iCARE PHARMACY SERVICES, INC.

Critical Importance of Lowering LDL-C and Applying GDMT

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SPEAKER DISCLOSURE

I do not have (nor does any immediate family member have):

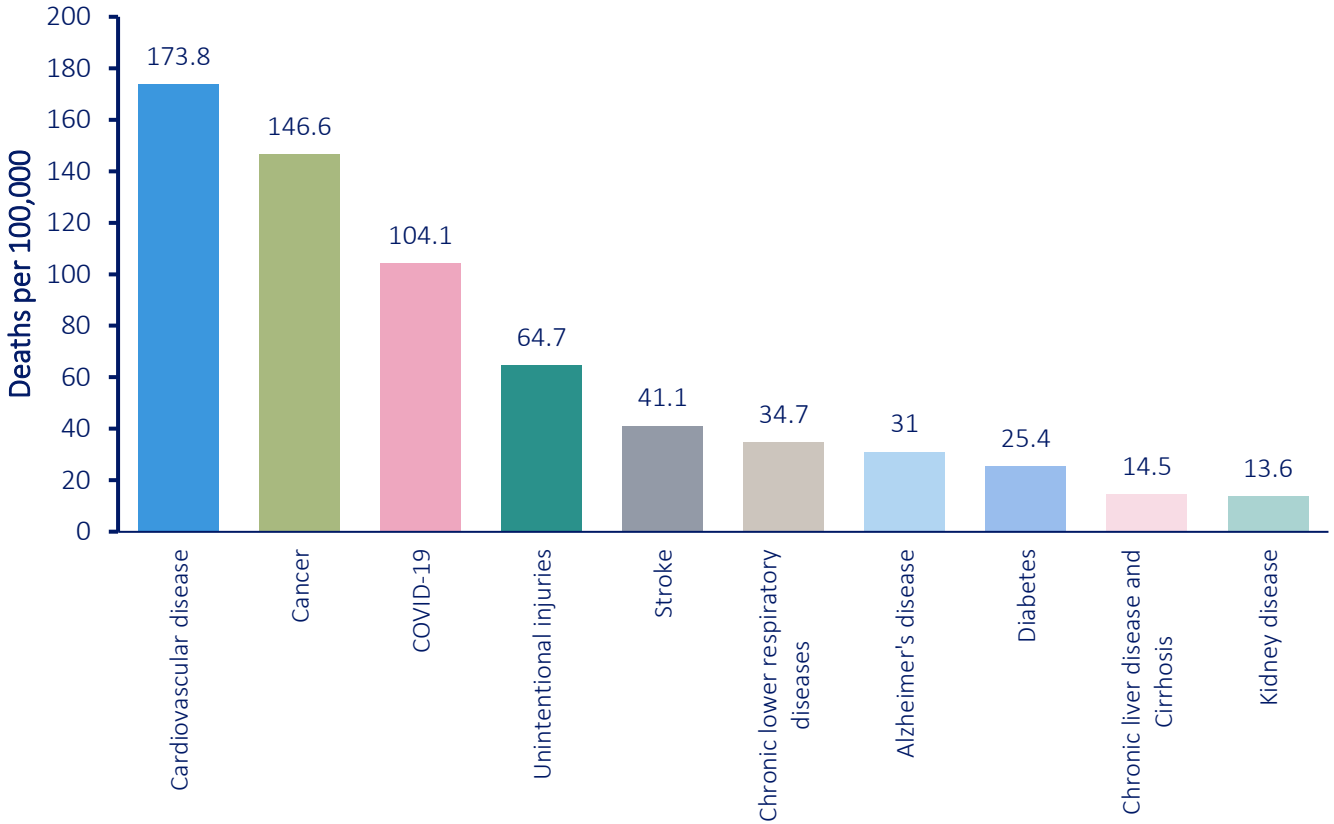
- a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity
- any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

