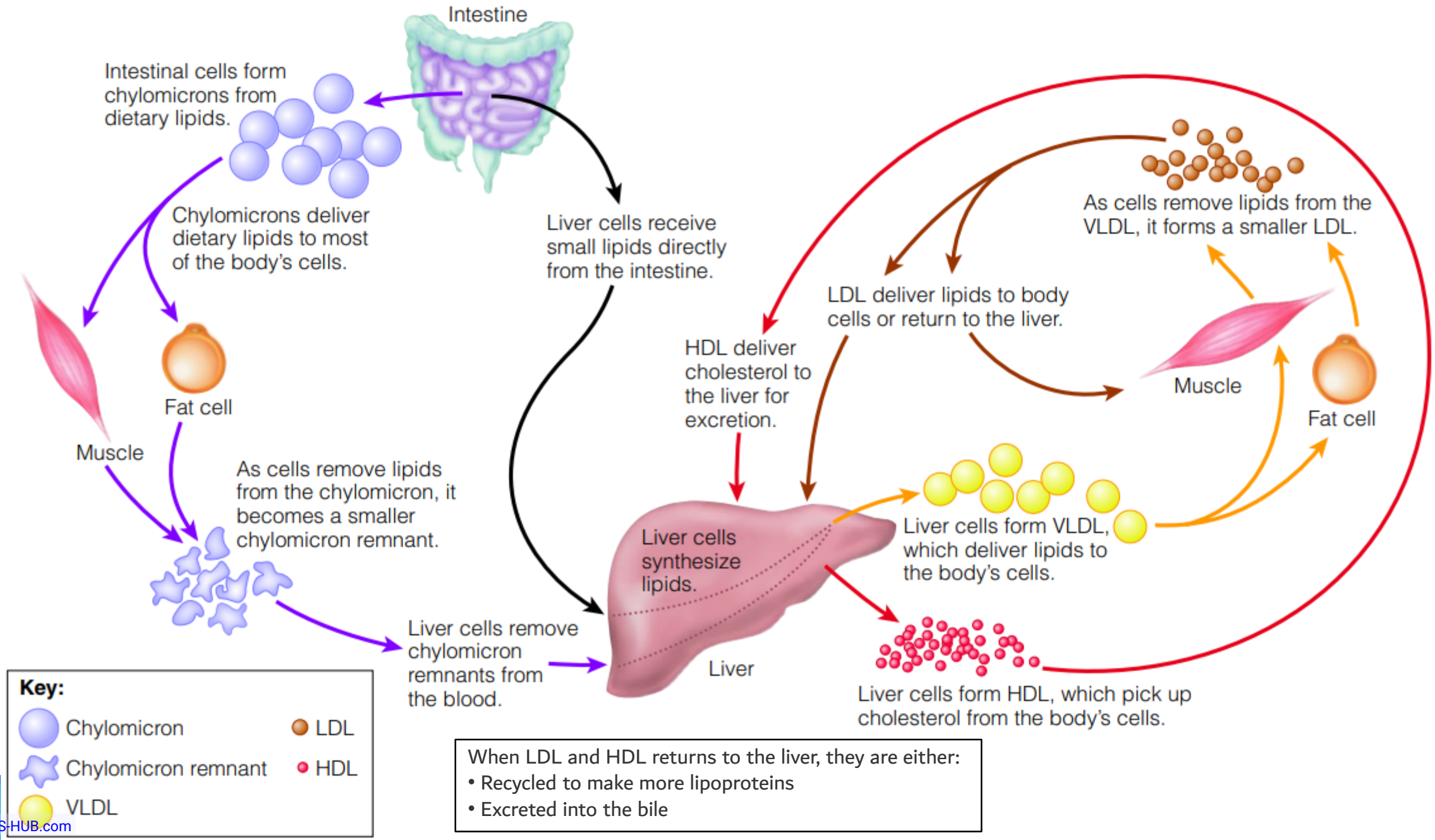
# Serum lipoproteins

- Lipids are insoluble in plasma
  - Lipids combine with Proteins for transport → Lipoprotein complexes

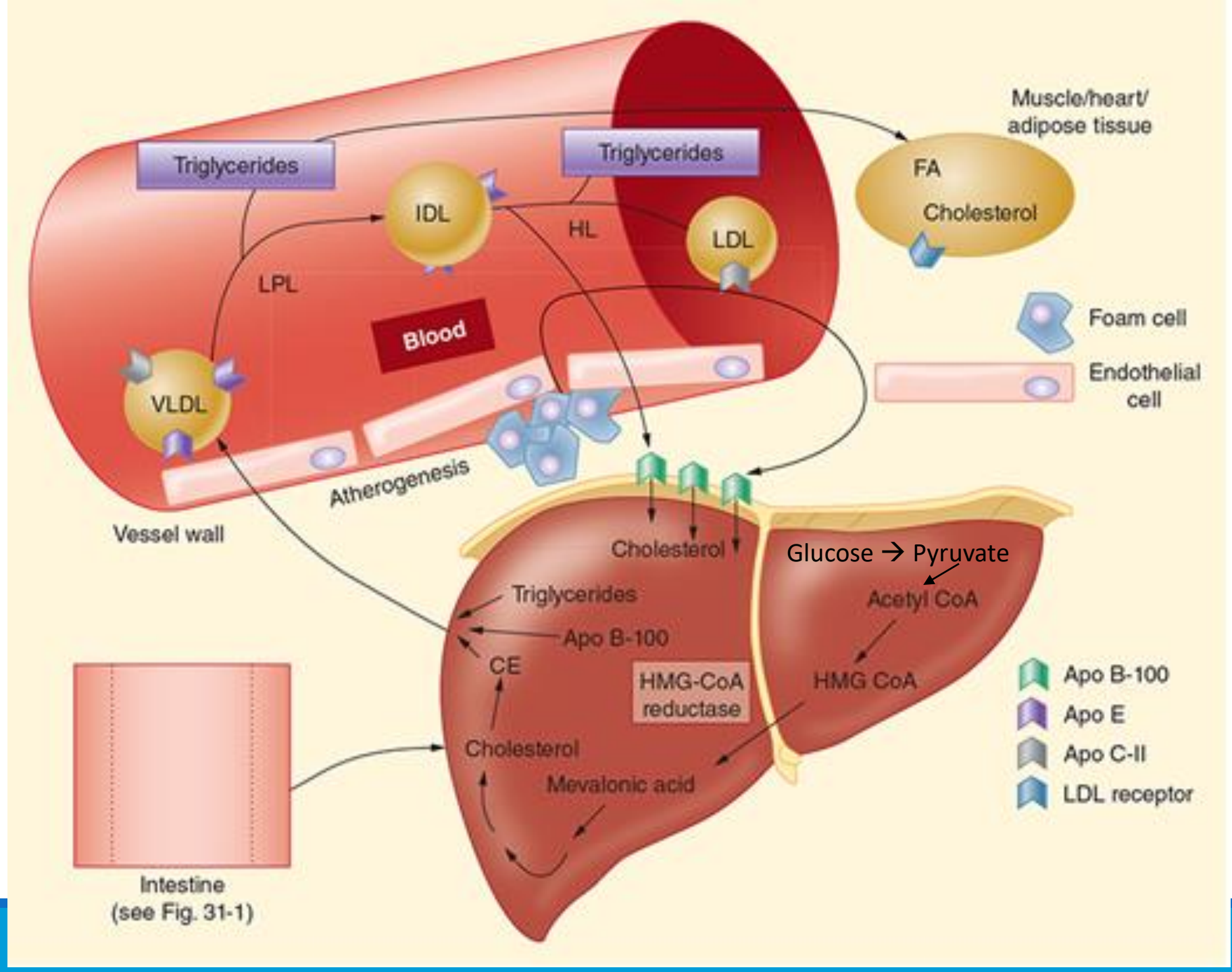


## > FIGURE 5-17 Lipid Transport via Lipoproteins




When LDL and HDL returns to the liver, they are either:
- Recycled to make more lipoproteins
- Excreted into the bile

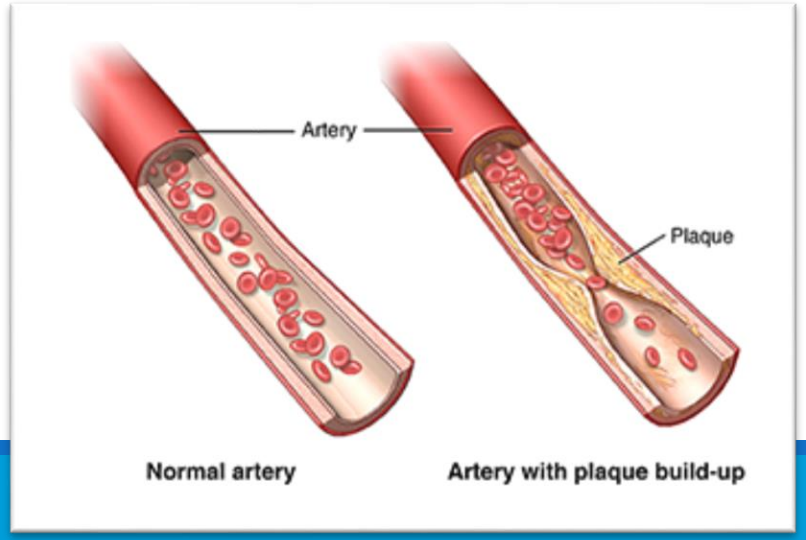


# Atherosclerotic cardiovascular disease

- Lipid abnormalities (genetic/environmental factors) → Risk of ASCVD → Risk of death
  - ASCVD = Coronary, Cerebrovascular, & Peripheral vascular arterial disease

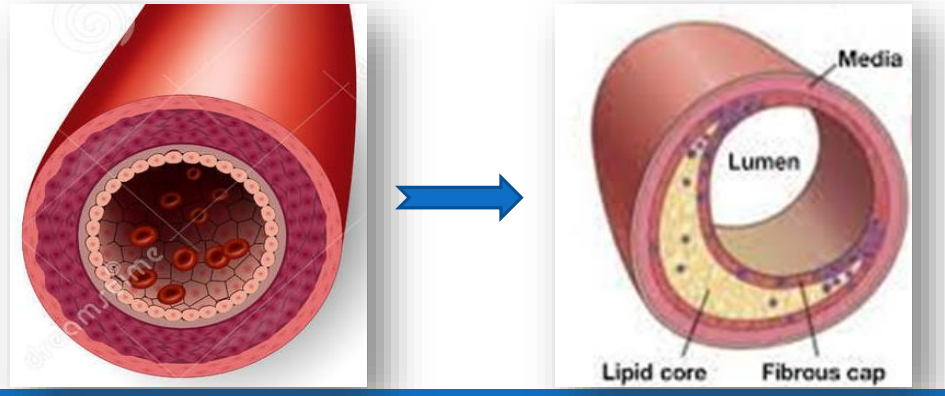
- Framingham Heart Study:
  - Risk of developing CV disease is related to the degree of LDL-C elevation (atherogenic)

