Hyperlipidemia
(part 1)

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Required Reading

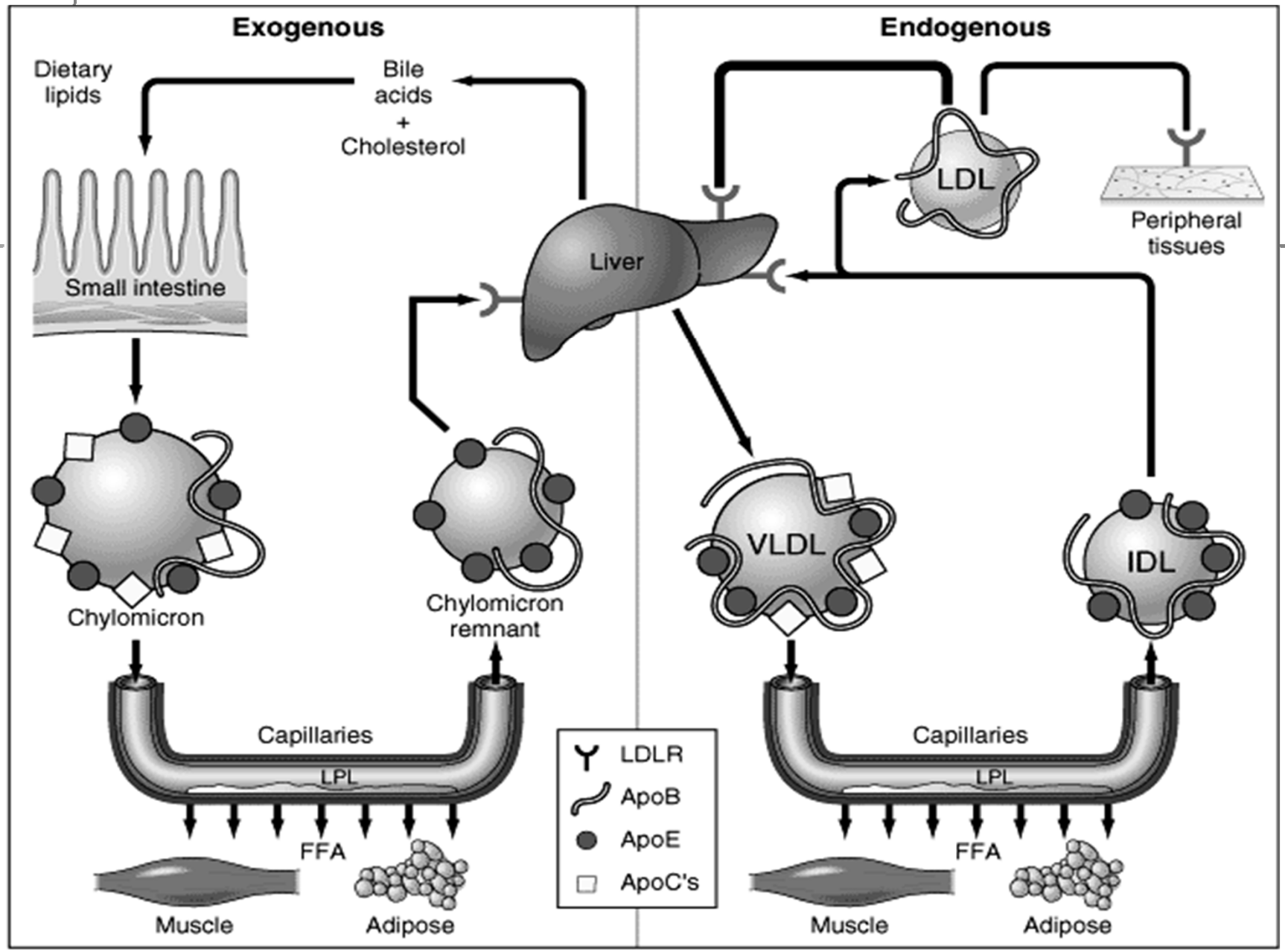
Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, *Journal of the American College of Cardiology* (2018), doi: https://doi.org/10.1016/j.jacc.2018.11.003.

Objectives

- Based on a patient's profile, select the appropriate drug to improve lipid profile and decrease CVD risk.
- Identify significant drug interactions that may result in adverse patient outcomes.

Hyperlipidemia

- Hyperlipidemia is a major risk factor in the development of coronary artery disease (CAD)
- 12 million people in the US affected by CAD- accounting for nearly 1 millions deaths annually
- Preventative efforts are key
- 100 million Americans have cholesterol levels above the desirable range



Lipid Panel Notation

Total chol/TG/HDL/LDL

- TC = (TG/5) + HDL + LDL
- LDL = TC – {HDL + (TG/5)}
- Example:
  - TC=240, HDL=40, TG=200
  - LDL=240-{40+(200/5)}=160

Friedewald Equation for LDL-C

Calculated LDL-C = Total Cholesterol – TG/5-HDL-C

- Elevated Triglycerides (TGs) falsely lowers LDL-C
- Ignore low calculated LDL-C in the presence of high TGs
  - Inaccurate calculation starting at TGs $\geq$ 200 mg/dL
  - Invalid calculation once TGs reach 400 mg/dL
- Persistently elevated TGs is a **risk enhancing feature**
  commonly founds in people with diabetes (PWD)
- Consider using Non-HDL-C for risk assessment
  - Non-HDL-C= total cholesterol – HDL-C

Primary Lipid Disorder

- Genetic defects in the synthesis or metabolism of the lipoproteins
- Genetic disease should be strongly suspected in a patient with an elevated total serum cholesterol greater than 300 mg/dL or in a patient with LDL cholesterol greater than or equal to 190 mg/dL.

Secondary Causes of Hyperlipidemia

- **Diseases**
  - **Hypothyroidism**
  - **Nephrotic syndrome**
  - **Obstructive liver disease**
  - **Diabetes mellitus**
- **Drugs**
  - **Alcohol**
  - **Progestins**
  - **Beta blockers**
  - **Thiazide diuretics**
  - **Glucocorticoids**
  - **Cyclosporine**

Why lower cholesterol?

- Elevated LDL associated with increased risk of:
  - CHD mortality
  - Nonfatal MI
  - Revascularization (CABG, PTCA)
  - Stroke

Lifestyle as the Foundation for ASCVD Risk Reduction Efforts

It must be emphasized that lifestyle modification (adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.

Lifestyle/Health Behavior

- Healthy eating
- Being active
- Monitoring
- Taking medication
- Problem solving
- Reducing risks
- Healthy coping

Pharmacotherapy

- Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions. Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.
- Triglyceride-lowering drugs are fibrates and niacin; they have a mild LDL-lowering action, but RCTs do not support their use as add-on drugs to statin therapy.

