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# DRUGS FOR DYSLIPIDEMIA

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# DISCLOSURE

None

## Use Statement

# OBJECTIVES

1. Identify clinical uses for HMG-CoA reductase inhibitors, bile acid resins, cholesterol absorption inhibitors, fibrates, PCSK9 inhibitors, and omega-3 fatty acids.
2. Explain the mechanism of action of HMG-CoA reductase inhibitors, bile acid resins, cholesterol absorption inhibitors, fibrates, PCSK9 inhibitors, and omega-3 fatty acids and how this relates to the underlying pathophysiology of their clinical use.
3. State adverse effects and contraindications to HMG-CoA reductase inhibitors, bile acid resins, cholesterol absorption inhibitors, fibrates, PCSK9 inhibitors, and omega-3 fatty acids.
4. Describe the clinically important drug interactions of HMG-CoA reductase inhibitors, bile acid resins, cholesterol absorption inhibitors, fibrates, PCSK9 inhibitors, and omega-3 fatty acids.

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# INTRODUCTION

Dyslipidemia

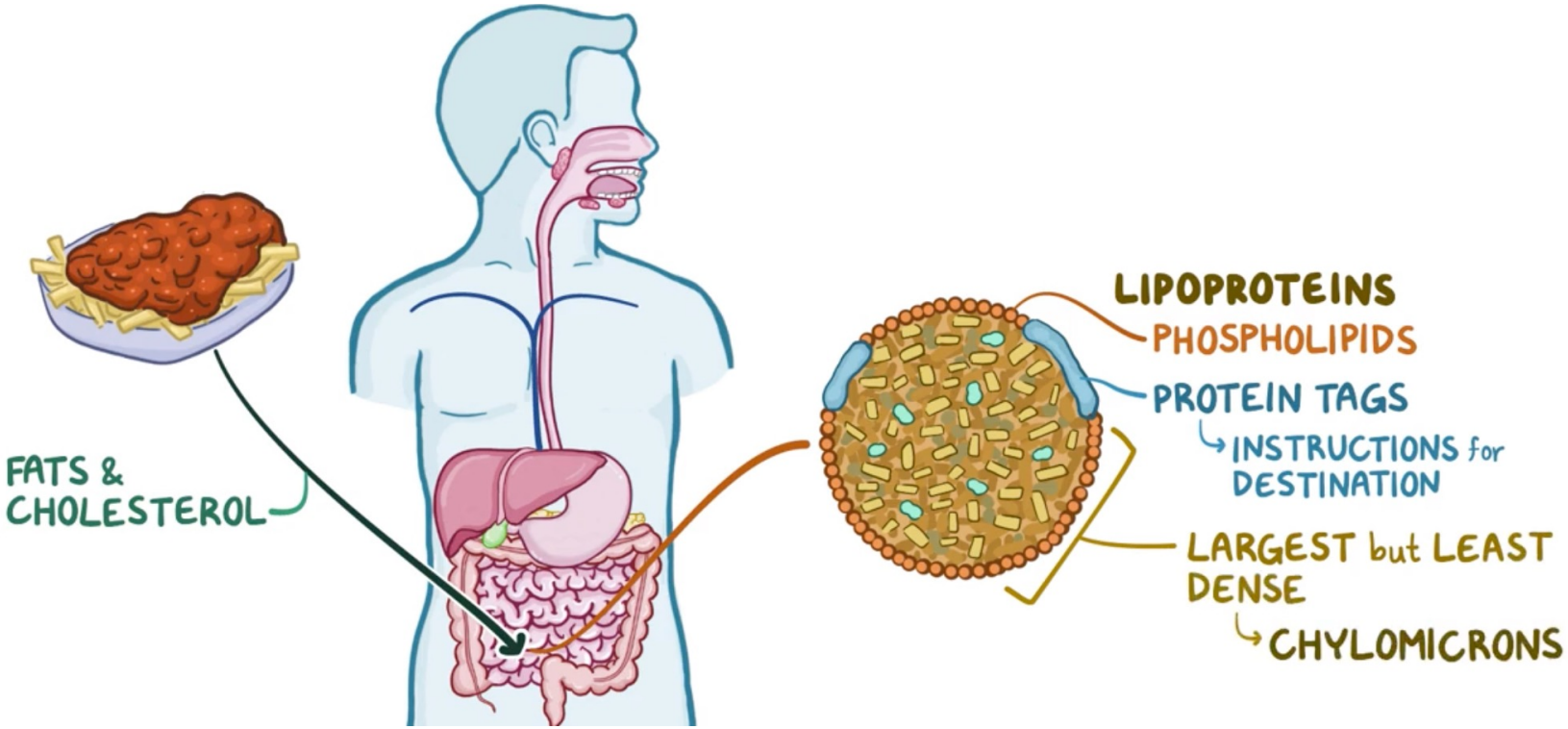
# 2018 ACC/AHA PRIMARY PREVENTION RECOMMENDATIONS