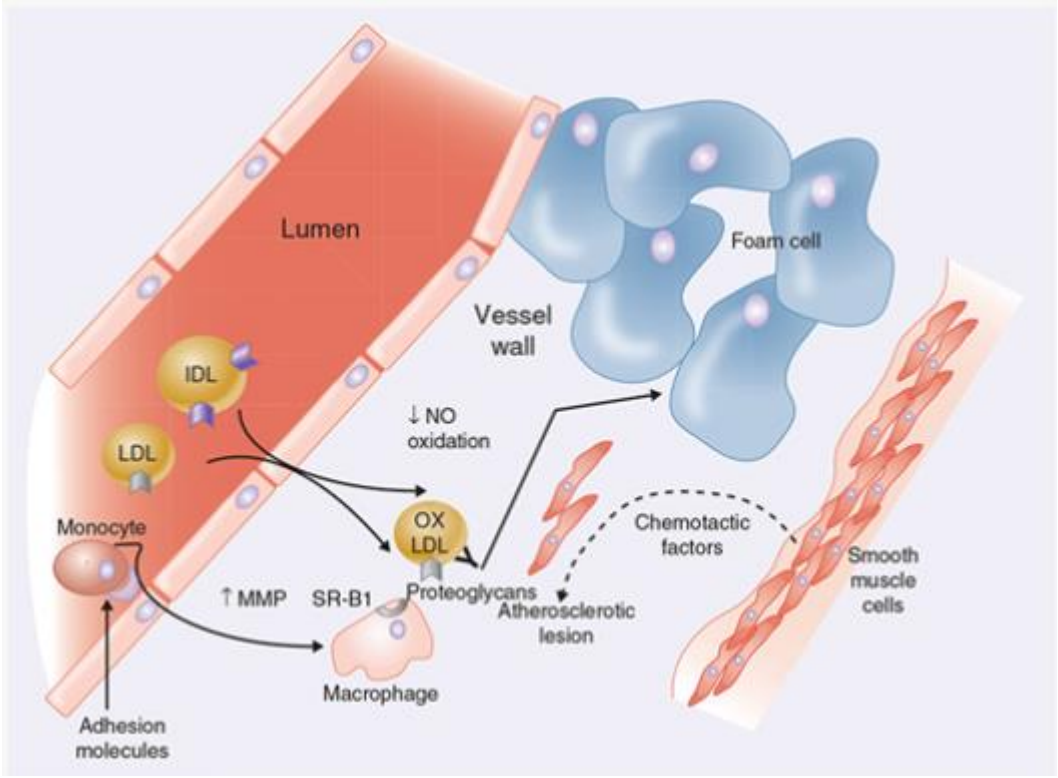
- For every 38 mg/dL reduction in LDL-C, ASCVD events reduce by 21%



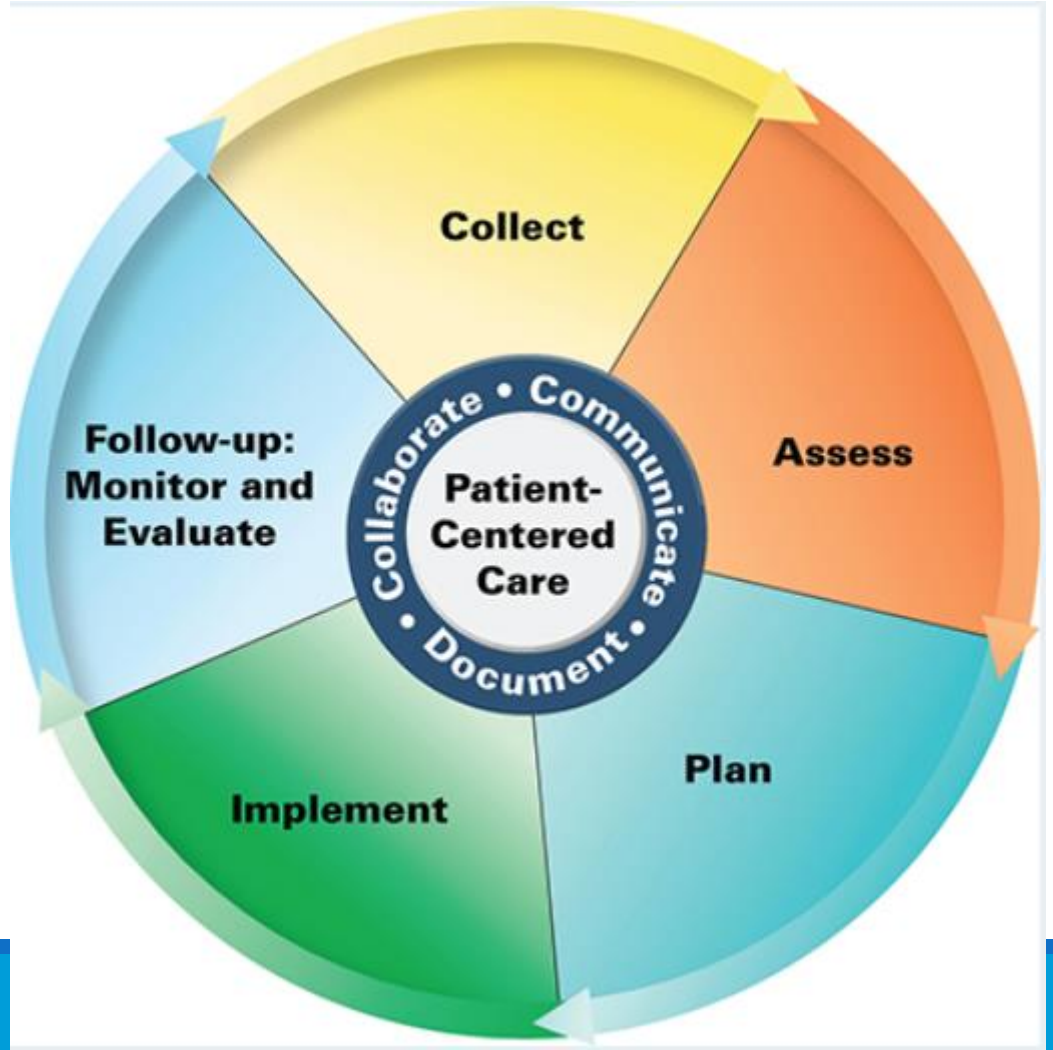
# Pathophysiology

- Plasma LDL-C migrates into the subendothelium; there it gets oxidized and glycated
- Oxidized LDL-C:
  - Recruits circulating monocytes
  - Enhances platelet aggregation and coagulation
  - Stimulates vasoconstriction
  - Provokes inflammatory response



# Patient care process



# Patient care process

**Collect**

- Patient characteristics (eg, age, race, gender, pregnant)
- Patients history: Past medical (eg, HTN), family (eg, early-onset coronary heart disease), social
- Current medications (including over-the-counter [OTC]) and prior lipid-lowering medication use
- Socioeconomic factors that may affect access to treatment or other aspects of care
- Lifestyle assessment: smoking status, exercise, diet, and alcohol intake
- Symptoms indicative of ischemic injury (eg, chest pain)
- Objective data
  - Height, weight, BMI, and blood pressure
  - Lipoprotein concentrations (eg, total cholesterol/LDL-C/HDL-C/triglycerides)
  - Laboratory findings (eg, AST/ALT, urinalysis, TSH, glucose, serum creatinine, and BUN at baseline)

# Patient care process

**Assess**

- Potential secondary causes (eg, diabetes mellitus, alcohol abuse, kidney dysfunction, liver disease, drug-induced, thyroid disorder)
- Special needs of specific patient populations such as children/adolescents, pregnant or menopausal women, older adults, ethnic/racial groups, or high-risk conditions/residual risks (eg, patients with rheumatoid arthritis or residual risk despite statin and lifestyle therapy)
- Presence of high-risk comorbid conditions: diabetes mellitus, peripheral arterial disease, coronary artery disease, chronic kidney disease, carotid artery stenosis, and abdominal aortic aneurysm
- Dyslipidemia-related complications (eg, heart disease, stroke)
- Ten-year ASCVD-risk assessment (only if primary prevention)
- Current medications that may contribute to dyslipidemia
- LDL-C reduction based on statin benefit group (see Table 32-5, Fig. 32-6, and Fig. 32-7)
- Appropriateness and effectiveness of current lipid-lowering therapy (if any)*

# Patient care process

**Plan**

- Tailored therapeutic lifestyle changes (eg, diet and nutrition)
- Drug therapy regimen including specific lipid-lowering medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 32-5, Fig. 32-6, and Fig. 32-7). Monitoring parameters including efficacy (eg, lipid panel, cardiovascular events), safety (medication-specific adverse effects), and time frame (3-month initial follow-up intervals, followed by 6 to 12 month intervals once at goal)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy). Self-monitoring of weight, exercise, diet, drug adherence/adverse effects
- Referrals to other providers when appropriate for coordination of care (eg, physician, dietician)

# Patient care process

**Implement**

- Provide patient education regarding all elements of the treatment plan, including self-management training
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up; consider the time frame to achieve goals of therapy

**Follow-up: Monitor and Evaluate**

- The occurrence of cardiovascular (CV) events
- Determine patient adherence to treatment plan using multiple sources of information
- Determine response to lipid-lowering therapy and weight-loss goals
- Presence of medication-induced adverse effects (eg, elevated transaminases or myalgia on statins)

** Collaborate with patient, caregivers, and other healthcare professionals.*

# Desired outcomes of treatment

- Abnormalities in Cholesterol and TGs may increase the risk for ASCVD events (surrogate markers)

- Treatment goal:
  - Not merely to correct lab abnormalities
  - But also to prevent the development/progression of ASCVD

- Desired outcome of treatment:
  - To prevent ASCVD-related morbidity and mortality (MI, ischemic stroke, revascularization procedures …)

- *Effective* lipid-lowering therapies have *good evidence* in reducing ASCVD risk