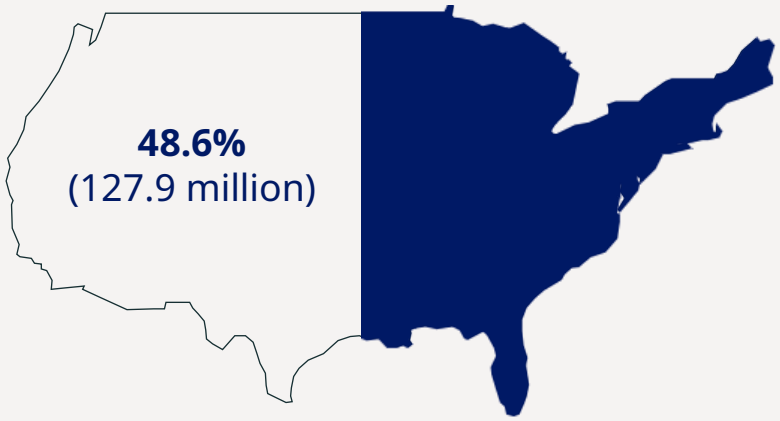
1. Correlate the relationship between plasma lipids and coronary heart disease.
2. Defend the rationale for drug selection among various classes of drugs used to reduce cholesterol.
3. Integrate guideline-recommended strategies for lowering LDL-C in primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD).
4. Develop evidence-based treatment plan for patients with elevated LDL-C.

Burden of CVD in the US

Age adjusted death rate for 10 leading causes in the US (2021)[1]

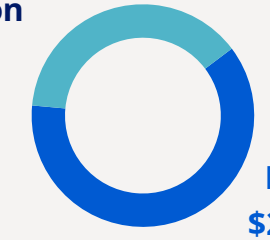


Prevalence of CVD* in adults aged ≥20 years(2020)[2]



The estimated cost of CVD (2018-2019)[2]

Lost productivity/mortality
$155.9 billion



Direct costs
$251.4 billion

**CVD is comprising CHD, HF, stroke, and hypertension*
CVD, cardiovascular disease US, United States
1. NCHS Data Brief, Number 456, December 2022 (cdc.gov); 2. Tsao CW et al. Circulation. 2023;147(8):e93-e621

ASCVD - Definition

ASCVD[1]

A history of an ACS or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be **atherosclerotic in origin**

Atherosclerosis is a progressive arterial disease

Fatty streaks in arterial walls gradually develop into atheroma and characteristic plaques[2]