MAJOR STATIN TRIALS IN CAD

Primary Prevention	Secondary Prevention	ACS
WOSCOPS	4S	MIRACL
AFCAPS/Tex CAPS	CARE	PROVE IT-TIMI 22
ASCOT-LLA	LIPID	A to Z (2004)
ALLHAT LLT	GREACE	STATIN STEMI
CARDS	TNT	ARMYDA-ACS
ASPEN	AVERT	ARMYDA-RECAPTURE
MEGA	IDEAL	
JUPITER		

Statins

- MOA
  - inhibit HMG-CoA reductase
  - up-regulation of LDL receptors
  - increased LDL clearance
  - decreased chol synthesis
- Cautions/Contraindications
  - Absolute: liver disease, pregnancy/lactation
  - Relative: renal disease, hx liver dz, niacin, gemfibrozil, cyclosporine, erythromycin

Cholesterol biosynthesis pathway

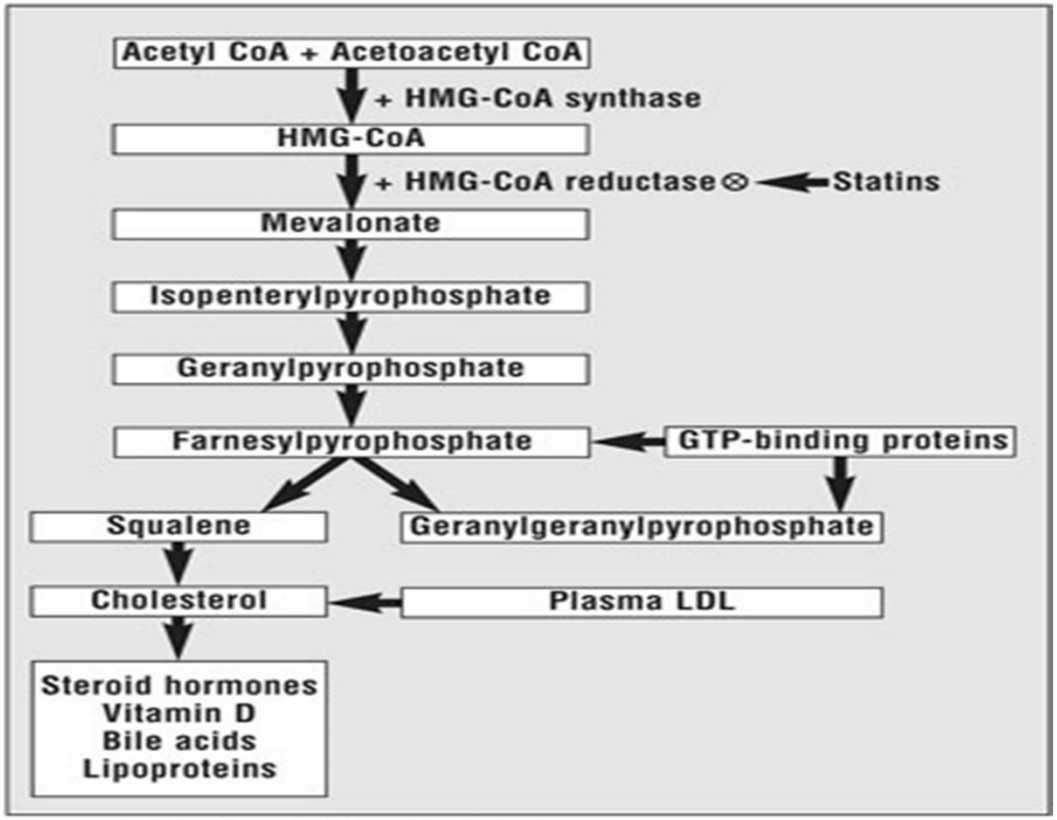


Figure 1. Cholesterol biosynthesis pathway.
CoA: coenzyme A; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; GTP: guanosine triphosphate.
Source: Reference 6.

Treat level of ASCVD Risk

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg***	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Statins

- Adverse effects
  - CNS: headache, insomnia (rare)
  - GI: epigastric discomfort, flatulence, diarrhea, constipation
  - Serious/dangerous: hepatitis, myopathy, rhabdomyolysis

Statins

Clinically Significant Statin Drug Interactions

- Drug interactions
  - warfarin: increased INR
  - bile acid resins: adsorption
  - cyclosporine: rhabdomyolysis
  - erythromycin: rhabdomyolysis
  - gemfibrozil: rhabdomyolysis
  - niacin: myopathy or rhabdomyolysis

Statins

Clinically Significant Statin Drug Interactions

- Cytochrome P450 3A4 Inhibitors
  - Itraconazole
  - Ketoconazole
  - Erthyromycin
  - Clarithromycin
  - Protease inhibitors (ritonavir)
  - Amiodarone
  - Verapamil, diltiazem

Statins

Characteristics of the various Statins

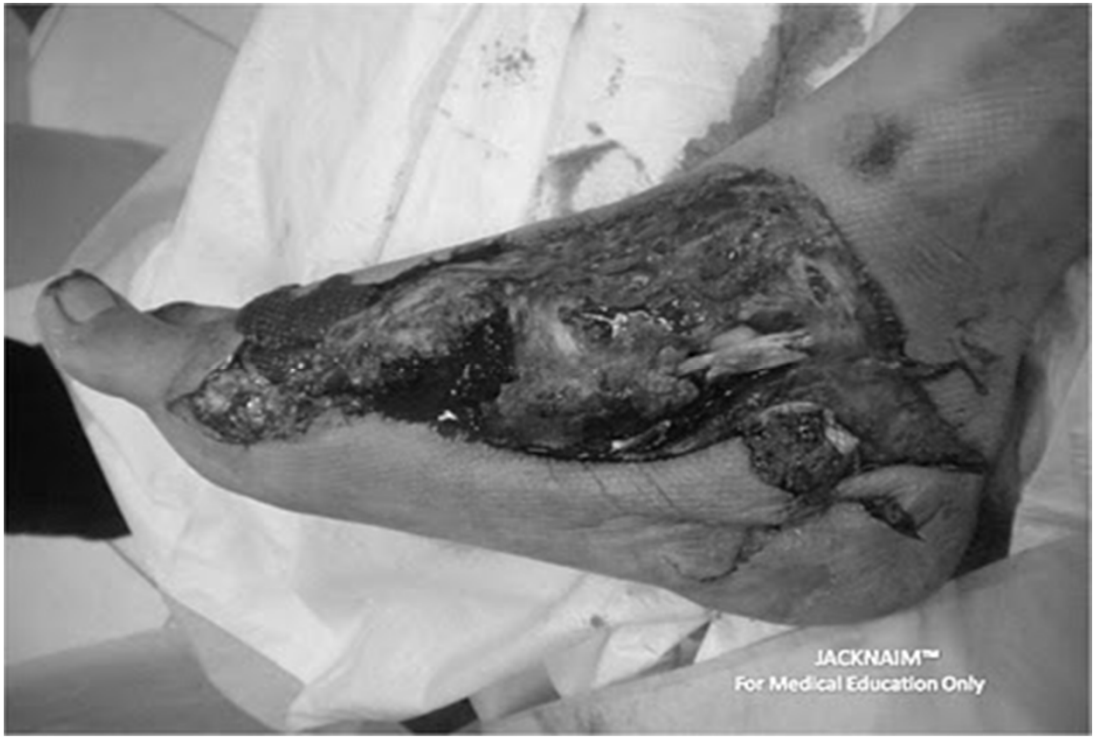
- Lab monitoring
  - efficacy
    - FLP: baseline; at 6-12 weeks, after dose adjustments, every 6-12 months once goal is reached
  -
    - CK: if muscle pain or weakness or concurrent high risk drugs