TABLE 32-2

**Classification of Total-, LDL-, HDL-Cholesterol, and Triglycerides in Adults**

| | |
|---|---|
| **Total Cholesterol** | |
| <200 mg/dL (5.17 mmol/L) | Desirable |
| 200-239 mg/dL (5.17-6.20 mmol/L) | Borderline high |
| ≥240 mg/dL (6.21 mmol/L) | High |
| **Low-Density Lipoprotein Cholesterol** | |
| <100 mg/dL (2.59 mmol/L) | Optimal |
| 100-129 mg/dL (2.59-3.35 mmol/L) | Near or above optimal |
| 130-159 mg/dL (3.36-4.13 mmol/L) | Borderline high |
| 160-189 mg/dL (4.14-4.90 mmol/L) | High |
| ≥190 mg/dL (4.91 mmol/L) | Very high |
| **High-Density Lipoprotein Cholesterol** | |
| <40 mg/dL (1.03 mmol/L) | Low (Men) |
| <50 mg/dL (1.29 mmol/L) | Low (Women) |
| **Triglycerides** | |
| <150 mg/dL (1.70 mmol/L) | Normal |
| 150-199 mg/dL (1.70-2.25 mmol/L) | Borderline high |
| 200-499 mg/dL (2.26-5.64 mmol/L) | High |
| ≥500 mg/dL (5.65 mmol/L) | Very high |

# General approach to treatment

- *Comprehensive approach* to treating dyslipidemia, ASCVD risk factors, & comorbid conditions (HTN, DM…)

- Therapeutic lifestyle changes:
  - Decreased intake of saturated and trans fats
  - Increased intake of soluble fiber
  - Weight reduction if overweight or obese
  - Increased physical activity
  - Avoiding or quitting tobacco use

- Lipid-lowering therapy:
  - Choice of agent depends on:
    - Which lipid is at undesirable level
    - Which agent decreases ASCVD risk more
  - Statins are typically the 'drug of choice' in dyslipidemia
    - Good evidence on reducing first and recurrent CV events/mortality
    - Pleiotropic effects (independent of LDL lowering): improve endothelial fxn, increase NO, antioxidant, anti-inflammatory, plaque stability
    - Benefit often outweighs risk

# Primary prevention of ASCVD

- **Primary prevention**: for patients *without* established clinical ASCVD

- Insufficient therapeutic lifestyle changes → *May* initiate lipid-lowering agents

- To initiate or Not to initiate lipid-lowering agents?
  - Not merely plasma levels of atherogenic lipoproteins
  - But also individual's ASCVD risk

- How to assess individual's ASCVD risk?
  - Consider risk factors (age, HTN…)
    - Online calculators (e.g. ASCVD Risk Estimator Plus)
    - 10-year vs lifetime ASCVD risk
    - High ASCVD risk? → Lipid-lowering therapy
  - On the other hand, consider risks of lipid-lowering therapy and patient preference

**App should be used for primary prevention patients (those without ASCVD) only.**

AMERICAN COLLEGE of CARDIOLOGY

# ASCVD Risk Estimator Plus

**Current Age** ℹ *

*Age must be between 20-79*

**Sex** *

Male | Female

**Race** *

White | African American | Other

**Systolic Blood Pressure** (mm Hg) *

*Value must be between 90-200*

**Diastolic Blood Pressure** (mm Hg) *

*Value must be between 60-130*

**Total Cholesterol** (mg/dL) *

*Value must be between 130 - 320*

**HDL Cholesterol** (mg/dL) *

*Value must be between 20 - 100*

**LDL Cholesterol** (mg/dL) ℹ ○

*Value must be between 30-300*

**History of Diabetes?** *

Yes | No

**Smoker?** ℹ *

Current ℹ | Former ℹ | Never ℹ

**On Hypertension Treatment?** *

Yes | No

**On a Statin?** ℹ ○

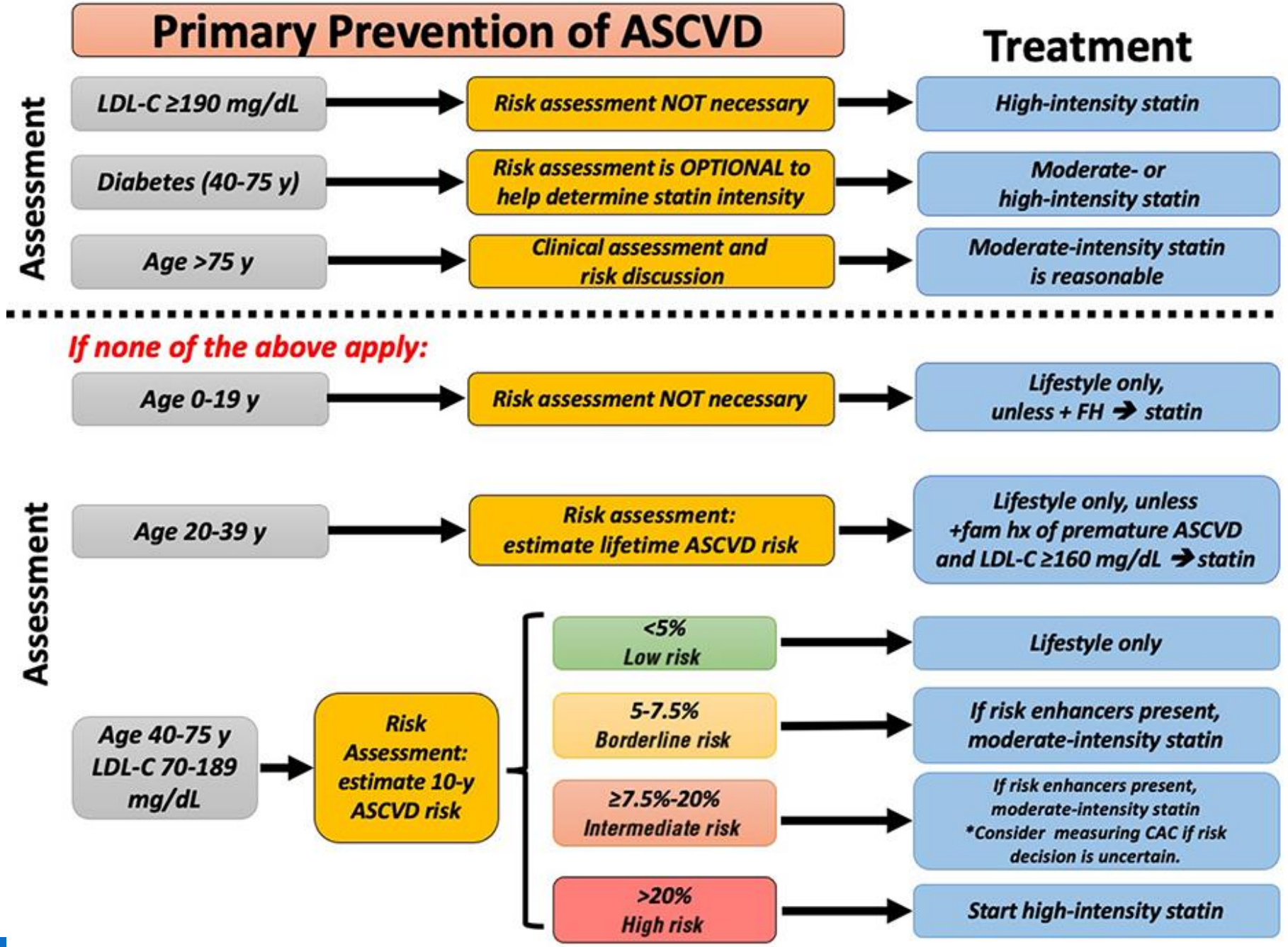
Yes | No

**On Aspirin Therapy?** ℹ ○

Yes | No

**Do you want to refine current risk estimation using data from a previous visit?** ℹ ○

Yes | No




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

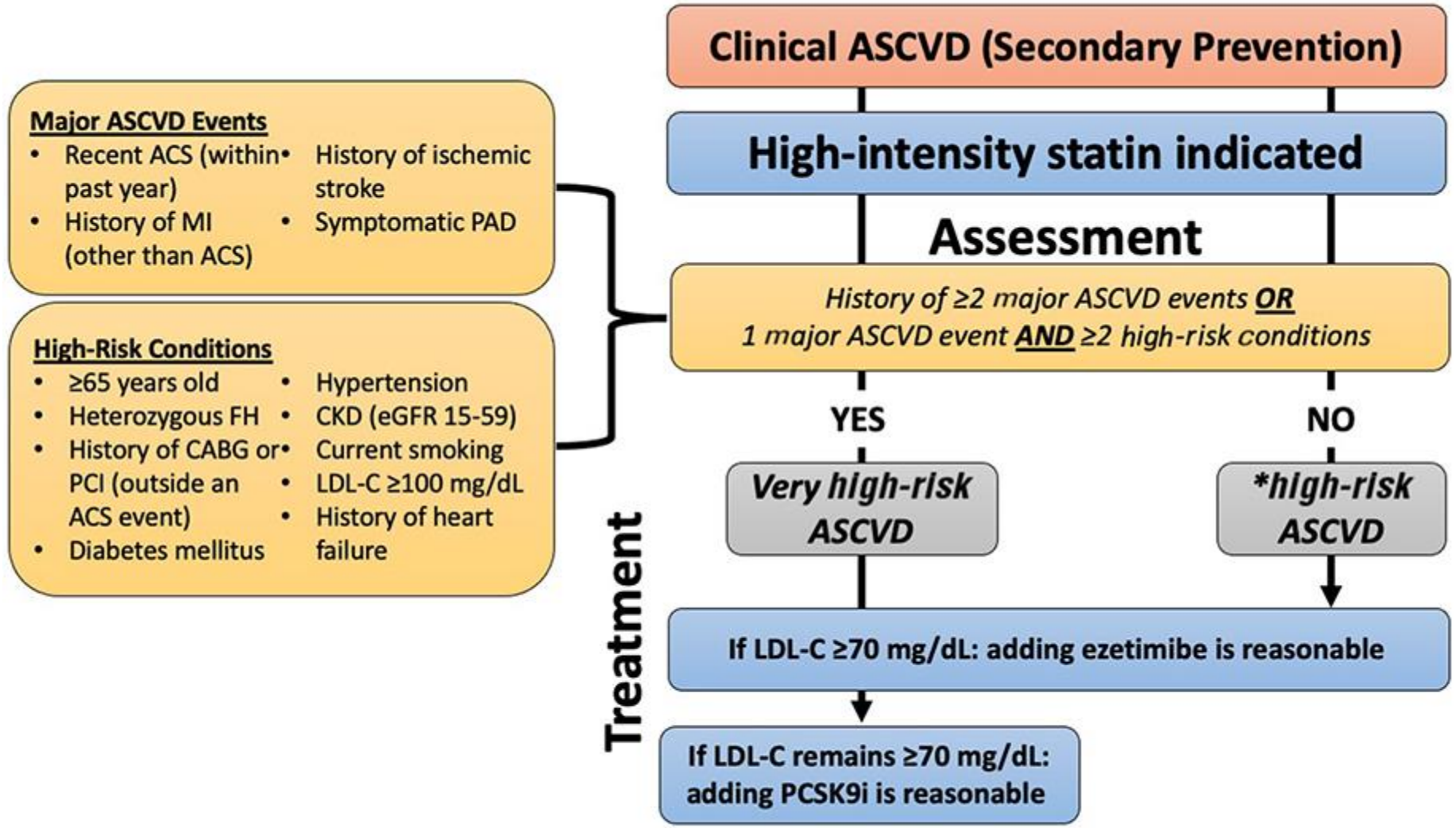
# Secondary prevention of ASCVD

- **Secondary prevention**: for patients *with* established clinical ASCVD

- Not all lipid-lowering agents that reduce LDL-C have resulted in reduced ASCVD events!