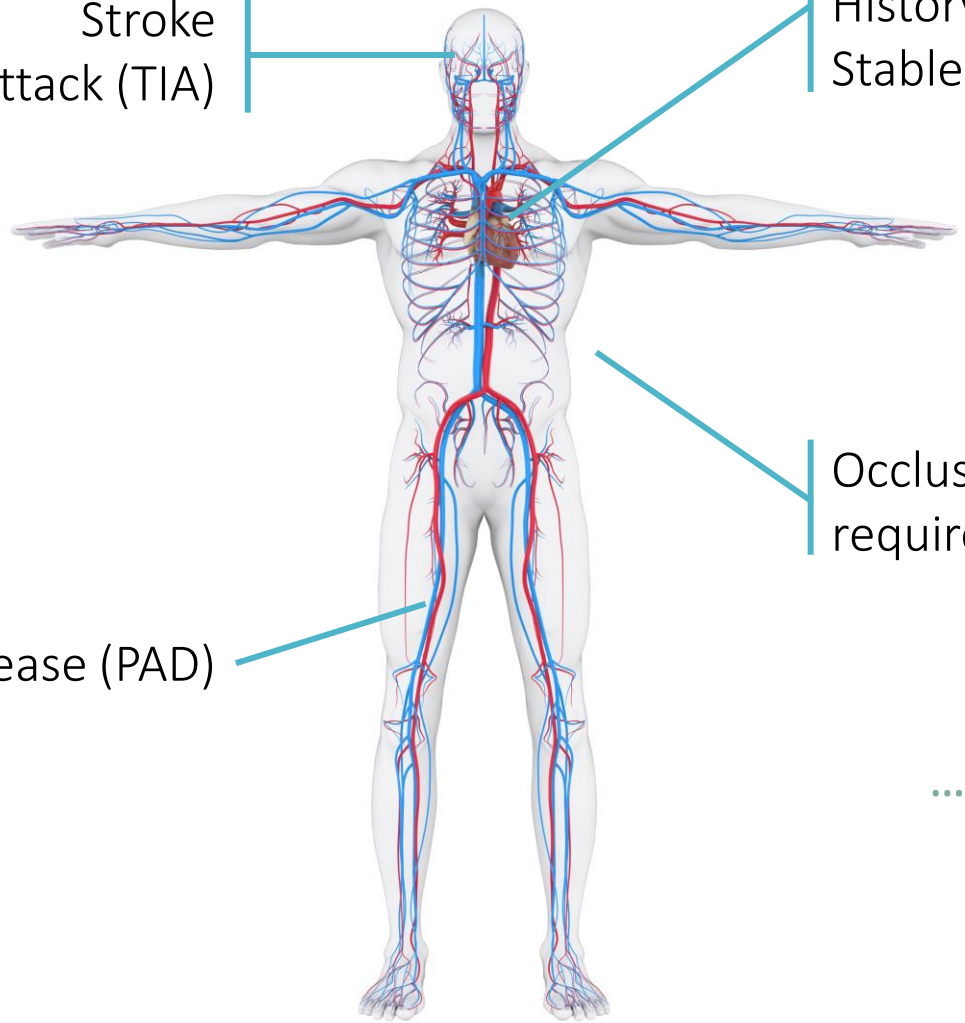
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction
1. Das SR et al. J Am Coll Cardiol. 2020; 76(9):1117-1145; 2. Herrington W et al. Circ Res 2016;118:535–546

Clinical ASCVD can present in many ways

CLINICAL ASCVD INCLUDES:

Stroke
Transient ischemic attack (TIA)

Acute coronary syndrome (ACS)
History of myocardial infarction (MI)
Stable or unstable angina



Occlusion of arteries that require revascularization

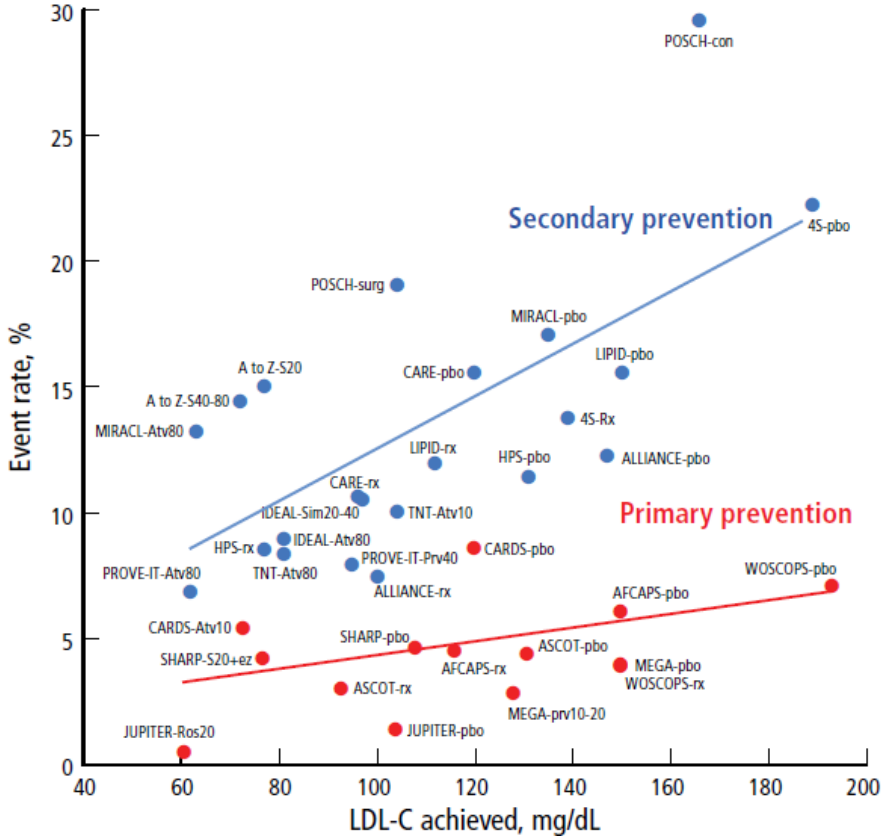
Peripheral artery disease (PAD)