A rule of thumb for comparing statin doses that lower LDL-C approximately 30%

Fluvastatiin	80 mg
Lovastatin	40 mg
Pravastatin	40 mg
Simvastatin	20 mg
Atorvastatin	10 mg
Rosuvastatin	5 mg
Pitavastatin	1 mg

Each doubling of the statin dose usually results in an additional 5% to 7 % reduction in LDL-C (i.e. the 6% rule)

Rhabdomyolysis



Rhabdomyolysis

- CK levels are the most sensitive indicator of myocyte injury in rhabdomyolysis. Normal CK enzyme levels are 45 to 260 U/L.
- Patients with chronic muscular disorders, patients who recently had surgery, and any one who just completed a marathon may have a CK level of several hundred.
- With rhabdomyolysis, however, total CK levels are massively elevated; values are anywhere from 10000 to 200000 U/L.

Clinical Findings in Rhabdomyolysis

Finding	Examples/comment
Signs and symptoms	Vague and nonspecific: muscle weakness, muscle tenderness, generalized malaise, nausea
History highly associated with rhabdomyolysis	History of tissue crushing, bruising, ischemia, peripheral neuropathies, serious infections, deep burns
Complications suggestive of rhabdomyolysis	Serum and urine electrolyte disturbances, metabolic acidosis, hypovolemia, coagulopathies
Acute muscle wasting	Decreased skeletal muscle mass, cardiac and respiratory failure
Myoglobinuric renal failure	Oliguric or nonoliguric Urine color ranging from pink tinged to cola colored to thick and black Findings on urinalysis: brown casts, low pH, uric acid crystals, electrolyte wasting
Serum electrolyte level	High or low levels of potassium, phosphate, and calcium Levels dependent on disease severity, time since onset, and interventions
Other serum findings	Levels of creatine kinase massively elevated (pathognomonic for rhabdomyolysis) Levels of myoglobin elevated Ratio of urea nitrogen to creatinine, 6:1 Clotting studies: indications of coagulopathy Arterial blood gas analysis: indications of metabolic acidosis

AST, ALT Monitoring: Statins

-
  - FDA now recommends that liver enzyme tests AST/ALT should be performed before starting statin therapy, and as clinically indicated thereafter. Creatine kinase if muscle pain/weakness or concurrent high risk drugs.

Statins

- Counseling pearls
  - timing of daily dose(s)
  - muscle pain/weakness
  - diet & exercise

Effects of Drug Classes

- Statins
  - decrease LDL 17-62% (see specific drug info)
  - slight increase HDL 5-10% (up to 17% for rosuvastatin)
  - decrease TG 7-30%
    - max: rosuvastatin (21-43% decrease)
    - Good: atorvastatin (25% decrease)
    - fair: simvastatin, pravastatin (10 to 15% decrease)
    - minimal: fluvastatin, lovastatin

Statin therapy- associated New Diabetes

13 statin trials: 9% increase in new diabetes [Odds Ratio,1.09 (CI,1.02-1.17)]

5 intensive trials, vs less intensive 12 % increase in new diabetes [Odds Ratio, 1.12 (CI, 1.04-1.22),

but 16 % decrease in incident CVD (CI, 0.75-0.94)

Mechanism: ? Insulin secretion or action or both

Most of those with new DM have pre-diabetes

Sattar N et al. *Lancet*. 2010;375:735-742

To Put It in Perspective

Incidence of diabetes with statin therapy:
~1 new case per 200 persons treated over 5 years
Incidence of major cardiovascular events:
~5 new events per 200 persons treated over 5 years

Cholesterol Absorption Inhibitors

- Drugs
  - Ezetimibe (Zetia®)
- Mechanism of action
  - Unknown. Decreases intestinal cholesterol absorption from 23% to 50%. (Rapidly absorbed by intestinal cells, glucuronidated, distributes into systemic circulation. Enterohepatic recirculation coordinated with meals.)

Effects of Drug Classes

- Cholesterol absorption inhibitors
  - Ezetimibe
    - Decrease LDL (18%)
    - Further LDL ↓ 25% with statin
    - Minimal increase HDL (1%); ↑ 3% with statin
    - Decrease TG (8%); further ↓ 14% with statin

Cholesterol Absorption Inhibitors

- Cautions/contraindications
  - Little justification for monotherapy
  - Active liver disease/LFT elevations
- Adverse effects (data with 4700 subjects)
  - Overall: similar to placebo

Cholesterol Absorption Inhibitors

- Dosing
  - 10mg once daily
  - Dosage adjustment
    - Mild hepatic impairment: no adjustment
    - Renal insufficiency: no adjustment
    - Geriatric patients: no adjustment

Cholesterol Absorption Inhibitors

- Drug interactions
  - Statins: 1.3% LFT elevation with combo therapy (vs. 0.4% LFT elevation monotherapy)
  - Cholestyramine: reduces ezetimibe AUC by 55%
  - Fibrates: potential for cholelithiasis
  - Cyclosporine: case report of 12-fold increase in serum ezetimibe