- Statins are the drugs of choice:
  - High-intensity statin is automatically indicated
  - Moderate-intensity statin only in adults > 75 yrs if reasonable or those not tolerating high-intensity statin

- Non-statin lipid-lowering therapies:
  - Supportive role in dyslipidemia management
  - Used in combination with statins when adequate LDL-C lowering cannot be achieved with statins alone
  - Used in patients unable to tolerate the recommended statin dose

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# Non-pharmacologic therapy

- Therapeutic lifestyle changes:
  - First-line therapy for any lipoprotein disorder
  - Cornerstone of ASCVD-risk reduction
  - Recommended in all patients, including those receiving lipid-lowering therapy

- No single diet is suitable for all patients!
  - Adapt to patient's caloric requirements, cultural food preferences, medical conditions (e.g. DM)

- Patients *without* ASCVD, DM, or high-risk features:
  - 12-week trial of lifestyle modification is recommended before considering lipid-lowering therapy

- Patients *with* established ASCVD or DM:
  - Lifestyle modification alone is inappropriate given the benefit of statins in these patients

# Non-pharmacologic therapy

| Recommendations to Modify Select Lipid Parameters | |
|---|---|
| Lower LDL cholesterol | • Increase soluble fiber intake<br>• Phytosterol (2 g/day) supplementation |
| Increase HDL cholesterol | • Increase physical activity<br>• Smoking cessation |
| Lower triglycerides | • Lose weight (5%-10% body weight loss)<br>• Increase physical activity<br>• Abstain from alcohol<br>• Reduce intake of refined carbohydrates and sugars |

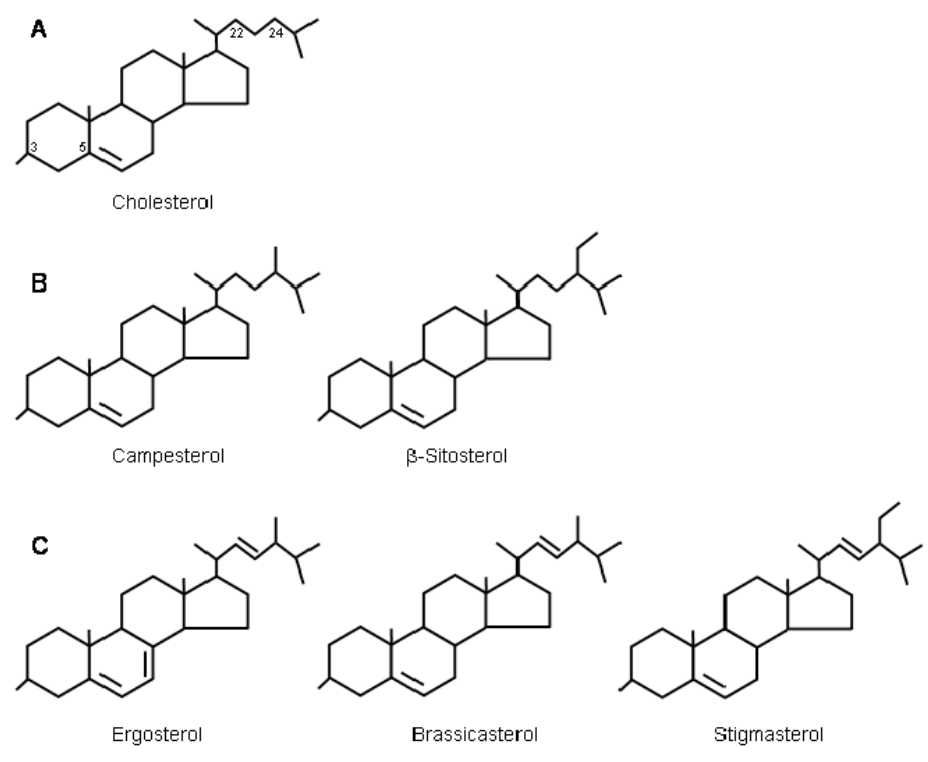
# Non-pharmacologic therapy

| Recommendations to Reduce ASCVD Risk | |
|---|---|
| Nutrition and diet | • Avoid eating trans fats<br>• Increase intake of vegetables, fruits, legumes, nuts, whole grains, and fish<br>• Replace foods containing saturated fats with unsaturated (monounsaturated and polyunsaturated) fats<br>• Minimize intake of processed meat products, refined carbohydrate foods, and sweetened beverages<br>• Reduce intake of cholesterol and sodium-containing foods<br>• For patients who are overweight or obese, reduce daily calories to achieve and maintain weight loss of 5%-10% |
| Physical activity | • Obtain at least 150 min/week of moderate-intensity or 75 minutes of vigorous-intensity physical activity<br>• Decrease sedentary behaviors |
| Other lifestyle factors | • Smoking cessation and avoiding tobacco products<br>• Avoid secondhand smoke exposure |

# Dietary supplements

- Fibers:
  - Bind cholesterol and bile acids in small intestines
  - Laxative effect (relieve constipation associated with bile acid sequestrants)
  - Recommended total daily fiber intake ~ 25 g/day
  - Consume with enough water to avoid GI distress

- Phytosterols:
  - Naturally found in plants
  - Interferes with intestinal cholesterol absorption
  - Ingestion of 2 g/day reduces LDL-C by 5% - 15%
  - Doses > 3 g/day confer no additional LDL-C lowering
  - Unknown long-term effects on ASCVD risk
  - Generally recognized as safe, may cause GI distress



# Dietary supplements

- Oily fish:
  - Oily fish (e.g. salmon) is associated with reduced ASCVD risk
  - AHA recommends eating oily fish at least twice a week
  - Concerns about environmental contaminants (e.g. in tuna)

- Fish oil supplementation:
  - Alternative to oily fish
  - Provides consistent daily intake of omega-3 PUFAs
    - e.g. eicosapentaenoic acid ‘EPA’, docosahexaenoic acid ‘DHA’
  - Significantly reduces TG and VLDL-C, but may increase TC and LDL-C (mainly DHA)
  - Low doses of omega-3 PUFA (< 2 g/day) do not reduce the risk of ASCVD events
    - Low doses are not recommended in primary prevention
  - Other potentially favorable CV effects: antiarrhythmic, antiplatelet, anti-inflammatory

# Dietary supplements

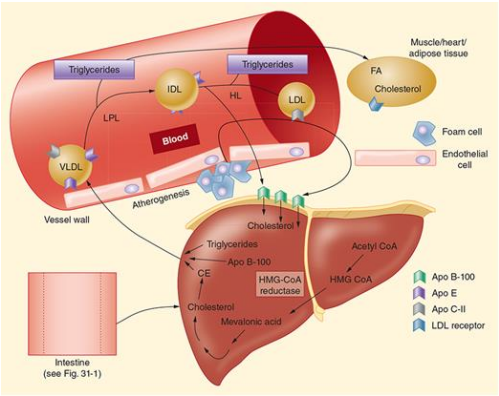
- Red yeast rice:
  - From Chinese medicine
  - Active ingredient is monacolin (chemically identical to lovastatin → '*natural statin!*')
  - Red yeast rice products in market have variable monacolin concentrations
    - From little/no monacolin to toxic levels causing rhabdomyolysis, liver toxicity, and renal failure
  - Not recommended as an alternative to statins
  - Avoid concurrent use with prescribed statins

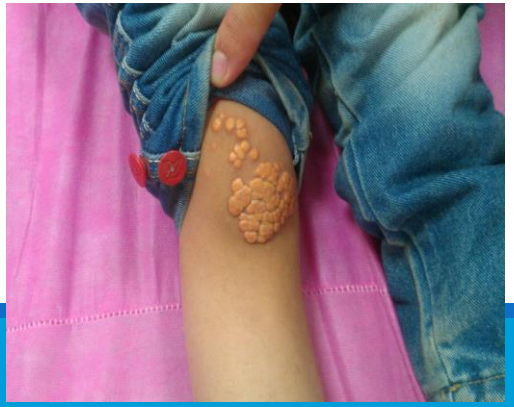
# Familial hypercholesterolemia

- Typically results from genetic mutation in LDL receptors
- Physical findings: Deposition of LDL-C in tendons (xanthoma), arteries (atheroma), eyelids, cornea

- Suspected in adults with:
  - LDL-C levels ≥ 190 mg/dL or non-HDL-C ≥ 220 mg/dL
  - Family history of high cholesterol or ASCVD in first-degree relatives

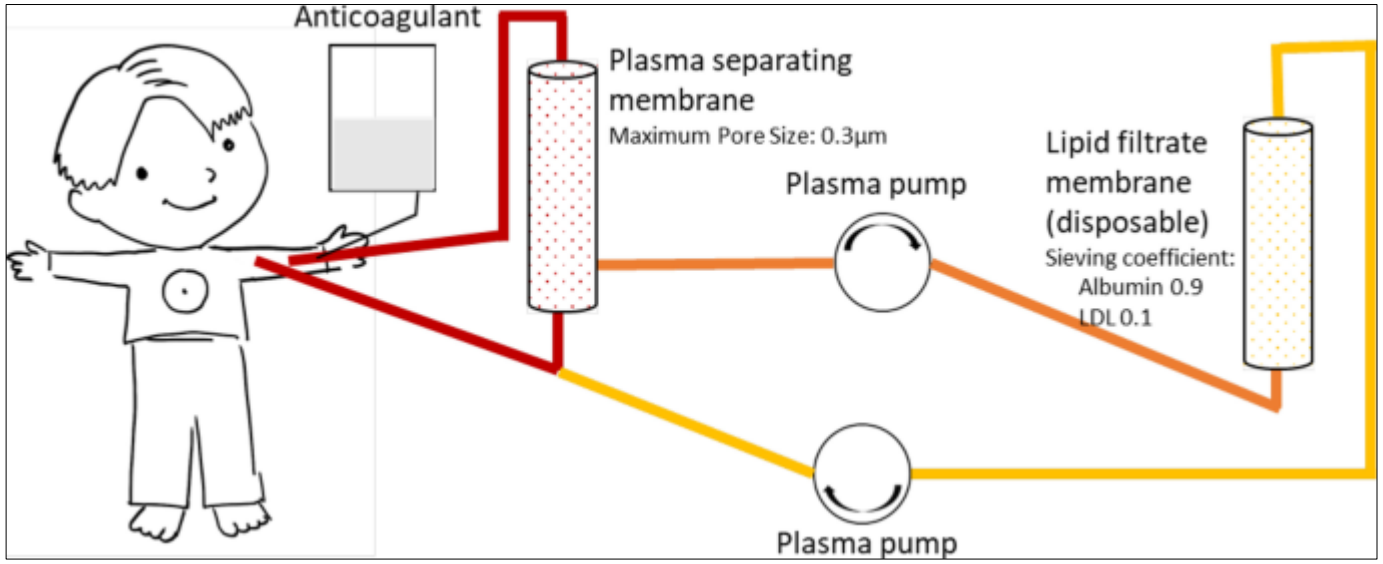
- Types of Familial Hypercholesterolemia:
  - Homozygous FH
    - The patient inherits two FH genes, one from each parent (both parents have FH)
    - More serious (higher LDL, earlier onset of ASCVD and death)
  - Heterozygous FH
    - The patient inherits one FH gene from a parent
    - More common