| Population | Recommendation |
|---|---|
| LDL-C 190 mg/dL | High-intensity statin therapy to goal of LDL-C <100 mg/dL<br>May add ezetimibe & then (if multiple risk factors present) a PCSK9 inhibitor |
| 40-75 years w/diabetes & LDL-C 70 mg/dL | Moderate-intensity statin therapy |
| Diabetes and LDL-C 70 mg/dL w/ multiple risk factors or age 50-75 years | High-intensity statin therapy to reduce LDL-C 50% |
| 40-75 years without diabetes, LDL-C 70 mg/dL, and 10-year ASCVD risk <20% | Consider LDL-C level and risk-enhancing factors in decision to start moderate-intensity statin therapy to reduce LDL-C 30-49% |
| 40-75 years old without diabetes, LDL-C 70 mg/dL, and 10-year ASCVD risk 20% | High-intensity statin therapy to reduce LDL-C 50% |
| >75 years old | Consider risks and benefits |

# 2018 ACC/AHA SECONDARY PREVENTION RECOMMENDATIONS

| Population | Recommendation |
|---|---|
| Patients with clinical ASCVD | High-intensity or maximally tolerated statin therapy to reduce LDL-C 50% |
| Patients with very high-risk ASCVD (multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions) | Maximally tolerated statin therapy to a goal of LDL-C <70 mg/dL, if necessary<br>adding ezetimibe and then possibly a PCSK9 inhibitor |

# CHOLESTEROL THROUGH DIET



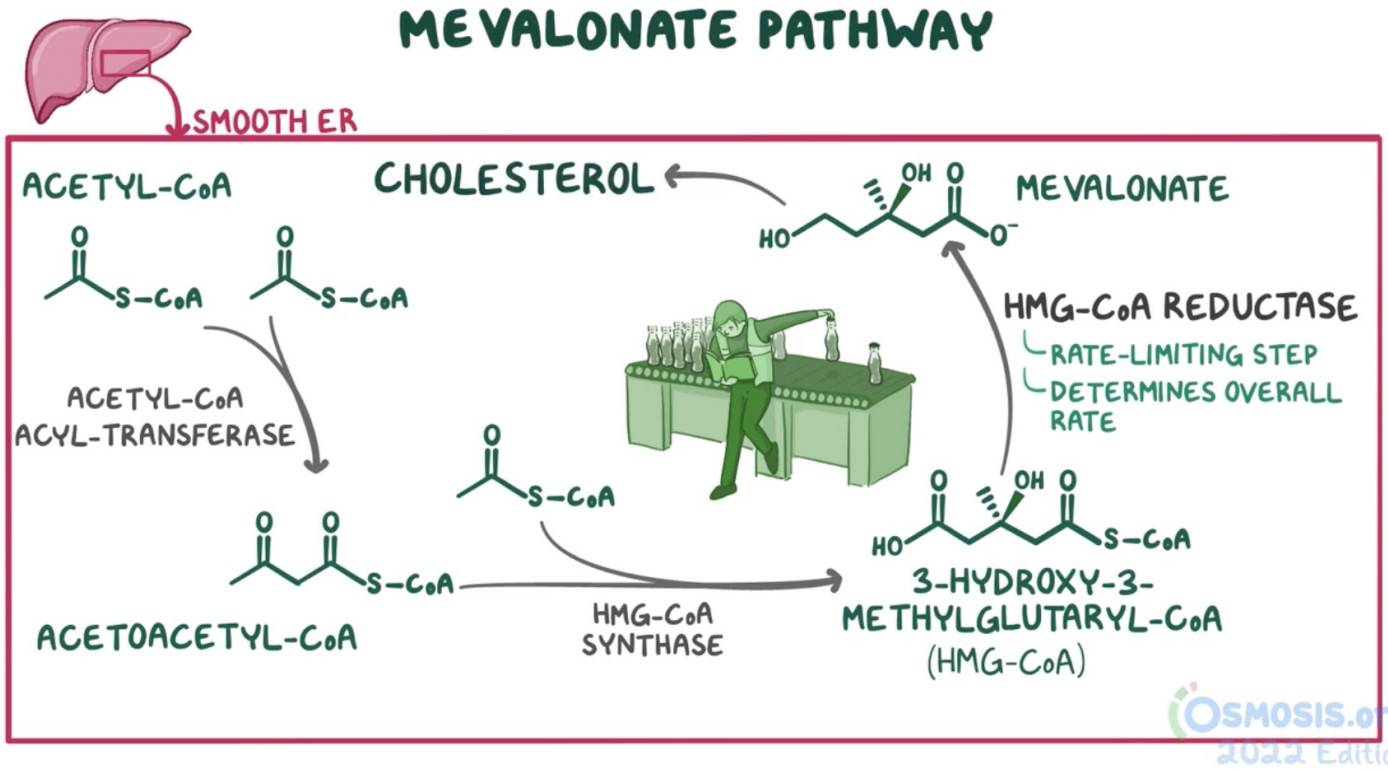
# ACTIVE LEARNING

Which pathway synthesizes intrinsic cholesterol?