…ALL OF ATHEROSCLEROTIC ORIGIN

Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24):e285-e350.

Reducing LDL-C Has a Linear Benefit in CV Risk Reduction

- Randomized controlled trials of statins and other studies investigating cholesterol-lowering show a linear relationship between achieved LDL-C levels and absolute risk of coronary events[1]



A 2010 CTTC meta-analysis reported that for **every 1 mmol/L reduction in LDL-C at 1 year** of statin therapy, there is a **22% relative risk reduction** in major vascular events[2]

- Data from 26 randomized trials and ~169,000 patients
- Prespecified CV outcomes were cause-specific mortality, major coronary event, coronary revascularization, and stroke

4S = Scandinavian Simvastatin Survival Study; **A to Z** = A to Z Trial; **AFCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **ALLIANCE** = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events Study; **ASCOT** = Anglo-Scandinavian Cardiac Outcomes Trial; **CARDS** = Collaborative Atorvastatin Diabetes Study; **CARE** = Cholesterol and Recurrent Events Trial; **HPS** = Heart Protection Study; **IDEAL** = Incremental Decrease in End Points Through Aggressive Lipid Lowering Trial; **JUPITER** = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; **LIPID** = Long-Term Intervention With Pravastatin in Ischaemic Disease; **MEGA** = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study; **MIRACL** = Myocardial Ischemia Reduction With Acute Cholesterol Lowering Trial; **POSCH** = Program on the Surgical Control of the Hyperlipidemias; **PROVE-IT** = Pravastatin or Atorvastatin Evaluation and Infection Therapy; **SHARP** = Study of Heart and Renal Protection; **TNT** = Treating to New Targets; **WOSCOPS** = West of Scotland Coronary Prevention Study.

LDL-C: 1 mmol/L = 38.6 mg/dL. CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol.

1. Raymond C, et al. *Cleve Clin J Med*. 2014;81:11–19; 2. Baigent C, et al. *Lancet*. 2010;376:1670–1681.

Definitions

- **Hyperlipidemia**- Abnormalities of serum lipids which contribute to plaque formation and lead to:
  1. CHD - Leading cause of death for men and women in the US
  2. PAD

- **Cholesterol** is lipid soluble substance

  Not soluble in water; packaged in carrier proteins known as lipoproteins

- **Lipoproteins** are mixtures of fatty cholesterol and proteins in the blood that transport cholesterol, TG, and other lipids to various tissues