# Familial hypercholesterolemia Treatment

- Treatment of FH in adults:
  - Intensive lifestyle modifications
  - Pharmacological therapy
  - LDL apheresis (for homozygous FH, similar to dialysis; removes LDL from blood)
  - Liver transplant (for homozygous FH)



# Familial hypercholesterolemia Treatment

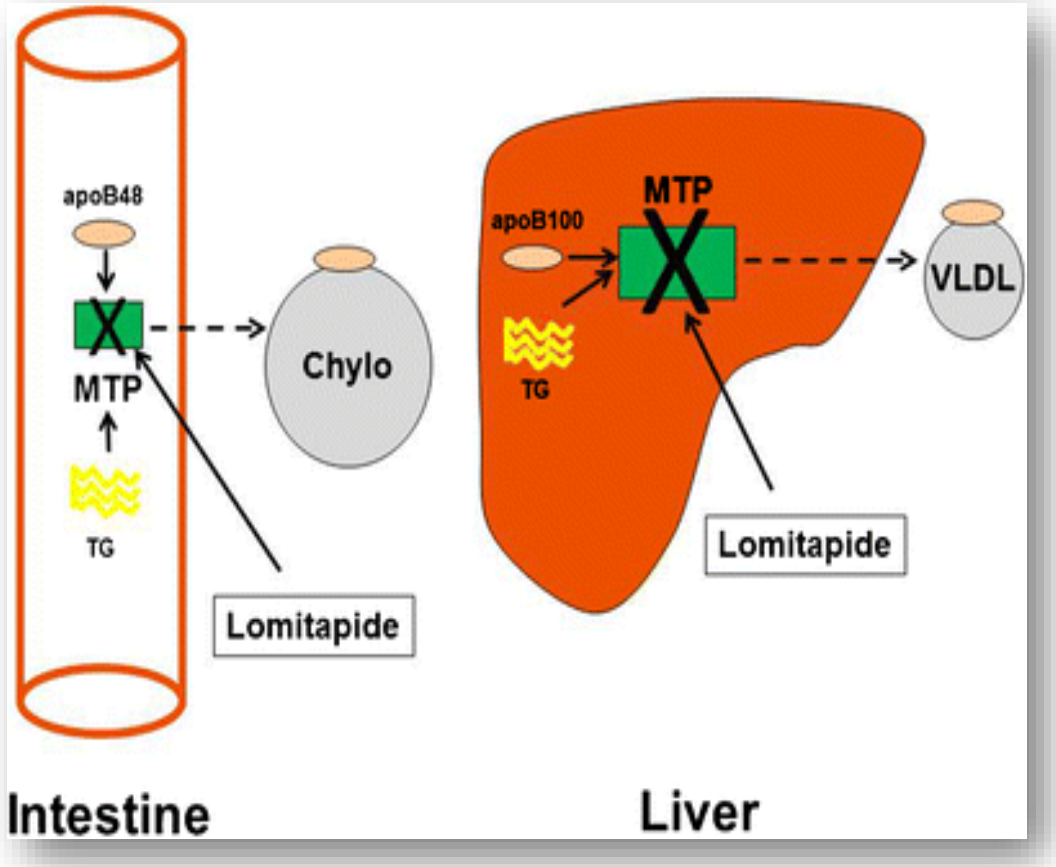
- Patients with FH and *negative* history of ASCVD:
  - High-intensity statin
  - Those with LDL-C ≥ 100 mg/dL despite max-tolerated statin should receive non-statin therapies
    - Ezetimibe, *and/or* Bempedoic acid, *and/or* PCSK9 inhibitor

- Patients with FH and *positive* history of ASCVD:
  - High-intensity statin
  - Those with LDL-C ≥ 70 mg/dL despite max-tolerated statin should receive non-statin therapies
    - Ezetimibe, *and/or* Bempedoic acid, *and/or* PCSK9 inhibitor

- Other agents (for homozygous FH):
  - Lomitapide, Mipomersen, Evinacumab

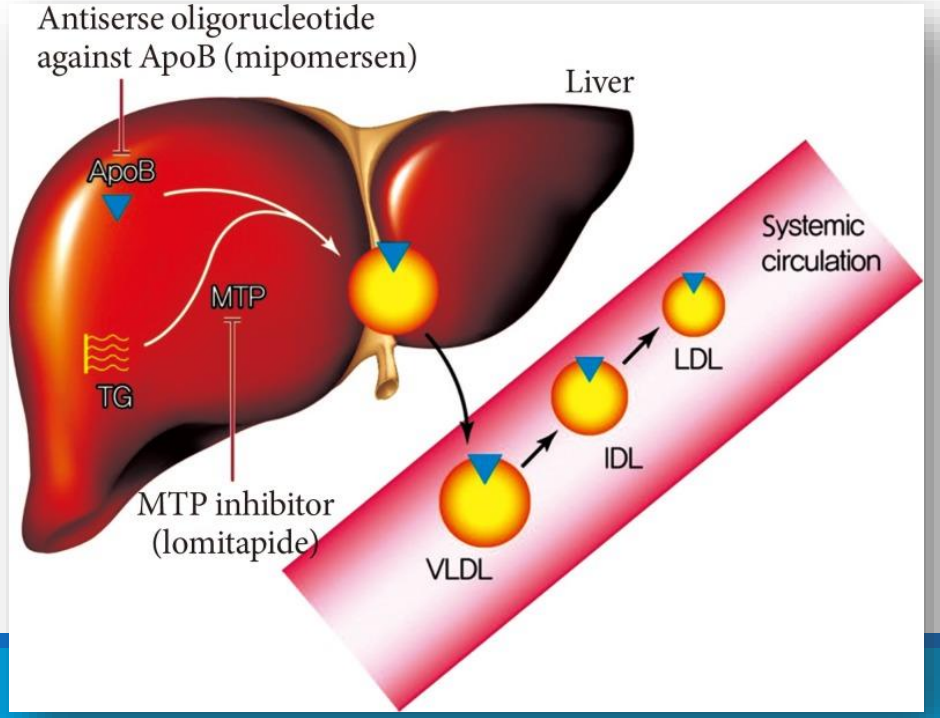
# Familial hypercholesterolemia Treatment

- Lomitapide:
  - Orphan drug
  - Reduces LDL-C levels by ~40%
  - Microsomal triglyceride transfer protein (MTP) inhibitor
  - MTP role: assembly of apoB-containing lipoproteins in liver and intestines and secretion into circulation
  - Administered orally
  - Black box warning for severe hepatotoxicity



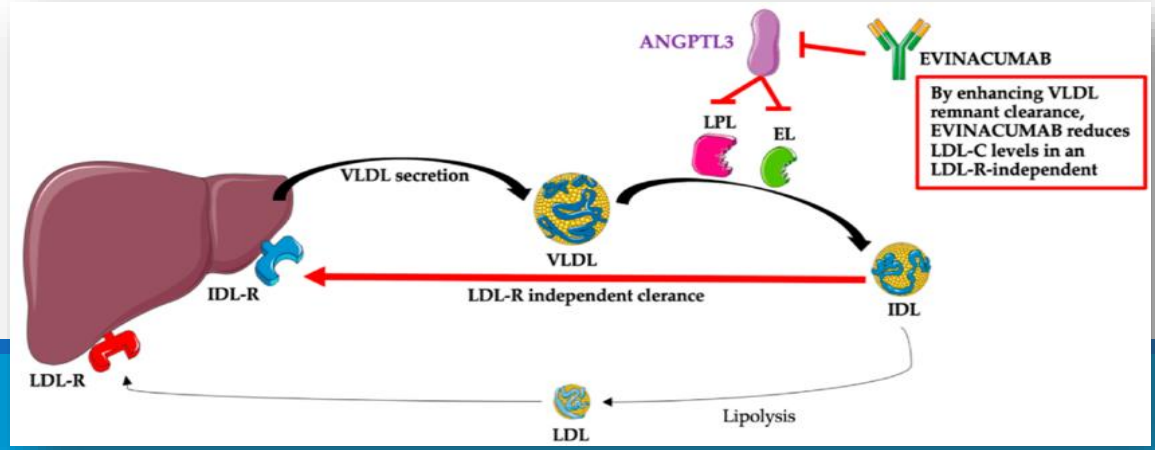
# Familial hypercholesterolemia Treatment

- Mipomersen:
  - Orphan drug
  - Reduces LDL-C levels by ~25%
  - Oligonucleotide inhibitor of apolipoprotein B-100 (ApoB-100) synthesis
  - ApoB-100: a main component of VLDL and LDL
  - Administered via subcutaneous injection
  - Injection site pain and reactions
  - Black box warning for severe hepatotoxicity
  - No longer available in the US



# Familial hypercholesterolemia Treatment

- Evinacumab:
  - Approved in patients ≥ 12 years
  - Reduces LDL-C by ~50%; Reduces TG by ~55%
  - Unknown whether it reduces ASCVD events
  - Humanized monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3) protein
  - ANGPTL3 protein: inhibits lipoprotein lipase (LPL) and endothelial lipase (EL)
  - LPL and EL role: lipid metabolism; leading to decreased LDL, HDL, and TG
  - Administered as an IV infusion every 4 weeks
  - Infusion-site reactions, influenza-like illness, rhinorrhea