Cholesterol Absorption Inhibitors

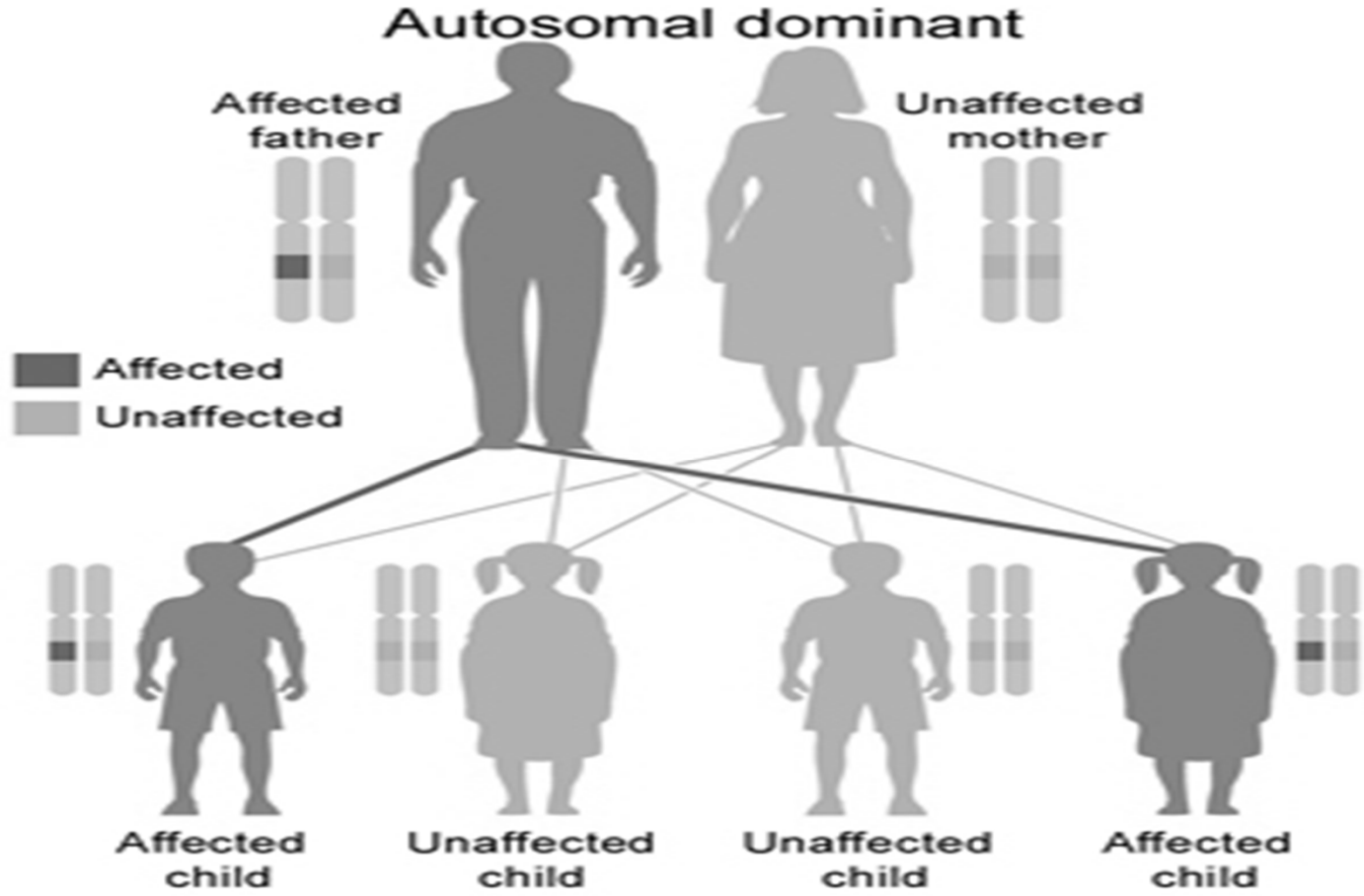
- Lab monitoring
  - As for statin in the combination therapy
- Counseling pearls
  - With or without food
  - Diarrhea: potentially worsened diarrhea or reduced ezetimibe efficacy
  - Combination therapy necessary for efficacy
  - Diet + exercise

Patient Populations with an Unmet Need for Additional LDL-C Lowering

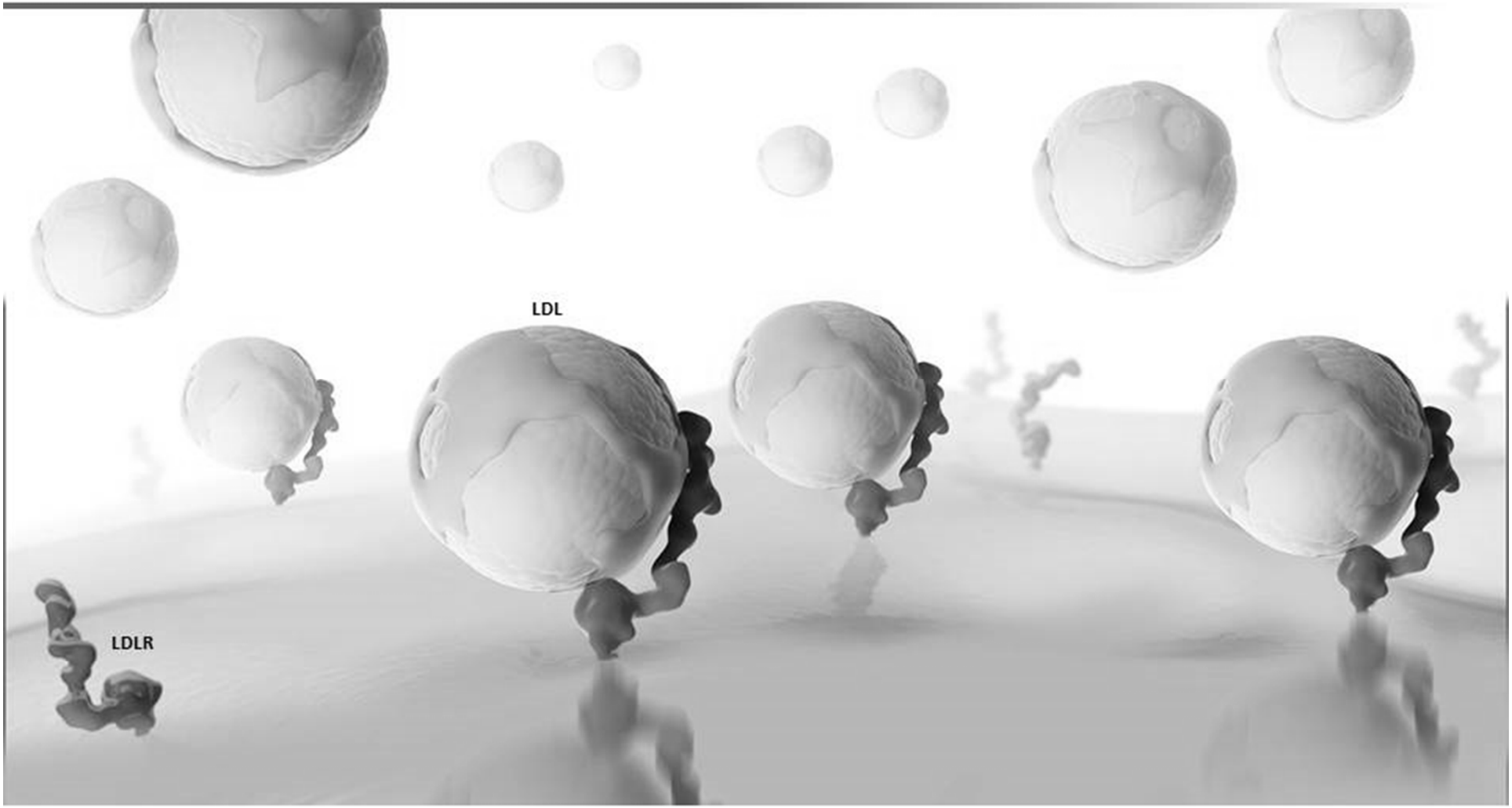
FH Population	High / Very High CV Risk Population	Statin-Intolerant Population
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250[1,2] • Untreated LDL-C of 200–400 mg/dL[3]	• Previous MI /stroke / CVD or multiple CV risk factors incl. T2DM • Difficult to achieve LDL-C goals, despite current therapies[5]	• 10-15% on high-intensity statins show intolerance[6] • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL)[4]	**• 20% with CHD not at goal (<100 mg/dL) • 59% at very high CV risk not at goal (<70 mg/dL)**	**Nearly all patients who need considerable LDL-C reductions will not reach goal**

1 Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. 2 Sjouke et al. *Eur Heart J* (in press).
3 2011 ESC/EAS Guidelines for the management of dyslipidaemias. 4 Pijlman et al. *Atherosclerosis* 2010;209:189-94.
5 Virani et al. *Am Heart J* 2011;161:1140-6. 6 Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-68.