Where does this occur?

What is the rate-limiting step of cholesterol synthesis?

# CHOLESTEROL THROUGH HEPATIC PRODUCTION



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# HMG-COA REDUCTASE INHIBITORS "STATINS"

# HISTORICAL PERSPECTIVE

Red yeast rice produced by fermentation of a yeast on rice

*Monascus purpureus*

Yeast can enrich rice with substances known as monacolins

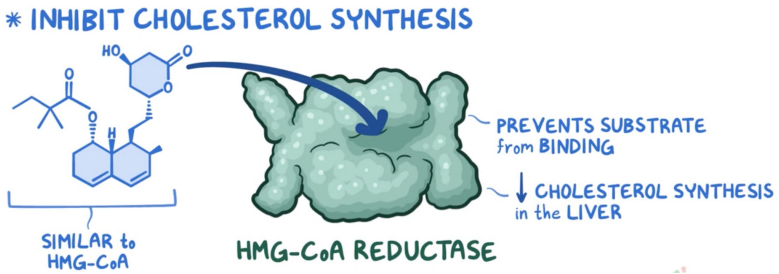
Monacolin K is structurally identical to lovastatin

# HMG-COA REDUCTASE INHIBITOR MECHANISM

Structural analogs of HMG-CoA

Bind to HMG-CoA reductase and prevent the actual substrate from binding

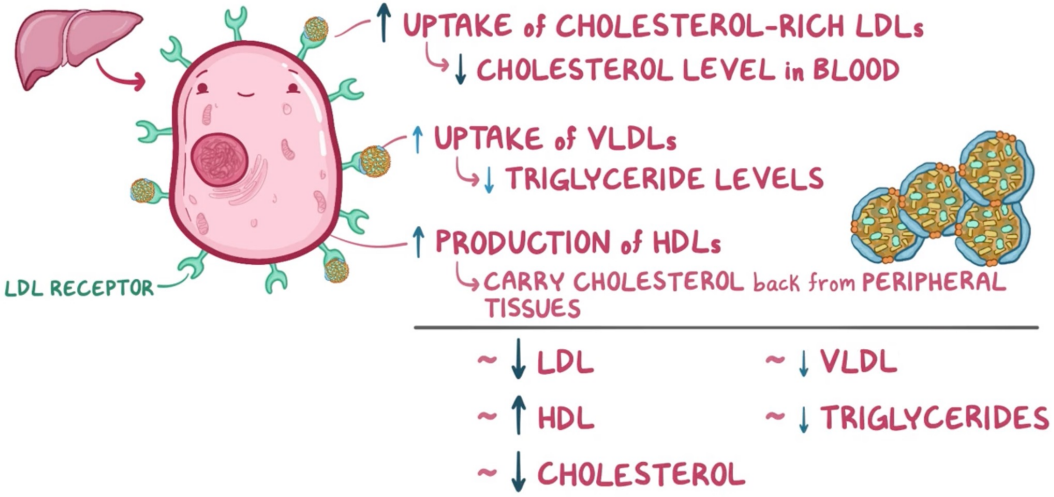
HMG-CoA is the rate-limiting step in cholesterol biosynthesis, statin can dramatically decrease hepatic cholesterol synthesis



# HMG-COA REDUCTASE INHIBITOR MECHANISM

When liver cannot make more cholesterol, will try to get cholesterol from the body

- Hepatic cells ↑ number of LDL receptors on their surface
  - Facilitates uptake of cholesterol-rich LDLs ⟶ ↓ cholesterol in blood
- LDL receptors also ↑ uptake of VLDLs ⟶ moderate ↓ in triglycerides
- Increase production of HDL
  - Carries cholesterol back from peripheral tissues



# NOTABLE ADVERSE EFFECTS

HEPATIC

MUSCLE

# HMG-COA REDUCTASE INHIBITORS

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| **Atorvastatin (Lipitor)**<br>Fluvastatin<br>Lovastatin<br>Pitavastatin (Livalo)<br>Pravastatin<br>**Rosuvastatin (Crestor)**<br>**Simvastatin (Simcor)**<br>**-statin** | Acute liver failure<br>Decompensated cirrhosis<br>Pregnancy/ breastfeeding (teratogen) | Myalgia<br>Myopathy (↑ when used with fibrates or niacin)<br>Myositis<br>Rhabdomyolysis<br>Hepatic dysfunction (↑ LFTs) | Most statins metabolized by the cytochrome P450 system; drugs or foods (eg, grapefruit juice) that inhibit cytochrome P450 activity increase the risk of hepatotoxicity and myopathy |

# CLINICAL USE

Established ASCVD (secondary prevention)

LDL-C >190 mg/dL

Other categories of intermediate to high-risk primary prevention

High-intensity statins generally recommended to patients at highest ASCVD risk

# ACTIVE LEARNING

It is recommended to take certain statins at bedtime. Why might this be? Which pharmacokinetic parameter could help you discern which statins should be taken at bedtime?