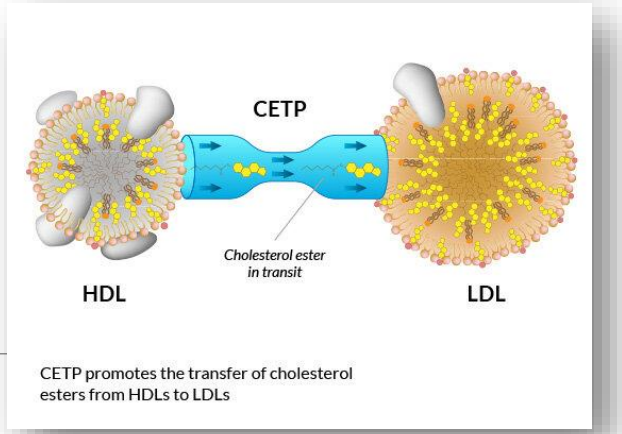
# Hypertriglyceridemia

- Elevated TG levels are strongly associated with ASCVD risk
- **Lifestyle interventions**: for all patients; 5% - 10% reduction in body weight, reducing sugar and refined CHOs, increasing physical activity, restricting alcohol, smoking cessation
- **Addressing secondary causes**: DM, CKD, drugs (protease inhibitors, atypical antipsychotics…)
- **Statins**: First-line agents (if TGs remain elevated after addressing the above two); reduce TG levels by up to 30% at higher doses; reduce LDL-C
- **Fibrates**: Effectively lower TG levels; not routinely used for borderline-high TG levels; no evidence in reducing ASCVD risk
- **Omega-3 PUFA**: Significantly lower TG levels at higher doses (2 - 4 g/d); only EPA prescription product is indicated for borderline-high TG levels and to reduce ASCVD risk

# Severe hypertriglyceridemia

- Fasting TG levels > 500 mg/dL
- Mostly a combination of genetic and acquired factors (e.g. DM)
- Large TG-rich chylomicrons (hyperchylomicronemia) occlude pancreatic capillaries → Ischemic damage + Release of lipase → Production of free fatty acids → Release of inflammatory mediators and free radicals → Inflammation, edema, necrosis → Pancreatitis
- Management:
  - Dietary fat restriction
  - Patients with ASCVD risk < 7.5%: Fibrates and omega-3 PUFA as first-line agents (effective in lowering TG)
  - Patients with ASCVD risk ≥ 7.5%: Statins as first-line agents
  - Patients with ASCVD risk ≥ 7.5% & persistent TGs > 500 mg/dL despite statin therapy: Statin + omega-3 PUFA or fibrate
- Success in treatment:
  - Reducing TGs < 500 mg/dL
  - Preventing pancreatitis

# Low HDL-C



CETP promotes the transfer of cholesterol esters from HDLs to LDLs

- Low HDL-C is a strong independent risk predictor of ASCVD
- Possible causes: Diabetes, physical inactivity, cigarette smoking, high CHO intake, drugs

- No evidence that increasing HDL-C reduces ASCVD risk
- No specific goal for HDL-C raising (the primary target remains LDL-C)

- Management:
  - **Lifestyle modification**: The preferred approach; smoking cessation, increasing physical activity
  - **Niacin**: Can increase HDL-C > other lipid-lowering agents (immediate-release > sustained-release)
  - **Cholesterol ester transfer protein (CETP) inhibitors**: Can increase HDL-C up to 135%
  - Although alcohol consumption increases HDL-C, it is not recommended

# Lipid-lowering therapies

- Medications primarily lowering atherogenic cholesterol:
  - 3-Hydroxy-3-MethylGlutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors (Statins)
  - Cholesterol Absorption Inhibitors
  - Bile Acid Sequestrants
  - Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors
  - Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitors

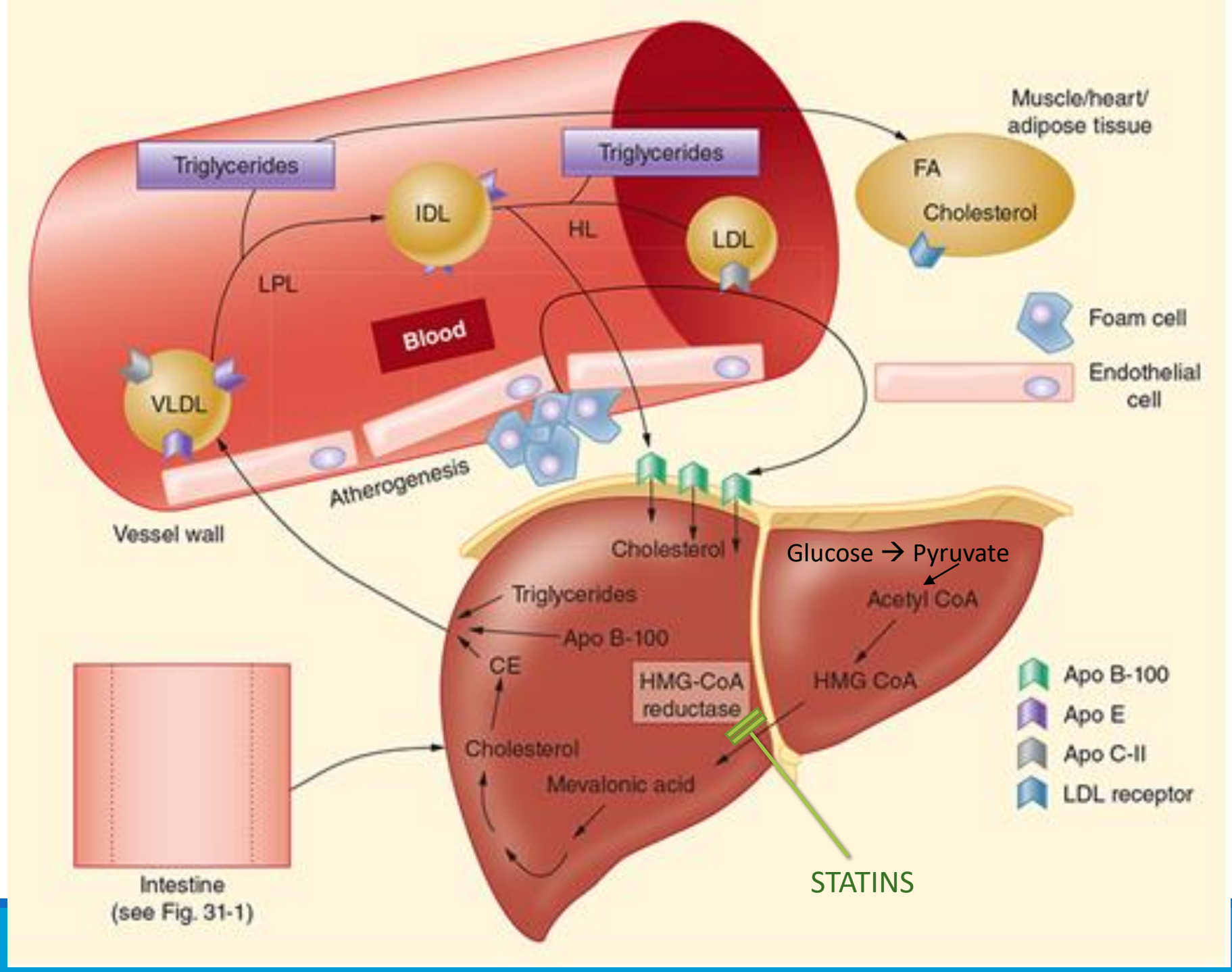
- Medications primarily lowering triglycerides:
  - Fibric Acid Derivatives (Fibrates)
  - Omega-3 Polyunsaturated Fatty Acids (PUFAs)
  - Nicotinic Acid (Niacin)

# Lipid-lowering therapies
## Statins

- First-line lipid-lowering therapies for dyslipidemia:
  - Evidence on decreasing the risk of first CV events (primary prevention)
  - Evidence on decreasing the risk of recurrent CV events (secondary prevention)

- Effects on lipids:
  - Significantly reduce LDL-C levels (20% - 60%)
  - Modestly increase HDL-C levels (6% - 12%)
  - Decrease TG levels (10% - 29%)

- Mechanism of action:
  - Inhibit the rate-limiting step in cholesterol de novo biosynthesis →
  - Enhance LDL catabolism through LDL receptors



# Lipid-lowering therapies
## Statins

- Statin selection:
  - ASCVD risk
  - Indicated intensity

- Order of LDL-C lowering potency:
  - Rosuvastatin > Atorvastatin > Pitavastatin > Simvastatin > Lovastatin > Pravastatin > Fluvastatin

- Plasma half-life:
  - Relatively short (1 - 3 hours) for most statins
  - Longer for rosuvastatin, atorvastatin, and pitavastatin → May account for their potency

- Adverse effects:
  - Generally, well tolerated; Low discontinuation rates due to adverse effects
  - Statin-associated muscle symptoms (SAMS)
  - Mild elevations in serum transaminase levels (mainly ALT)
  - Small increased risk of new-onset diabetes

TABLE 32-5

## Intensity of Statin Therapy by Drug and Daily Dose

| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Lowers LDL-C on average by ≥50% | Lowers LDL-C on average by 30% to <50% | Lowers LDL-C on average by <30% |
| **Atorvastatin 40-80 mg** | **Atorvastatin 10-20 mg** | Simvastatin 10 mg |
| **Rosuvastatin 20-40 mg** | **Rosuvastatin 5-10 mg** | **Pravastatin 10-20 mg** |
| | **Simvastatin 20-40 mg**[a] | **Lovastatin 20 mg** |
| | Pravastatin 40-80 mg | Fluvastatin 20-40 mg |
| | **Lovastatin 40 mg** | Pitavastatin 1 mg |
| | Fluvastatin XL 80 mg | |
| | **Fluvastatin 40 mg BID** | |
| | Pitavastatin 2-4 mg | |

[a] Simvastatin is not recommended by the FDA to be initiated at 80 mg/day due to increased risk of myopathy and rarely rhabdomyolysis.

FDA, Food and Drug Administration; RCT, randomized clinical trials.

Boldface type indicates medications that have cardiovascular outcome data from RCTs when given in the specified dose.