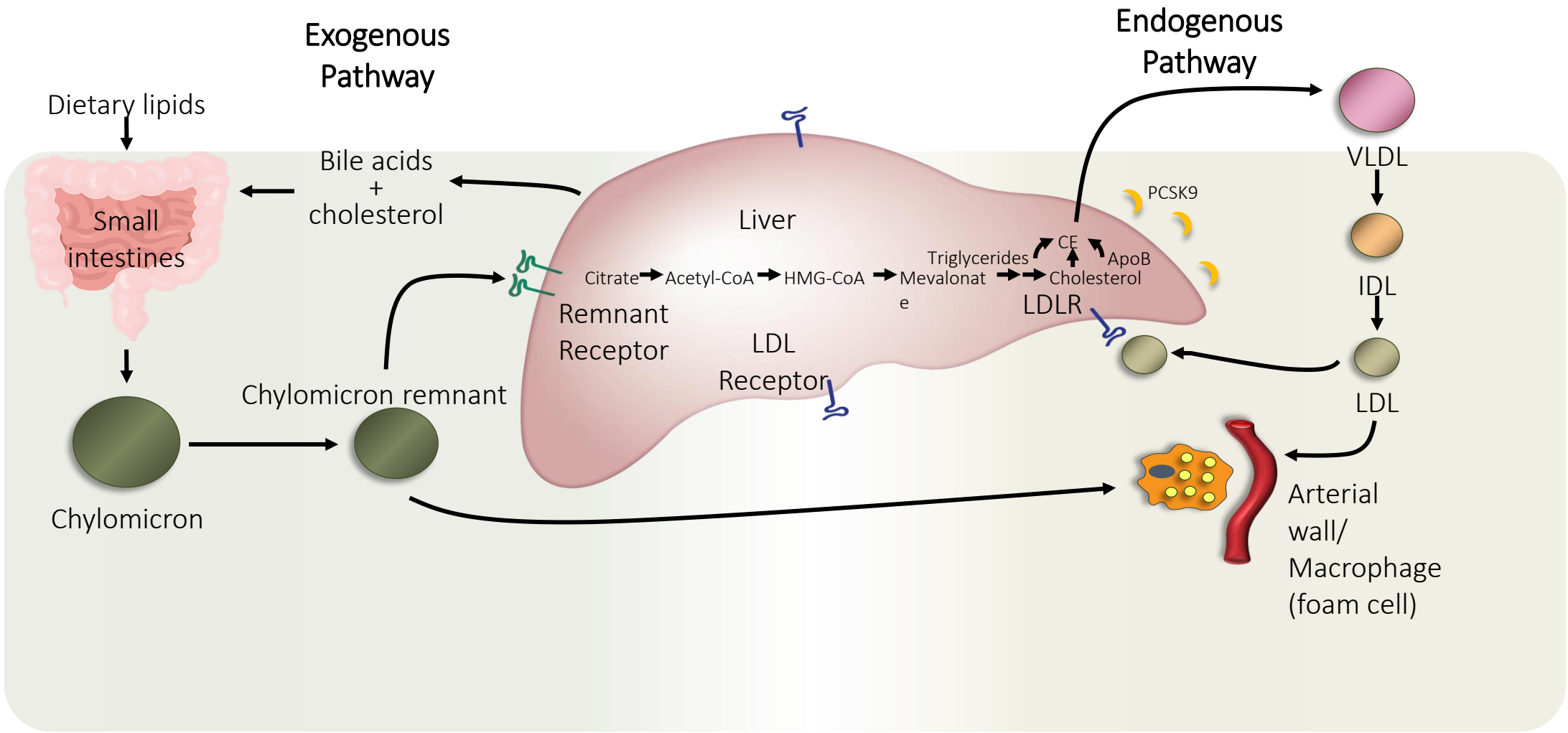
  VLDL: Very-low-density lipoprotein

  IDL: Intermediate lipoprotein

  LDL: Low-density lipoprotein

  HDL: High-density lipoprotein

Lipid Pathophysiology



LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; CE=cholesterol ester; ApoB = Apolipoprotein B; PCSK9 = proprotein convertase subtilisin kexin type 9; VLDL = very low-density lipoprotein; IDL = intermediate density lipoprotein.

Feingold KR. Introduction to lipids and lipoproteins. In: Diagnosis and Treatment of Diseases of Lipid and Lipoprotein Metabolism in Adults and Children. Feingold KR, Wilson DP, ed. Updated January 8, 2021. Accessed May 27, 2021. https://www.endotext.org/chapter/introduction-to-lipids-and-lipoproteins/. Semenkovich CF, et al. Disorders of lipid metabolism. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*. 12th edition. Elsevier Saunders; 2011:1633-1674.