# ADME

Half-lives

- Atorvastatin and rosuvastatin - 20 hours
- Pitavastatin and simvastatin - 12 hours
- Others - 1-2 hours
- Hepatic cholesterol synthesis is maximal between midnight and 2:00 AM
  - Statins with half-lives of <4 h should be taken in the evening

Metabolism and excretion

- Pitavastatin - glucuronidation
- Rosuvastatin - via CYP2C9
- Atorvastatin, lovastatin, simvastatin via CYP3A4
- Elimination occurs mostly in the feces

# STATIN-ASSOCIATED MUSCLE SYMPTOMS (SAMS)

Myalgia

Myopathy

Myositis

Myonecrosis

Rhabdomyolysis

Increased risk

- Statins extensively metabolized by CYP3A4 (simvastatin, lovastatin, atorvastatin)
- Higher doses
- Preexisting neuromuscular disorders (i.e., ALS)
- Hypothyroidism, hypovitaminosis D
- Concurrent drug therapy – CYP3A4 inhibitors (i.e., protease inhibitors, amiodarone, cyclosporine, calcium channel blockers, etc.), fibrates, niacin

# MANAGEMENT OF SAMS

Statin discontinuation until symptoms improve

Followed by rechallenge with a reduced dose, alternative agent, or alternative dosing regimen while monitoring for recurrent symptoms

Majority of patients will be able to be successfully treated with at least one or several statins

# ACTIVE LEARNING

Complete the following table by outlining the mechanism of action and adverse effects of drugs for dyslipidemia.

| Drug Class | Representative Generic Drugs | Mechanism of Action | Adverse Effects |
|---|---|---|---|
| HMG-CoA reductase inhibitors | | | |
| Bile acid resins | | | |
| Cholesterol absorption inhibitors | | | |
| Fibrates | | | |
| PCSK9 inhibitors | | | |
| Omega-3 fatty acids | N/A | | |

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# CHOLESTEROL ABSORPTION INHIBITORS

# CHOLESTEROL ABSORPTION INHIBITOR MOA

Not fully understood

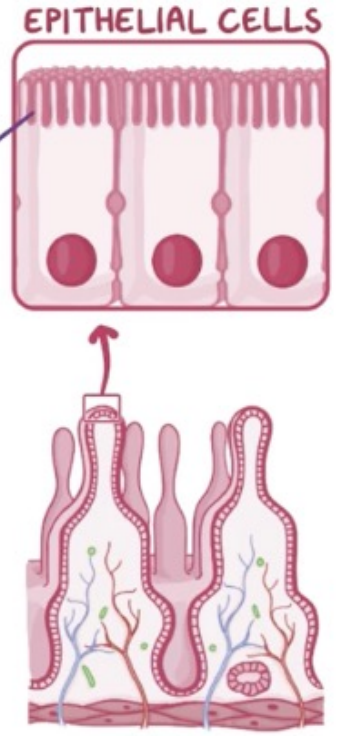
Inhibits NPC1L1 (Niemann-Pick C1-Like 1) protein, a critical mediator of cholesterol absorption

# EZETIMIBE

~ MECHANISM not FULLY UNDERSTOOD

~ BLOCK CRITICAL MEDIATOR of CHOLESTEROL ABSORPTION

NIEMANN-PICK C1-LIKE 1 PROTEIN




~ DOESN'T AFFECT VLDL or HDL

~ TREAT HIGH LEVELS of LDL

~ ↓ OVERALL LDL

↳ USED in COMBINATION w/ OTHER LIPID-LOWERING AGENTS (e.g. statins)

## SIDE EFFECTS

~ GI UPSET

~ LIVER DAMAGE

# CHOLESTEROL ABSORPTION INHIBITOR

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Ezetimibe (Zetia) | Use with gemfibrozil<br>When used with a statin:<br>• Active hepatic disease or unexplained persistent elevations in serum transaminase<br>• Pregnancy and breastfeeding | Hepatoxicity<br>Myositis<br>GI upset | May enhance anticoagulant effect of warfarin (may be due to inhibition of NPC1L1-mediated vitamin K uptake)<br>May increase serum concentrations of cyclosporine; cyclosporine may increase serum concentrations of ezetimibe<br>Gemfibrozil may enhance adverse effects of ezetimibe, specifically myopathy and cholelithiasis - concurrent use is contraindicated<br>Bile Acid resins may decrease the absorption of ezetimibe |

# CLINICAL USE & PK

## Clinical Use

Hypercholesterolemia

Phytosterolemia, a rare genetic disorder that results from impaired export of phytosterols

## PK

Metabolized by glucuronidation

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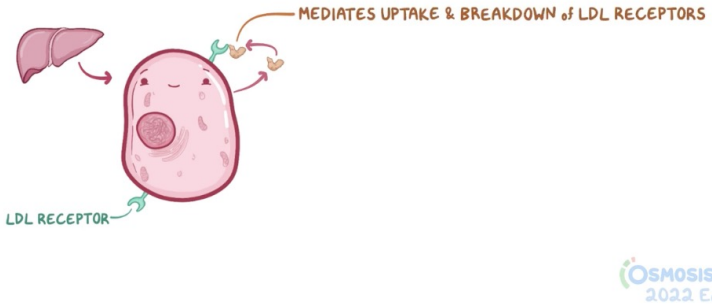
# PCSK9 INHIBITORS

# ACTIVE LEARNING

Write down what you remember PCSK9 from your pre-work video.