# Lipid-lowering therapies
## Statins: **ADRs (SAMS)**

- ~ 10% - 25% of statin users
- Frequently reported as a reason for statin discontinuation
- Various definitions; Subjective clinical assessment

- **Myalgia**: Bilateral muscle achiness, weakness, or cramps affecting larger muscles (e.g. thighs, back)
  - The most reported muscle-related adverse effect with statin therapy

- **Myopathy**: A general term for any muscle-related symptoms
  - However, often used interchangeably with myalgia

- **Rhabdomyolysis**: Rapid breakdown of skeletal muscle → CK elevations > 10 times the upper limit of normal
  - The most concerning of SAMS, but very rare (0.1% of patients)
  - Release of myoglobin (and other proteins and electrolytes) from damaged muscles → Systemic complications (e.g. AKI)
  - Dark or “tea-colored” urine, nausea, vomiting, confusion, coma, cardiac arrhythmias, electrolyte disturbances, death
  - Non-statin causes: extreme physical exercise, metabolism disorders (e.g. DKA), drugs (e.g. colchicine), toxins, infection

# Lipid-lowering therapies
## Statins: **ADRs (SAMS)**

- Risk factors for SAMS development:
  - Elderly, female, low BMI, frequent heavy exercise, comorbidities (kidney disease, hypothyroidism), DDIs
- ~ 80% of all medications are metabolized by hepatic CYP450 (mainly CYP3A4)
- All statins (except pravastatin) are metabolized by hepatic CYP450
  - Lovastatin, simvastatin, and atorvastatin are predominantly metabolized by CYP3A4 → More significant DDIs
  - Fluvastatin, pitavastatin, and rosuvastatin are predominantly metabolized by other CYP isoenzymes (CYP2C8, CYP2C9, CYP2C19)
- Drugs that compete with statins for CYP450 or inhibit CYP450 increase statin levels & SAMS risk
  - e.g. verapamil, gemfibrozil
- Patients with multiple risk factors: Start low and Titrate slow (to the desired potency)

# Lipid-lowering therapies
## Statins: **ADRs (SAMS)**

- Discontinue statin if intolerable symptoms
- If symptoms resolve, initiate a different statin at a lower dose
  - Some statins (e.g. rosuvastatin) are better tolerated than others (e.g. simvastatin)
- If symptoms do not resolve, identify other potential causes of muscle pain
  - e.g. hypothyroidism, vitamin D deficiency
- Alternative dosing strategies using statins with long half-lives
  - e.g. atorvastatin, rosuvastatin, pitavastatin QOD
- Non-statin therapies if patients fail multiple statins
- CK measurement prompted by patient symptoms (routine monitoring not recommended)
- Assure patients that statins are effective and safe, and SAMS is reversible with statin discontinuation

# Lipid-lowering therapies
## Statins: **ADRs (Serum transaminase elevation)**

- Most liver enzymes are not a specific measure of liver function

- No causal relationship between statin use and liver failure
  - Statins may be initiated in chronic liver disease, compensated cirrhosis, non-alcoholic fatty liver disease
  - Statins are contraindicated in decompensated cirrhosis, acute liver failure

- Routine periodic monitoring of liver enzymes is not required
  - Measure at baseline and if patients have S/S suggestive of liver injury (to assess change over time)

- <u>Other potential causes for elevated liver enzymes</u>:
  - Excessive alcohol intake, infection, medications…

# Lipid-lowering therapies
## Statins: **ADRs (New-onset diabetes)**

- Risk factors:
  - Higher doses of statins
  - Risk factors for DM: obesity, metabolic syndrome, impaired fasting glucose…

- Unknown mechanism:
  - Disruption of cholesterol-sensitive cellular functions that affect insulin secretion and sensitivity?

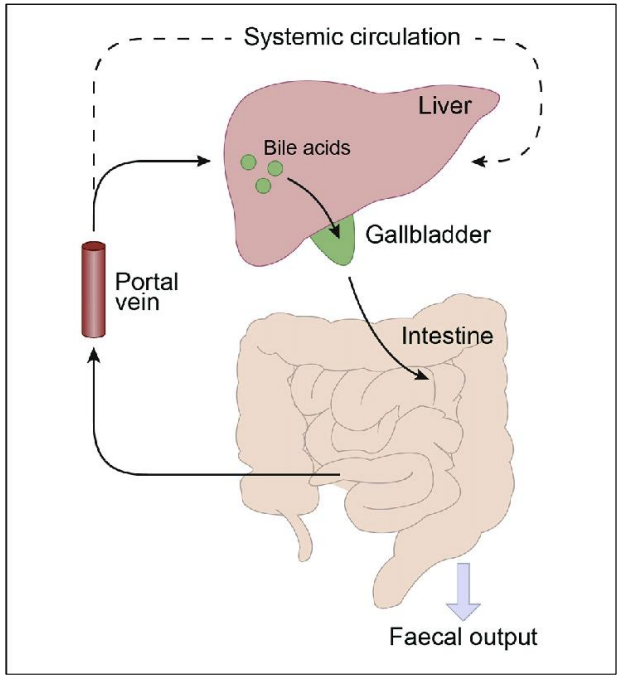
- Benefit of statin therapy greatly outweighs the Risk of new-onset diabetes

# Lipid-lowering therapies
## Cholesterol absorption inhibitors

- Ezetimibe
- Adjunct therapy with statin
  - Monotherapy: modest reduction in LDL-C (15% - 24%)
  - Combination with statin: higher reduction in LDL-C, lower risk of recurrent CV events
- MOA:
  - Inhibiting Niemann-pick C1-like 1 (NPC1L1) protein
  - NPC1L1 role: mediating intestinal cholesterol absorption (and delivery to liver), inhibiting hepatobiliary cholesterol excretion
- Adverse effects:
  - Generally, well tolerated
  - Mild GI complaints (diarrhea)
  - Myalgia and mild ALT elevations when used in combination with statins
  - No effects on CYP450

# Lipid-lowering therapies
## Bile acid sequestrants

- Colesevelam, Colestipol, Cholestyramine
- Adjunct therapy with statin
  - Monotherapy: modest reduction in LDL-C (13% - 20%) and CV events
  - Combination with statin: no data
- Colesevelam is approved for type 2 DM
  - Enhancing incretins secretion (GIP, GLP-1) and β-cell function
- <u>MOA</u>:
  - Cholesterol is a major precursor of bile acids
  - Binding bile acids in the intestinal lumen → Fecal excretion of bile acids →
  - Decreased enterohepatic circulation of bile acids → Increased hepatic synthesis of bile acids from cholesterol → Depleted hepatic cholesterol → Increased number of hepatic LDL-R to bring in cholesterol from blood → Decreased circulating LDL-C



# Lipid-lowering therapies
## Bile acid sequestrants: **ADRs**

- Poor tolerability
  - Reserved for those unable to tolerate ezetimibe who need additional LDL lowering despite maximally tolerated statin
- GI complaints
  - Early powder formulations ‘cholestyramine’ > Tablet forms ‘colesevelam’ (fewer DC rates)
  - Constipation, bloating, fullness, nausea, flatulence
- Increased hepatic VLDL production (contraindicated when TG > 300 mg/dL)
- Impaired absorption of fat-soluble vitamins and drugs
  - e.g. warfarin, levothyroxine, phenytoin
  - Take other medications 1 hour before or 4 hours after BAS
- No fetus risk (not systemically absorbed)
  - First-line agents during pregnancy

# Lipid-lowering therapies
## PCSK9 inhibitors

- Alirocumab, Evolocumab
- Monotherapy: approved for familial hypercholesterolemia
- Combination with statin: reduces LDL-C by up to 60% (potent) and recurrent CV events

- MOA:
  - PCSK9 binds to and degrades hepatic LDL-R
  - Inhibiting PCSK9 → Increased available hepatic LDL-R → Increased LDL-C clearance from circulation

- SQ administration, Q 2 weeks or once monthly

- Adverse effects:
  - Favorable safety profile
  - Injection site reactions (most common)
  - 'Flu-like' symptoms

# Lipid-lowering therapies
## PCSK9 inhibitors

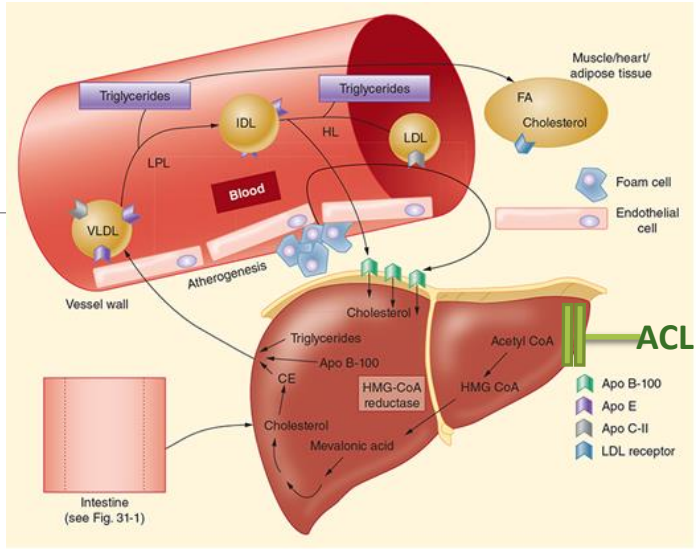
- Inclisiran
- Combination with statin: reduces LDL-C by ~ 50% (approved for familial hypercholesterolemia)

- MOA:
  - Small interfering RNA molecule → Inhibiting messenger RNA → Reducing synthesis of PCSK9

- SQ administration, Q 6 months

- Adverse effects:
  - Injection site reactions (most common, transient, mild)

# Lipid-lowering therapies
## ACL inhibitors




- Bempedoic acid
- Monotherapy: modest reduction in LDL-C (15% - 20%)
- Combination with statin: modest reduction in LDL-C (15% - 20%)
- Combination with ezetimibe: reduces LDL-C by 36%

- MOA:
  - ACL: Enzyme responsible for generating Acetyl CoA (needed for cholesterol de novo biosynthesis)
  - ACL inhibition → Depletion of hepatic Acetyl CoA → Depletion of hepatic cholesterol → Overexpression of LDL-R → Decreased circulating LDL-C
- Oral administration
- Indication: Patients not achieving desired treatment goals on maximally tolerated statin + ezetimibe who prefer non-injectable therapy

# Lipid-lowering therapies
## ACL inhibitors: **ADRs**

- Generally, well tolerated
- Fewer muscle symptoms compared to statins
- Hyperuricemia (acute gout)
  - Inhibit the renal tubular organic anion transporter 2 (OAT2) responsible for uric acid secretion
- Tendon rupture
  - Rare
  - Risk factors: age > 60 years, concurrent use of corticosteroids or fluoroquinolones, renal failure, history of tendon disorders

# Lipid-lowering therapies
## Fibrates

- Gemfibrozil, Fenofibrate
- Monotherapy:
  - Reduce TGs by 20% - 50% (potent) and CV events
  - Increase HDL by 10% - 15%
- Combination with statin: Less evidence

- MOA:
  - Gemfibrozil: Increasing LPL activity; Decreasing synthesis/secretion of VLDL from liver into plasma
  - Fenofibrate: Peroxisome proliferator-activated receptor α (PPARα) agonist → Inhibiting apoprotein C-III (an inhibitor of LPL) → Increasing LPL activity

- Indication: TG levels > 500 mg/dL to reduce the risk of acute pancreatitis

# Lipid-lowering therapies
## Fibrates: **ADRs**

- Generally, well tolerated
- Modest rise in LDL-C
- GI complaints
- Transient elevations in transaminase levels
- Gallstone formation (rare)
- Worsening renal function ‘fenofibrate’ (transient, self-limiting)
- Enhancing warfarin effect ‘fenofibrate’ (closely monitor INR)
- Muscle-related adverse effects (more common when combined with statins)
  - Gemfibrozil has potent effects on CYP450 enzymes and renal transporters → Significantly increases serum statin levels and risk of SAMS
  - Gemfibrozil should not be initiated in patients receiving statin therapy (fenofibrate is favored)