Heterozygous vs Homozygous FH



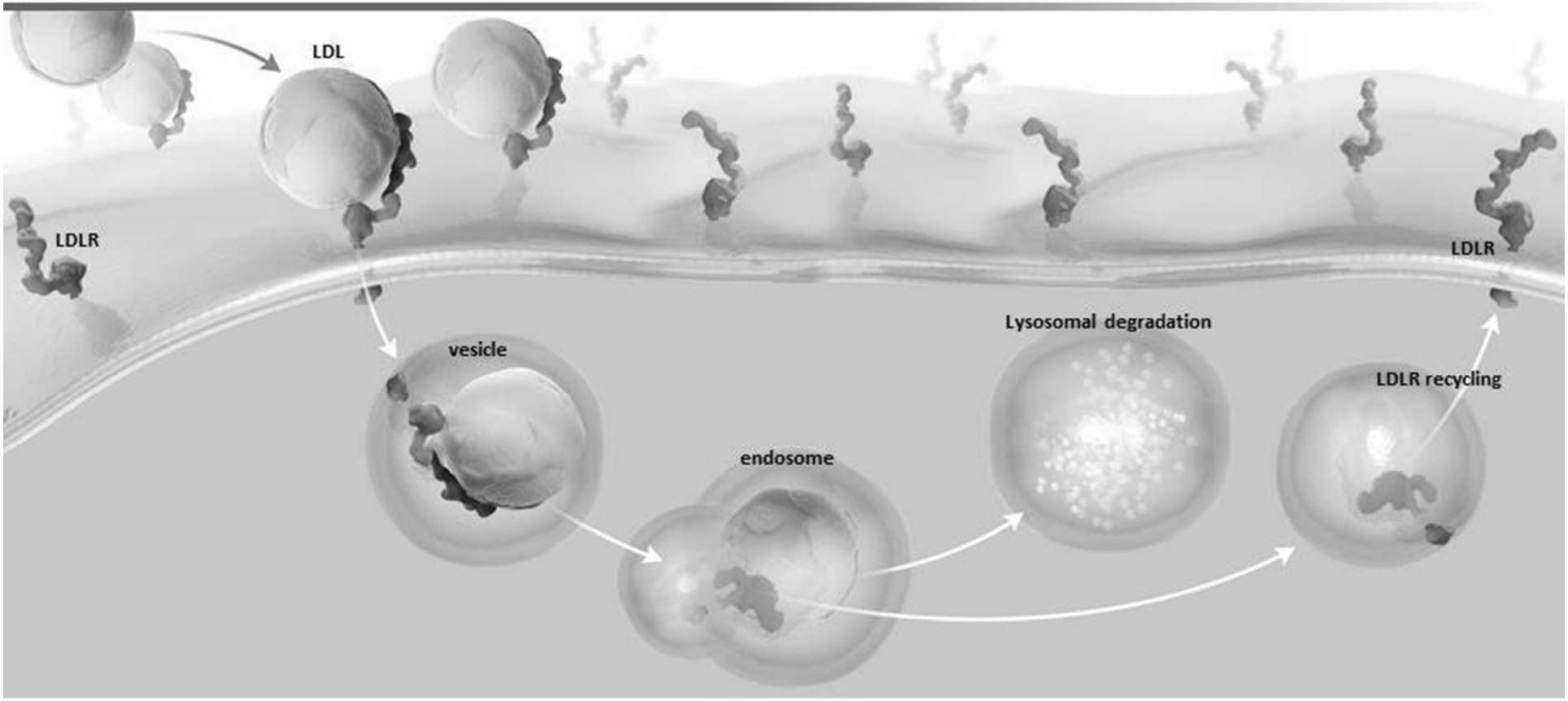
LDL Receptors (LDLRs) Play a Central Role in the Regulation of Plasma LDL-C



LDL = low density lipoprotein; LDLR = low density lipoprotein receptor

1. Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337. 2. Brown MS, et al. *Science*. 1986;232:34-47. 3. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438. 4. Horton JD, et al. *J Lipid Res*. 2009; 50(suppl):S172-177. 5. Brown MS, et al. *J Lipid Res*. 2009;50 Suppl:S15-27.