How might inhibiting PCSK9 be advantageous in the treatment of dyslipidemia?

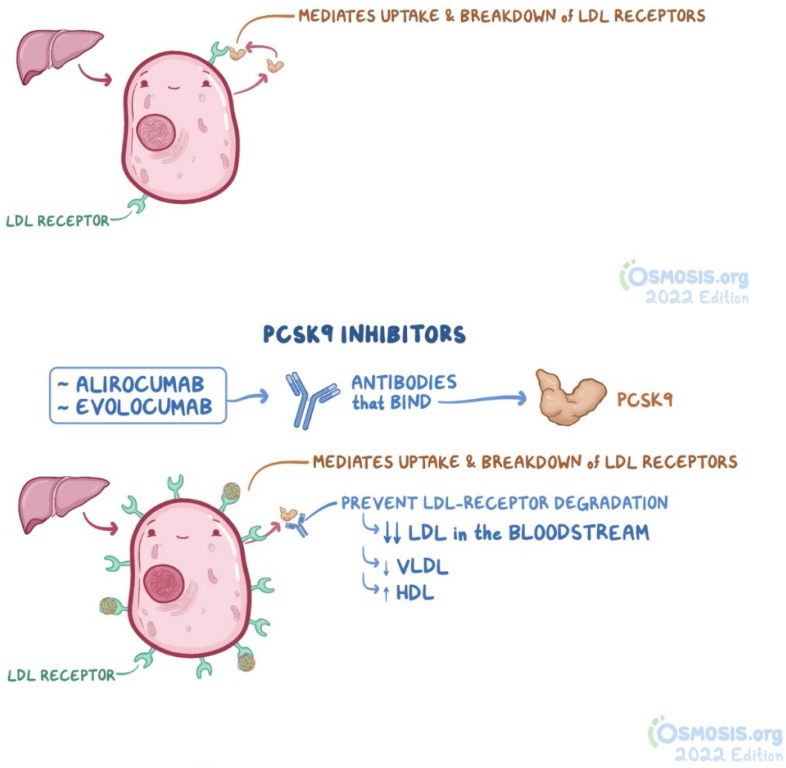
# PCSK9




PCSK9 secreted by liver cells

- Bind to LDL receptors on the cell's surface
- Mediates the uptake and breakdown of LDL receptors intracellularly

# PCSK9 INHIBITOR MOA




PCSK9 INHIBITORS bind to PCSK9

- This prevents LDL-receptor degradation
- Increases overall quantity of LDL receptors on liver cells →
  - Large decrease in LDL in the bloodstream
  - Slight decrease in VLDL
  - Slight increase in HDL

# PCSK9 INHIBITORS

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Alirocumab (Praluent)<br>Evolocumab (Repatha)<br>***-ocumab***<br>  | Cautions:<br>Hypersensitivity reactions | Hypersensitivity reactions (angioedema, urticaria)<br>Myalgias<br>Neurocognitive defects<br>Local injection site reactions<br>Upper respiratory and flu-like symptoms | Work complementarily with statins |

# CLINICAL USE

Homozygous familial hypercholesterolemia

Heterozygous familial hypercholesterolemia

Established ASCVD with LDL-C > 70 mg/dL in need of additional LDL-c lowering

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# BILE ACID RESINS (SEQUESTRANTS)

# BILE ACID RESIN MECHANISM OF ACTION

Highly positively charged and bind negatively charged bile acids

- Resins not absorbed and bound bile acids excreted in stool

As pool of bile acids is reduced, hepatic bile acid synthesis ↑ (uses cholesterol)