# Lipid-lowering therapies
## PUFAs

- EPA, DHA
- Monotherapy: high doses (2 - 4 g/day) significantly reduce TG and VLDL levels (20% - 50%)
- Combination with statin: EPA reduces CV risk

- MOA:
  - Increasing hepatic oxidation of free fatty acids
  - Activating PPARα → Inhibiting apoprotein C-III (an inhibitor of LPL) → Increasing LPL activity
  - Increasing LDL hydrolysis (EPA only)

- Product quality:
  - Prescription omega-3 PUFA products (~ 1 g EPA/DHA per capsule) vs.
  - OTC “fish oil” supplement products (often < 300 mg EPA/DHA per capsule; not regulated by FDA)

# Lipid-lowering therapies
## PUFAs: **ADRs**

- GI complaints (abdominal pain)
- Caution in patients with allergy to fish
- Prolong bleeding time (caution when used concomitantly with antiplatelets/anticoagulants)
- Minimal drug-drug interactions
- Atrial flutter/fibrillation

# Lipid-lowering therapies
## Niacin

- Monotherapy:
  - Increases HDL-C (5% - 30%)
  - Lowers TG (20% - 50%)
  - Lowers LDL-C modestly (5% - 20%)
- Combination with statin: does not improve CV outcomes

- MOA:
  - Increasing HDL-C: reducing HDL catabolism and hepatic removal of HDL apoA-I
  - Decreasing TGs: enhancing LPL and inhibiting the release of free fatty acids from adipose tissue to plasma
  - Decreasing LDL-C: reducing the hepatic synthesis of VLDL, and subsequently LDL

# Lipid-lowering therapies
## Niacin: **ADRs**

- Poorly tolerated
- Cutaneous flushing, itching, pruritus
  - Mainly immediate-release products; reduced by taking niacin with meals, slowly titrating the dose upward, using extended-release products
  - Mediated by PGs; reduced by administering aspirin 325 mg shortly before niacin
  - Increased by concomitant alcohol and hot beverages; avoid at time of ingestion
- Hepatotoxicity, elevated liver function tests (often transient and mild with doses < 3 g/day)
- Hyperuricemia, hyperglycemia
- Contraindicated in active liver disease and active peptic ulcer disease

| Lipid-Lowering Drug Class | Adverse Effects | | Contraindications |
|---|---|---|---|
| | Common/possible (1%- 10%) | Rare/unlikely (<1%) | |
| Statins | • Statin associated muscle symptoms (myalgia/myopathy)<br>• New-onset diabetes mellitus<br>• Transient, mild elevation in transaminase levels | • Rhabdomyolysis<br>• Severe hepatotoxicity | • Pregnancy/breastfeeding **(No More!)**<br>• Decompensated cirrhosis<br>• Acute liver failure |
| Cholesterol absorption inhibitors | • GI adverse effects<br>• Myalgias (when used with statin)<br>• Elevated transaminase levels (when used with statin) | • Thrombocytopenia | • Pregnancy/breastfeeding<br>• Acute liver failure |
| Bile acid sequestrants | • GI adverse effects and/or obstruction<br>• Impaired absorption of fat-soluble vitamins<br>• Reduced bioavailability of select drugs | • Ileus<br>• Cholecystitis<br>• Severe hypertriglyceridemia | • History of bowel obstruction<br>• Fasting TG are 300 mg/dL or higher |

| Lipid-Lowering Drug Class | Adverse Effects | | Contraindications |
|---|---|---|---|
| | Common/possible (1%- 10%) | Rare/unlikely (<1%) | |
| ACL inhibitors | • Hyperuricemia | • Increased risk of tendon rupture<br>• Increased risk of benign prostate hyperplasia | |
| PCSK9 mAbs | • Injection-site reactions<br>• Flu-like symptoms post-injection | | • Hypersensitivity reaction to alirocumab or evolocumab |
| Inclisiran | • Injection-site reactions | | • Pregnancy/breastfeeding |

| Lipid-Lowering Drug Class | Adverse Effects | | Contraindications |
|---|---|---|---|
| | Common/possible (1%- 10%) | Rare/unlikely (<1%) | |
| Fibrates | • GI adverse effects<br>• Transient elevation in transaminases<br>• Myalgias (especially when used with statin)<br>• Mild increase in serum creatinine | • Increased risk of gallstones | • Pre-existing gallbladder disease<br>• CrCl of 30 mL/min (0.5 mL/s) or lower |
| Omega-3 PUFA | • GI adverse effects<br>• Eructation<br>• Increased risk of bleeding when used with antiplatelets or anticoagulants<br>• Increased risk of atrial fibrillation or flutter | | • Caution in patients with allergy or sensitivity to fish and/or shellfish |
| Niacin | • Dermatologic effects (flushing/itching)<br>• Increased transaminases<br>• Hyperuricemia<br>• Hyperglycemia | • Increased risk of atrial fibrillation or flutter<br>• Rhabdomyolysis (with statin)<br>• Hepatotoxicity (with statin) | • Active peptic ulcer<br>• Arterial hemorrhage<br>• Persistently elevated transaminase levels |

# Special populations
## Elderly

- ASCVD risk increases with age

- Benefit of moderate-high intensity statin for secondary prevention > primary prevention
  - Especially in those > 75 years

- Higher risks of statin (and other antilipemic agents) in older adults:
  - Changes in body composition, renal function…
  - More prone to developing SAMS → Risk of falls and functional deterioration?
  - Cognitive decline?
  - Cataracts?
  - New-onset type 2 diabetes

- Factors favoring discontinuing statins in adults > 75 years taking them for primary prevention:
  - Worsening physical or cognitive function
  - Worsening or multi comorbidities
  - Advancing frailty
  - Reduced life expectancy

# Special populations
## Pregnancy/Breastfeeding

- Pregnancy is associated with a progressive rise in cholesterol and TG levels
- No enough efficacy/safety data of antilipemic agents in pregnant women
- Increased intake of omega-3 PUFA (mainly DHA) is important for fetal brain development
- Statins are no longer contraindicated in pregnancy
  - Advise most pregnant patients to DC statin
  - Advise non-pregnant young women who use statin and do not plan to become pregnant to use contraception method
  - Advise non-pregnant young women who use statin and plan to become pregnant to DC statin 1 - 2 months before attempting pregnancy
- Statins are not recommended while breast feeding
- Treatment:
  - Dietary therapy (mainstay of treatment; nutritionally balanced diet)
  - Consider BAS if pregnant patient is at high risk of CV events or has FH
  - Statins in select pregnant patients (e.g. established CV disease, homozygous FH)

# Special populations
## Diabetes

- **Diabetic dyslipidemia**: high TGs, low HDL, modestly elevated LDL (dense, highly atherogenic)
- Diabetes is a major risk factor for ASCVD
- Statins are first-line therapy for diabetic dyslipidemia:
  - Evidence in reducing ASCVD events and mortality
- Statin intensity in diabetic dyslipidemia:
  - Primary prevention: Moderate- or High- intensity statin (optional 10-year risk score to determine intensity)
  - Secondary prevention: High-intensity statin

# Special populations
## Diabetes

- Fenofibrate:
  - Reduces the progression of diabetic retinopathy
- BAS (Colesevelam):
  - Approved for both glycemic and lipid control
  - Can exacerbate hypertriglyceridemia (common in diabetes)
- Niacin:
  - Modestly increases FPG (~ 4% - 5%) and HbA1c (~ 0.25%)
  - Should not be routinely used in diabetics

# Special populations
## Kidney disease

- Dyslipidemia is highly prevalent among patients with kidney disease
- Dyslipidemia pattern: high TG, slightly elevated TC and LDL-C, low HDL-C

- Possible mechanisms:
  - Deficiency in apolipoprotein C-II and LPL (both enhance TG hydrolysis)
  - Loss of carnitine during hemodialysis (carnitine enhances FA oxidation)
  - Use of acetate buffer during hemodialysis (acetate is a precursor to FA synthesis)
  - Decreased activity of lecithin-cholesterol acyltransferase (LCAT) during hemodialysis (LCAT transports cholesterol from peripheral tissues to liver for elimination)

- Dialysis does not correct the lipid abnormalities
- Renal transplantation:
  - May correct lipid abnormalities
  - May aggravate lipid abnormalities as a result of immunosuppressants (corticosteroids, cyclosporine…)

# Special populations
## Kidney disease

- Statins effectively reduce LDL-C, but less evidence on CV event reduction
- Moderate-intensity statins are preferred to minimize adverse effects (SAMS)

- Ezetimibe + statin: Reduce CV events in advanced kidney disease
- Other non-statin therapies: Routine use is not recommended (lack of efficacy data, safety concerns)

- Patients on hemodialysis: Rosuvastatin failed to prevent CV events
  - Do not initiate statins in hemodialysis patients
  - Continue statins if patients were already on statins before hemodialysis

- Kidney transplant recipients: At high risk of future CV events
  - Statin should be given
  - Potential for DDI (statin-cyclosporine) → Choose less-interacting statin (pravastatin, fluvastatin)

# Special populations
## Chronic inflammatory disorders

- Chronic inflammation and immune activation →
- Atherosclerosis development and progression →
- ASCVD risk

- 3 – 6 months trial of lifestyle interventions → Estimate 10-year ASCVD risk
  - If 10-year ASCVD risk ≥ 5% → May initiate moderate-intensity statin

- Anti-inflammatory therapies may affect lipid levels and ASCVD risk
  - e.g. tociluzimab and methotrexate used in RA (mixed results)

# Evaluation of therapeutic outcomes

- Short-term evaluation:
  - Complete lipid panel 4 - 12 weeks after initiation of lipid-lowering therapy or following dose adjustment
- Long-term evaluation:
  - Complete lipid panel Q 3 - 12 months to ensure adherence to therapy and maintenance of desired LDL levels

- Non-fasting lipid panel is generally acceptable
- Fasting lipid panel is preferred in hypertriglyceridemia to minimize interference from chylomicrons

- Other monitoring parameters:
  - Lesions regression in patients with xanthomas
  - Modifiable risk factors (hypertension, smoking, lack of exercise, weight, poor diet, blood glucose in diabetics)

# Evaluation of therapeutic outcomes

- Statins:
  - Routine monitoring of hepatic function and CK levels is not recommended
  - Periodic monitoring of HbA1c in patients at high risk for developing diabetes

- Niacin:
  - Monitor hepatic function tests at baseline, after each dosage increase, and Q 6 months thereafter
  - Periodic monitoring of HbA1c in diabetics

- Patients on lipid-lowering therapy for secondary prevention:
  - Monitor CV symptoms (e.g. angina, intermittent claudication)