LDLRs Are Recycled After Delivery of LDL to Endosomes for Degradation



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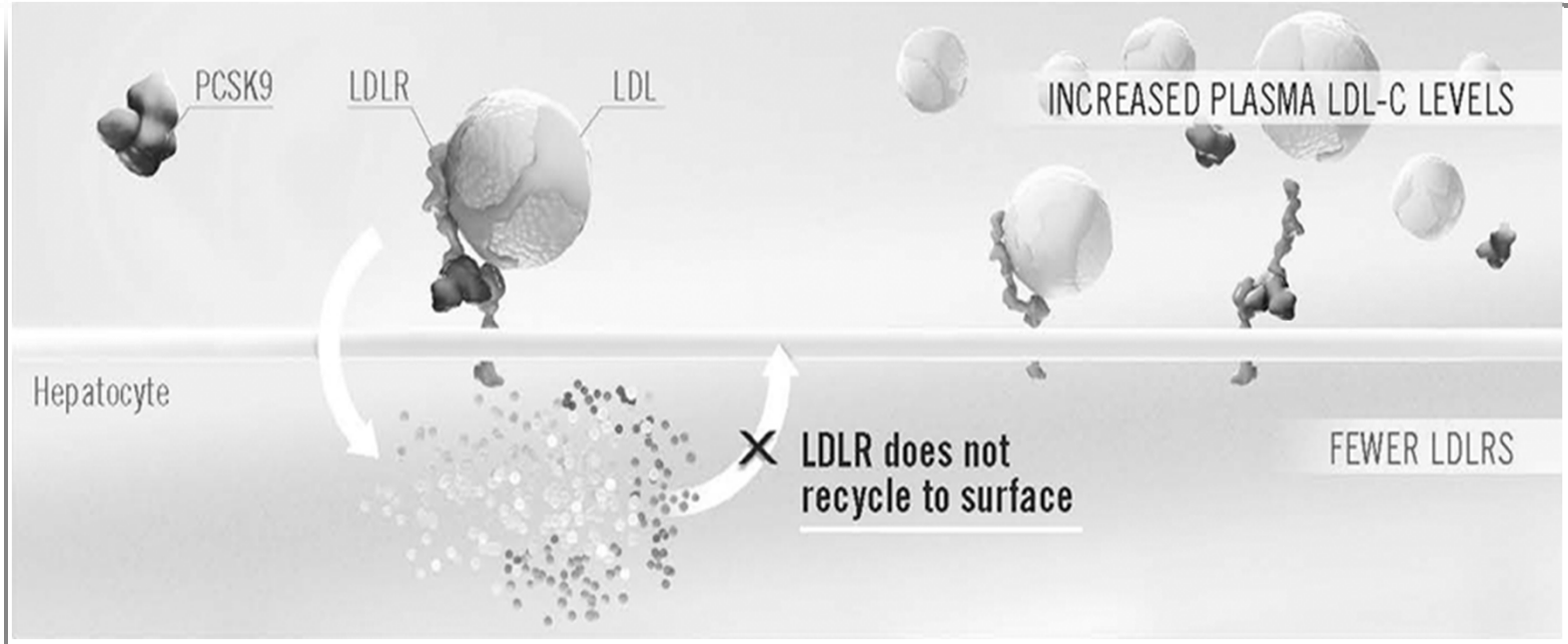
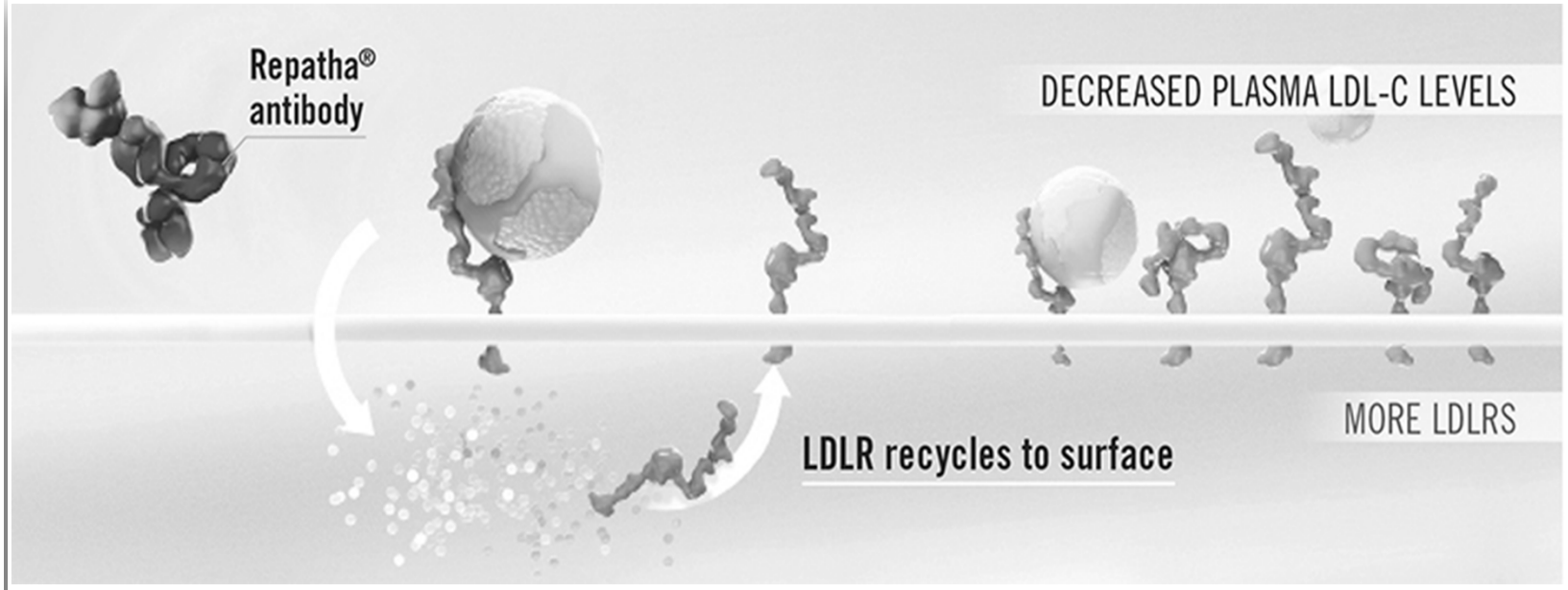


PCSK9 is a protein that promotes degradation of LDLRs. This results in fewer LDLRs on the liver cell surface, increasing plasma LDL-C levels



Repatha® and Pravulent® Inhibits PCSK9, thereby Preventing LDLR Degradation

Proprotein convertase subtilisin-kexin type 9 (PCSK9) Inhibitors

- **Evolocumab** (REPATHA ® Amgen, Thousand Oaks, CA)
- **Alirocumab** (Praluent ® Regeneron Pharmaceuticals, Tarrytown, NY)
- **Bococizumab** (Pfizer, New York).

PCSK9 Inhibitors are indicated:

- along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (HeFH-an inherited condition that causes high levels of LDL) or atherosclerotic heart or blood vessel problems, who need additional lowering of LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia (HoFH - an inherited condition that causes high levels of LDL), who need additional lowering of LDL cholesterol.

REPATHA ® (**evolocumab**)

Administer by subcutaneous injection.

- Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 140 mg every 2 weeks or 420 mg once monthly in abdomen, thigh, or upper arm.

- HoFH: 420 mg once monthly.

- To administer 420 mg, give 3 REPATHA injections consecutively within 30 minutes.

PRALUENT® (alirocumab)

PRALUENT (alirocumab) dosing can be adjusted based on your patients' LDL-C lowering needs

As an adjunct to diet and maximally tolerated statin therapy, the recommended starting dose for PRALUENT is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage

If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks

PCSK9 Inhibitors Side Effects:

- Nasopharyngitis, itching, flu, injection site reactions, and serious allergic reactions have been reported.
- CVS Health predicts cost could run $7,000-$12,000 per year.

Range of LDL Cholesterol Lowering with Drugs

• PCSK9 inhibitors	35-65%
• *Statins*	*15-60%*
• Bile Acid Sequestrants	5-35%
• Ezetimibe	15-20%
• Fibrates (TG normal)	10-20%
• Nicotinic acid	0-25%

Non-Statins

- There is **NO** evidence that adding non-statins improves CV outcomes.

Tolerability

- **Bile acid resins: fair to poor**
- **Nicotinic acid: poor (acceptable for niaspan)**
- **Statins: good**
- **Fibrates: good**
- **Cholesterol absorption inhibitors: good**

Bile Acid Resins

- Drugs
  - Cholestyramine (Questran®)
  - Colestipol (Colestid®)
  - Colesevelam (Welchol®)

Bile Acid Resins

- MOA
  - bind bile salts in GI tract
  - up-regulation of LDL receptors
- Cautions/Contraindications
  - TG > 500: absolute
  - TG > 200: relative
  - constipation
  - pregnancy, lactation

Bile Acid Resins

- Adverse effects
  - constipation
  - bloating
  - nausea
  - epigastric fullness
  - flatulence

Bile Acid Resins

- Dosing
  - Cholestyramine: :
    - Initial: 4g (1 scoop) once daily
    - usual: 4g BID; max: 8g BID
  - Colestipol: :
    - Initial: 5g pwd or 2g tab once daily
    - usual: 5g pwd BID or 4g tab BID
    - max: 10g pwd BID or 8g tab BID
  - Colesevelam:
    - Initial: 1875mg BID or 3750mg once daily
    - Max: 4375 mg daily
    - With a meal

Bile Acid Resins

- Major drug interactions: adsorption
  - thyroid hormones
  - warfarin
  - digoxin
  - thiazides
  - β-blockers
  - corticosteroids
  - amiodarone