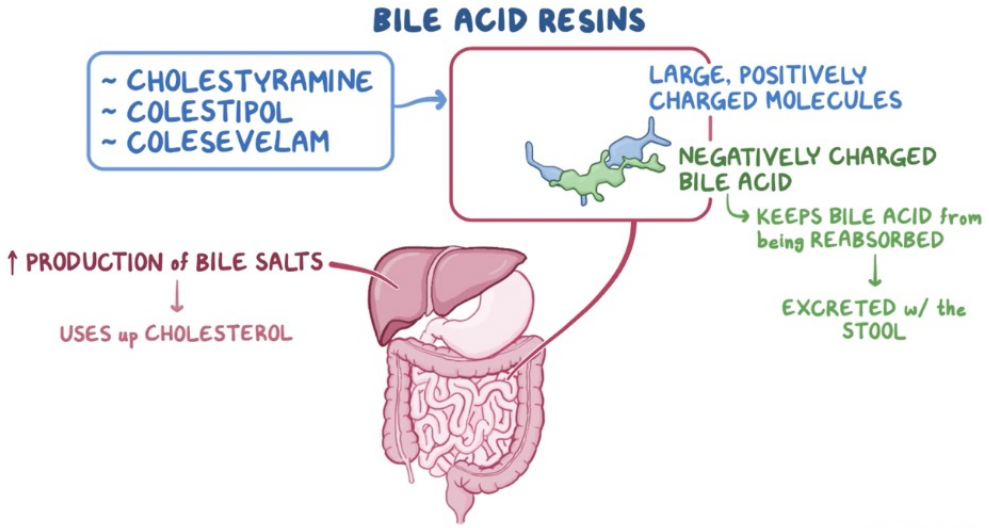
- Hepatic cholesterol content ↓ → ↑ production of LDL receptors
- ↑ LDL receptors → ↑ LDL clearance and ↓ LDL-C levels

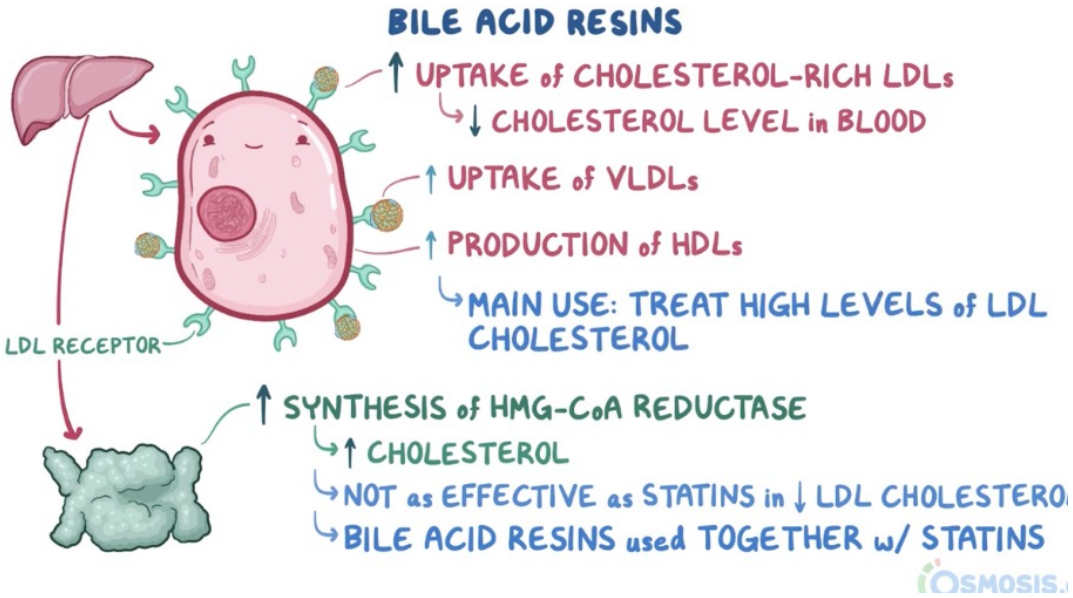
Effect partially offset by enhanced cholesterol synthesis via HMG-CoA reductase upregulation

- HMG-CoA reductase inhibition via statins substantially increases effectiveness

Resin-induced ↑ in bile acid production → ↑ in hepatic triglyceride synthesis

- Aware in patient with hypertriglyceridemia


BILE ACID RESINS
~ CHOLESTYRAMINE
~ COLESTIPOL
~ COLESEVELAM
LARGE, POSITIVELY CHARGED MOLECULES
NEGATIVELY CHARGED BILE ACID
KEEPS BILE ACID from being REABSORBED
EXCRETED w/ the STOOL
↑ PRODUCTION of BILE SALTS
USES up CHOLESTEROL


BILE ACID RESINS
↑ UPTAKE of CHOLESTEROL-RICH LDLs
↓ CHOLESTEROL LEVEL in BLOOD
↑ UPTAKE of VLDLs
↑ PRODUCTION of HDLs
MAIN USE: TREAT HIGH LEVELS of LDL CHOLESTEROL
LDL RECEPTOR
↑ SYNTHESIS of HMG-CoA REDUCTASE
↑ CHOLESTEROL
NOT as EFFECTIVE as STATINS in ↓ LDL CHOLESTERO
BILE ACID RESINS used TOGETHER w/ STATINS

# ACTIVE LEARNING

Based on the mechanism of bile acid resins, what cautions might you expect?