Cholesterol

LDL-C = Total Cholesterol − (HDL + Triglycerides/5)

- "Bad cholesterol"
- Carries cholesterol from the liver to the rest of the body
- Primary diagnostic and therapeutic target

HDL-C

- "Good cholesterol"
- Carries cholesterol from the body to the liver

VLDL-C: carries fat from the liver to adipose tissue

- composed mostly of cholesterol, with little protein
- deposits cholesterol on the walls of arteries
- associated with atherosclerosis and CHD

IDL-C: not detectable in blood

TYPES of Hyperlipidemia

Primary
- No signs of CHD

Secondary
- Patient has had an event
  - *examples: angina, stroke, CAD, CHD*

Causes of Secondary Dyslipidemia
- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that raise LDL cholesterol and lower HDL cholesterol
  - *progestins*
  - *anabolic steroids*
  - *corticosteroids*

What are the treatment options?

Cholesterol Treatment Options

Lifestyle modifications

- Diet
- Exercise

Medications Classes

1. HMG-CoA reductase inhibitors
2. Bile acid sequestrans
3. Cholesterol absorption inhibitor
4. PCSK9 inhibitors
5. ATP Citrate lyase inhibitor
6. siRNA

Patient Centered Pharmacology, Tindel et al

Drug Therapy

HMG CoA Reductase Inhibitors (Statins)

- Fluvastatin(Lescol)
- Pravastatin (Pravachol)
- Lovastatin (Mevacor)
- Simvastatin (Zocor)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)

Bile Acid Sequestrants

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

Cholesterol Absorption Inhibitor

- Ezetimibe (Zetia)

PCSK9 inhibitors

- Alirocumab (Praluent)
- evolocumab (Repatha)

ATP Citrate lyase inhibitor

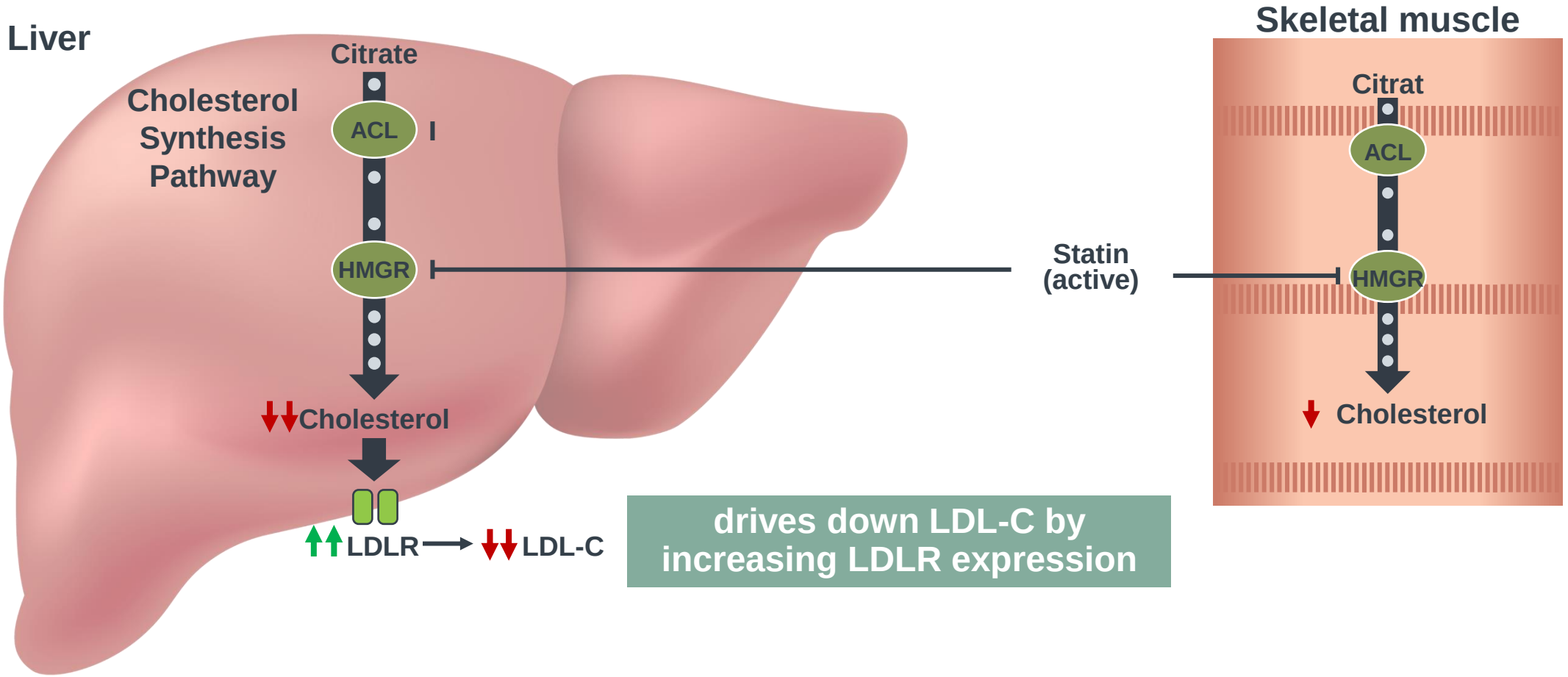
- Bempedoic Acid (Nexletol)