Bile Acid Resins

- Major drug interactions (con't)
  - ? statins
  - acetaminophen
  - NSAIDs
  - fat soluble vitamins

Bile Acid Resins

- Lab monitoring
  - toxicity: none
  - efficacy: FLP
    - initial check at 4-6 weeks
    - max effect at 12 weeks

Bile Acid Resins

- Counseling pearls
  - mix powders with noncarbonated fluids/foods
  - mix in advance

    titrate weekly
  - prevent constipation
    - water
    - stool softener
    - dietary fiber
  - space other meds-2 hours before meds or 2 hours after meds
  - diet & exercise

Fibrates

- Drugs
  - Gemfibrozil (Lopid®) -avoid
  - Fenofibrate (Antara®, Lofibra®, Tricor®, and Triglide™, Trilipix)
  - Clofibrate (Atromid-S)
- MOA
  - decreased hepatic VLDL production
  - increased lipoprotein lipase activity
  - increased biliary cholesterol excretion

Effects of Drug Classes

- Fibrates
  - Effect LDL (20%)
  - modest increase HDL 11%
  - decrease TG 20-30%

Fibrates

- Cautions/Contraindications
  - Relative
    - hepatic dz
    - severe renal dz
    - gallstones
    - concurrent statin therapy

Fibrates

- Adverse effects
  - GI: epigastric discomfort, dyspepsia, abdominal pain, diarrhea
  - CNS: dizziness
  - serious: cholelithiasis, myopathy, hepatitis, neutropenia

Fenofibrate-Antara
(43 mg, 87 mg, 130 mg)

- Give with meals to optimize bioavailability.
- Primary hypercholesterolemia or mixed hyperlipidemia: initiate at 130 mg daily.
- Hypertriglyceridemia: initiate at 43 mg to 130 mg daily.
- Impaired renal function or elderly: initiate at 43 mg daily.
- Maximum dose is 130 mg daily.

Fibrate-Trilipix
(45 mg, 135 mg)

- Can be taken without regard to meals.
- Severe hyperlipidemia:
  initiate at 45 mg to 135 mg daily.
- Primary hyperlipidemia or mixed dyslipidemia:
  initiate at 135 mg daily.
- Impaired renal function:
  initiate at 45 mg daily.
- Co-administration therapy with statins for mixed dyslipidemia: 135 mg daily. May be taken at the same time as a statin.
- Maximum dose is 135 mg daily.

Fenofibrate-Tricor

48 mg, 145 mg

- Can be taken without regard to meals.
- Primary hypercholesterolemia or mixed hyperlipidemia: initiate at 145 mg daily.
- Hypertriglyceridemia: initiate at 48 mg to 145 mg daily.
- Impaired renal function or elderly: initiate at 48 mg daily.
- Maximum dose is 145 mg daily.

Fenofibrate 54mg, 160 mg

- Give with meals to optimize bioavailability.
- Primary hypercholesterolemia or mixed hyperlipidemia: initiate at 160 mg daily.
- Hypertriglyceridemia: initiate at 54 mg to 160 mg daily.

Fibrates

- Drug interactions
  - statins: myopathy, rhabdomyolysis
  - warfarin: increased INR
- Lab monitoring
  - toxicity
    - CBC: baseline, 6 months, 1 year
    - LFTs: baseline, 3-6 months, 1 year
  - efficacy: FLP baseline; at 4, 6, 8 or 12 weeks, then every 6-12 months

Prescription Fish Oils (Lovaza formerly Omacor)

- Lovaza (FDA-approved 2005) indicated for patients with TG levels above 500 mg/dL
  - More reliable purity than OTC products
  - Increased fish oil concentration than OTC products
  - Each capsule contains approximately 465 mg of eicosapentenoic acid (EPA) and 375 mg of docosahexanoic acid (DHA)
- Omega-3 doses
  - 1 g/day reduce cardiovascular and overall mortality
  - Up to 4 g/day reduce TG by 44.9% TG from baseline
  - Dose before meals to minimize GI upset and fishy taste

Vascepa, icosapent ethyl

- *Vascepa* contains only EPA (eicosapentaenoic acid)...instead of both EPA and DHA (docosahexaenoic acid) like *Lovaza* and most supplements.

- *Vascepa* 4 g/d lowers TGs about 27% compared to baseline in patients with very high triglycerides.

- *Lovaza* 4 g/d lowers TGs about 45%...but can increase LDL by 45%.

Fish Oil

- Greenland Eskimo diet high in n-3 PUFA
- Diet and Reinfarction Trial (DART)
  - Fiber advice (increase fiber intake to > 18 g per day)
  - Fat advice (> 2 weekly portions (200 – 400 g) of fatty fish (mackerel, herring, kipper, pilchard, sardine or salmon)
  - 29% reduction in CHD mortality with fish advice
- Effects of fish oil
  - 3 g (30% TG reduction) to 9 g (50% TG reduction)
  - Decrease Lp(a) by 14%

What are the concerns with fish oil?

Concern:

- Increased levels of mercury, polychlorinated biphenyls, dioxins and other environmental contaminants found in larger, predatory fish
- Pregnant women and children may be especially susceptible

Diet Recommendations from FDA and EPA:

- Women who may become pregnant, pregnant women, nursing mothers, and young children should avoid some fish and eat those lower mercury content
  1. Do not eat fish with high mercury levels (shark, swordfish, or King Mackeral)
  2. Eat up to 12 ounces (2 average meals) a week of fish that are lower in mercury (shrimp, canned light tuna, salmon, pollock, and catfish)
  3. Check local advisories about the safety of fish caught by family and friends

OTC product Issues:

- Manufacturing processes of most fish oil capsules may avoid mercury contamination
- However, lack of manufacturing regulation raises questions about true differences between sampled batches

Fish Oil

- Recommend saving fish oil for patients with triglycerides OVER 500 mg/dL.