# BILE ACID RESIN

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Colestipol<br>Cholestyramine<br>Colesevelam | Complete biliary obstruction<br>Caution:<br>Increases TGs | Constipation<br>Bloating<br>Heartburn<br>Eructation<br>Nausea | Can interfere with the absorption of other oral drugs, including statins and ezetimibe; they should be taken several hours before or after other drugs<br>• Colesevelam does not appear to interfere with the absorption of most statins<br>Can interfere with absorption of fat-soluble vitamins<br>Complementary effect - statins |

# CLINICAL USE & ADME

Used typically 3rd or 4th line agent after statins + ezetimibe (if not PCSK9i eligible)

For LDL-C reduction among those intolerant of statins or still in need of LDL-C lowering despite maximally tolerated doses of statins+ezetimibe

Colesevelam and colestipol – tablets or powders

Cholestyramine powder

Powders mixed with fluid and drunk as slurry

Not absorbed systemically

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# FIBRATES

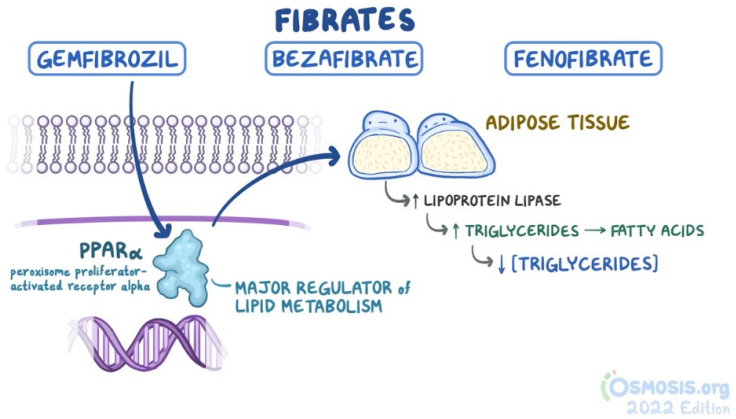
# FIBRATE MECHANISM OF ACTION

Activate PPAR-α (proliferator-activated receptor alpha)

- Intranuclear receptor
- Major regulator of lipid metabolism

PPAR-α activation → ↑ lipoprotein lipase production by adipose cells → ↑ conversion of triglycerides to free fatty acids

- Lowers triglyceride levels

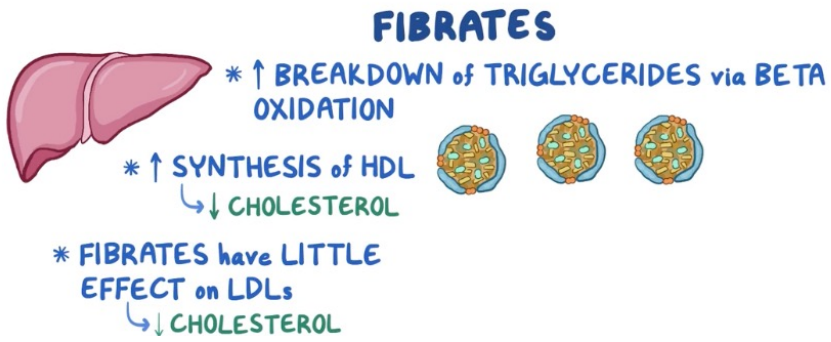


# FIBRATE MECHANISM OF ACTION

In the liver, fibrates ↑ the breakdown of triglycerides through beta oxidation

↑ synthesis of HDL

- Can provide a moderate decrease in cholesterol.



# FIBRATES

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Fenofibrate<br>Gemfibrozil | Renal failure<br>Hepatic dysfunction<br>Pregnancy<br>Biliary tract disease | GI<br>**Cholesterol gallstones**<br>Rashes<br>Myopathy<br>Increased liver enzymes | Risk of myopathy increases when fibrates are given with statins (see above)<br>Gemfibrozil may enhance adverse effects of ezetimibe, specifically myopathy and cholelithiasis - concurrent use is contraindicated<br>Potentiation of the actions of warfarin - reduction of warfarin dose maybe necessary |