siRNA

- Inclisiran (Leqvio)

HMG-CoA Reductase Inhibitors

MOA: Block the enzyme that catalyzes the early steps of cholesterol synthesis



ACL=ATP citrate lyase; ACSVL1=very long-chain acyl-CoA synthease-1; HMGR=3-hydroxy-3-methylglutarate-CoA reductase; LDLR=low-density lipoprotein receptor.
Pinkosky SL, et al. *Nat Commun*. 2016;7:13457.

HMG-CoA Reductase Inhibitors

"-statins"

First-line treatment for hyperlipidemia

Preferred drugs for lowering LDL-C

<u>Demonstrated Therapeutic Benefits</u>

- ↓ major coronary events (MI)
- ↓ CHD mortality
- ↓coronary procedures (PTCA/CABG)
- ↓ stroke
- ↓ CV death

Rule of 6

- A substantial reduction in LDL-C occurs at the usual starting dose
- Each doubling of the daily dose produces only an additional 6% average reduction
- Important to consider dose escalation vs. adding an additional LDL- lowering drug

Intensity of Statin Therapy

Not primary choice
Reserved for pts that can't tolerate high dose statins

High Intensity	Moderate Intensity	Low Intensity
Lowers LDL-C by ≥50%	Lowers LDL-C by 30-50%	Lowers LDL-C by ≤ 30%
Atorvastatin (Lipitor) 40-80mg Rosuvastatin (Crestor) 20-40 mg	Atorvastatin (Lipitor) 10-20mg Rosuvastatin (Crestor) 5-10mg Simvastatin (Zocor) 20-40mg Pravastatin (Pravachol) 40-80mg Lovastatin (Mevacor) 40-80mg Fluvastatin(Lescol) 40mg bid	Simvastatin (Zocor) 10mg Pravastatin (Pravachol) 10-20mg Lovastatin (Mevacor) 20mg Fluvastatin(Lescol) 20-40mg

PATIENT CENTERED PHARMACOLOGY, TINDEL ET AL

HMG-CoA Reductase Inhibitors ADRs

Adverse effects:

- CV: Chest pain, peripheral edema
- DERM: Rash, photosensitivity
- EENT: Rhinitis
- GI: Abdominal cramps, constipation, flatus, diarrhea, heart-burn, altered taste
- **SERIOUS elevation in liver function tests** (rarely develop liver failure)
- MS: SERIOUS myopathy, including **rhabdomyolysis**, depletion of coenzyme Q-10, and **development of myalgias**
- NEURO: Dizziness, insomnia, headache, weakness
- Other: DM