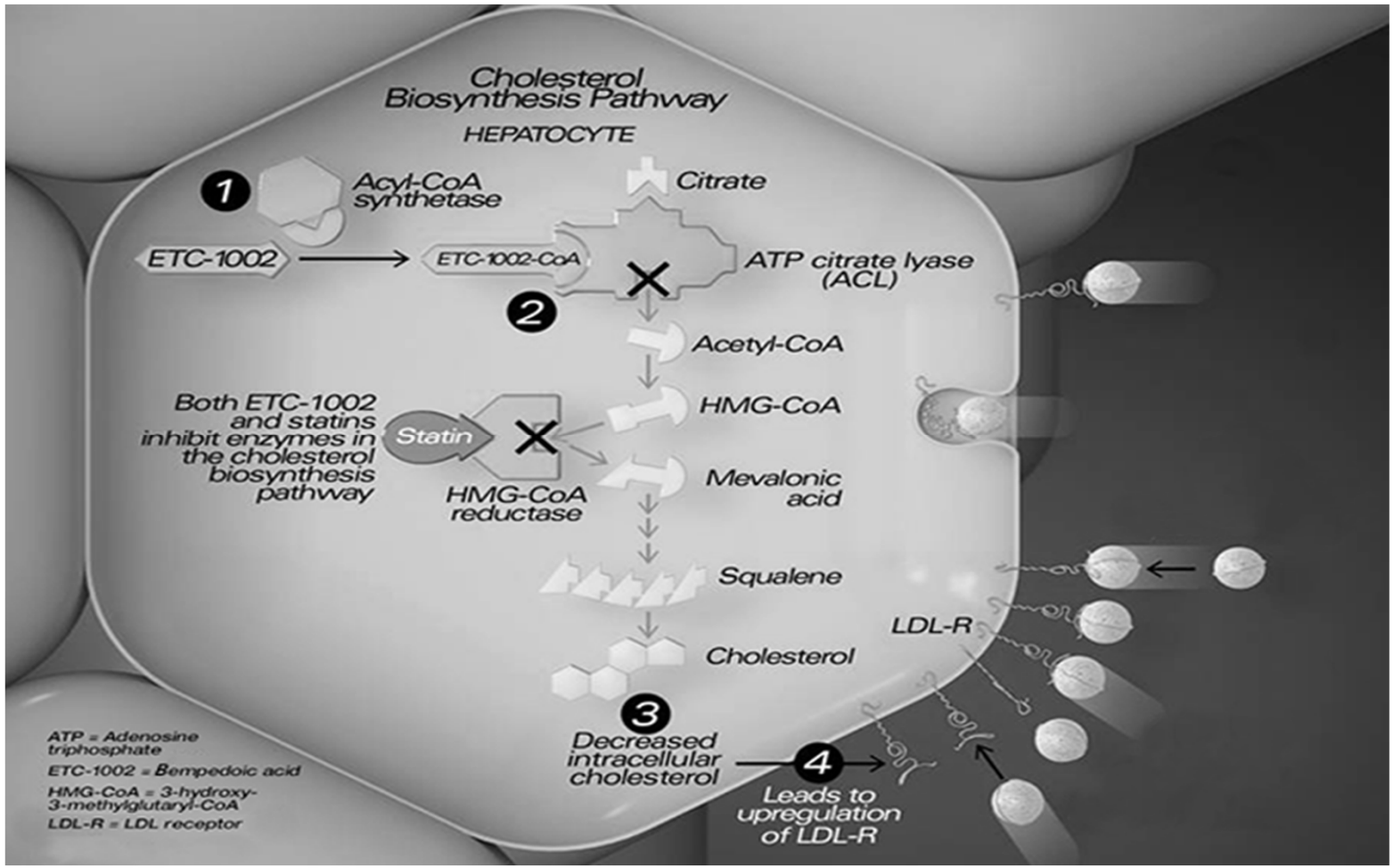
- If fish oil is used, suggest either *Lovaza* or *Vascepa*. Both cost about $185 a month.

- The following nonstatins are not recommended under the current lipid guidelines.
- These agents are included in the handout because you may still encounter a patient who is taking one of these medications.
- Material on slides 72-88 will not be on exam

Bempedoic, Nexletol®
approved 2/21/20)

- Bempedoic acid is a novel nonstatin drug that inhibits cholesterol biosynthesis in the same pathway as statins. It is administered as a prodrug and is only converted to active drug in the liver and not muscles.

Bempedoic, Nexletol®
approved 2/21/20)



Bempedoic, Nexletol®
approved 2/21/20)

- Indicated as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
- 180 mg po daily in combination with maximally tolerated statin therapy

Bempedoic, Nexletol®
approved 2/21/20)

- Cardiovascular outcomes trials evaluating the impact of bempedoic acid on hard cardiovascular endpoints are currently ongoing.

Bempedoic Nexletol®

- Side Effects : 1-10%
  - Upper respiratory tract infection (4.5%)
  - Muscle spasms (3.6%)
  - Hyperuricemia (3.5%)
  - Back pain (3.3%)
  - Abdominal pain or discomfort (3.1%)
  - Bronchitis (3%)
  - Pain in extremity (3%)
  - Anemia (2.8%)
  - Elevated liver enzymes (2.1%)
  - Gout (1.5%)
  - Benign prostatic hyperplasia (1.3%)
  - Atrial fibrillation (1.7%)

Niacin

- Recent large randomized clinical studies – AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides) and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) – delivered some disappointing results, leading to the conclusion that no further benefit (decreased parameters of cardiovascular risk) is achieved by adding niacin to existing statin therapy in patients with high cardiovascular risk. Moreover, in these studies, several adverse effects of the treatment were observed; therefore, niacin treatment for hypolipidemias is not recommended.

Antioxidants

- Oxidized cholesterol damages arteries
- Antioxidants may protect arteries
  - Theoretical; no studies prove benefit (?harm)
  - Dietary vs. supplemental sources
    - Vitamin E – increased risk for heart failure
    - Vitamin C
- Not recommended by AHA to be taken as a supplement (get it from food)

Garlic

- Lipid benefits at 3 months
  - Lowered t. chol 12-25mg/dL (6%)
  - Lowered LDL 0-13.5 mg/dL
  - Lowered TG 7-34 mg/dL
  - No change HDL
  - Unknown if benefit past 3 months
- No data on cardiovascular outcomes

Dietary Fiber

- 2 categories
  - Insoluble: lignins, cellulose
  - Soluble: oats, psyllium, pectin, guar gum
- Efficacy of soluble fiber
  - Lowers t. chol, LDL: 1-2 mg/dL
  - Example: 3 servings of oatmeal (3 g soluble fiber total) would lower t.chol, LDL: 5mg/dL
- Toxicity of soluble fiber: GI distress
- RDA: 20-35 gm/day

Fiber foods

- Insoluble
  - Bran cereal
  - Whole grain bread
  - Blackberries
  - Parsnips
  - Kidney beans
  - Lentils
  - White beans
  - Popcorn
- Soluble
  - Oranges
  - Pinto beans
  - Brown rice
  - Apples

Insoluble Fiber

- Functions
  - move bulk through the intestines
  - control and balance the pH (acidity) in the intestines
- Benefits
  - promote regular bowel movement and prevent constipation
  - remove toxic waste through colon in less time
  - keep an optimal pH in intestines to prevent microbes from producing cancer substances; therefore preventing colon cancer

Soluble Fiber

- Functions of Soluble Fiber
  - bind with fatty acids
  - prolong stomach emptying time so that sugar is released and absorbed more slowly
- Benefits of Soluble Fiber
  - lower total and LDL cholesterol therefore reducing the risk of heart disease
  - “regulate” blood sugar for people with diabetes

Plant Stanol Esters

- Products ($)
  - Benecol (J&J)
  - Take Control (Lipton)
  - Cholox (capsules)
- Plant stanol esters at a level of 2–3 g/d have been shown to reduce LDL cholesterol by 10–15% without side effects
- MOA: reduces cholesterol absorption from gut
- “Neutraceutical”: food that acts as a drug

Cholestin®

- Red yeast from fermented rice OR extract from honeybee wax (policosanol)
- MOA: inhibits HMG-CoA reductase
- Efficacy: lowers cholesterol 25-40 mg/dL
- Toxicity: consider it a statin

(Note: lovastatin is derived from a different yeast species)