# CLINICAL USE & ADME

Persistently elevated triglycerides

Excretion impaired in renal failure

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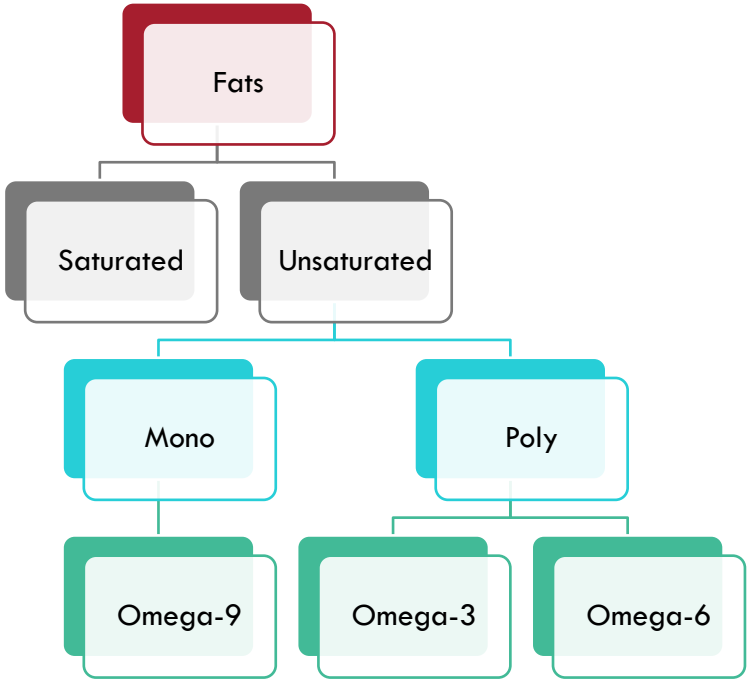
# OMEGA-3 FATTY ACIDS

# FAT CLASSIFICATIONS



# OMEGA-3 FATTY ACID MECHANISM OF ACTION

Mechanism not fully elucidated

Reduce VLDL-TG production in the liver (main effect)

Increase TG clearance from the circulation

Reduce TG by 20-30%

# OMEGA-3 FATTY ACID

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Icosapent ethyl | Caution:<br>Increased risk atrial fibrillation in those with history | Nausea<br>Fish like taste<br>Eructation<br>Bleeding (high doses) | Antiplatelet and anticoagulants increase risk of bleeding |

# CLINICAL USE & ADME

Adjunctive therapy in high-risk patients treated with statins who have residual TG 150 to 500 mg/dL.

Patients must also have either established cardiovascular disease or diabetes and 2 or more additional risk factors for cardiovascular disease.

Absorbed in small intestine

Oxidized in liver

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# NIACIN

# NIACIN (VITAMIN B3)

Water soluble B-complex vitamin

Vitamin effect

Larger doses hypolipidemic effect

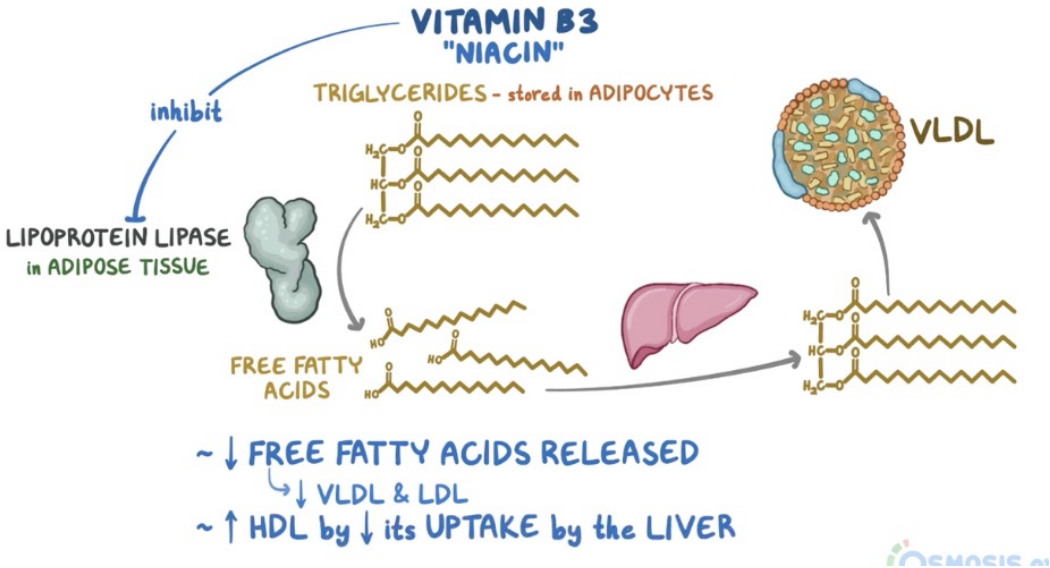
# NIACIN MECHANISM OF ACTION

Inhibits lipoprotein lipase in adipose tissue

- Lipases cut up TGs stored within adipocytes and release them as free fatty acids (FFAs)
- Liver uses FFAs to create TGs which forms VLDLs
- Niacin ↓ amount of FFAs released → ↓ in VLDL and LDL levels

Niacin can cause ↑ in HDL

- ↓ HDL uptake by the liver



# NIACIN

| Name | CIs & Cautions | Adverse Effects | Selected Interactions |
|---|---|---|---|
| Niacin | Pregnancy<br>Peptic disease<br>Active hepatic disease<br>Caution:<br>Gout<br>Diabetes | Flushing<br>Dyspepsia<br>Hepatotoxicity<br>Insulin resistance<br>Increases uric acid | Concurrent use of niacin and a statin can cause myopathy |

# CLINICAL USE & ADME

Generally no longer recommended

Metabolite and unchanged drug excreted in urine

# REFERENCE LIST

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# ANY QUESTIONS?