HMG CoA Reductase Inhibitors

- Rhabdomyolysis: breakdown of muscle fibers, resulting in release of muscle fiber contents (myoglobin) into the bloodstream

- Baseline creatine kinase (CK) should be obtained for patients who develop persistent muscle discomfort or weakness or brown urine while taking a statin

- Follow-up CK should be attained only in patients complaining of muscle pain, weakness, tenderness, or brown urine.

- Routine monitoring of CK is of little value in the absence of clinical signs or symptoms.

HMG-CoA Reductase Inhibitors

Interactions

- Statins undergo biotransformation by the CP-450 system
- CYP-450 inhibitors: use cautiously, statin metabolism could be impaired, leading to elevated serum levels and risk of rhabdomyolysis
- Extreme caution with: gemfibrozil, protease inhibitors, niacin, cyclosporine, amiodarone, erythromycin
- Bile acid sequestrants will reduce bioavailability and effectiveness of the statins, give 1 hour before or 4 hours after bile acid resins
- St John's wort may reduce serum levels and effectiveness
- Large quantities of grapefruit juice increase blood levels of statins and hence risk of myopathies and rhabdomyolysis
- Coenzyme Q- 10 may decrease muscle-related symptoms

HMG CoA Reductase Inhibitors

Contraindications

- Liver disease
- Unexplained, persistent elevated LFTs
- Hx of alcoholism
- use with certain drugs (P450)
- Pregnancy

USE STATINS CAUTIOUSLY IN PATIENTS OF ASIAN ANCESTRY

- Higher blood levels of statins occur in Asians because of their dietary intake of red rice yeast as a basic food staple
- Red Rice Yeast, and Chinese red barbecued pork contain the active ingredient lovastatin, which, when isolated, became the first statin drug

HMG CoA Reductase Inhibitors

Monitor

- LFTs
- Baseline, 6-12wks, and annual
- Creatine kinase (CK)
- Lipid profile
- S & SX myopathy

  6-12 wks after initiation of therapy

Bile Acid Sequestrants

MOA:

- Bind to bile acids in the intestine, forms an insoluble complex, decreasing reabsorption and increases fecal excretion of LDL
- Liver is stimulated to convert hepatocellular cholesterol into bile acids

FDA-approved indication(s): As an adjunct to diet and exercise to:

- Colesevelam:
  1. Decrease LDL-C in adults with primary hyperlipidemia
  2. Increase glycemic control in adults with T2DM

- Cholestyramine & Colestipol: Decrease LDL-C with primary hyperlipidemia, as adjunct to diet

US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Bile Acid Sequestrants

Dose and route of administration:

- Colesevelam:
  - ✓Tablets: 6 tablets orally once daily or 3 tablets orally twice daily; take tablets with a meal and liquid.
  - ✓Suspension: one 3.75-g packet orally daily, or one 1.875-g packet orally twice daily; mix powder with 8 ounces of water, fruit juice, or soft drink; take with meal.
  - ✓3.75 g is equivalent to 6 tablets. 1.875 g is equivalent to 3 tablets;
- Cholestyramine: 8-16 g/day orally, divided into 2 doses;
- Colestipol: 2-16 g/day orally, given once or in divided doses

US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Bile Acid Sequestrants

Mean % LDL reduction:

- Colesevelam: Monotherapy -15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy—additional 10%-16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg).

- Cholestyramine: Monotherapy -10.4% vs placebo.

- Colestipol: In dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively

US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Bile Acid Sequestrants

Contraindications:

- Colesevelam: TG >500 mg/dL; history of hypertriglyceridemia-induced pancreatitis; bowel obstruction.
- Cholestyramine: History of serious hypersensitivity to this medication.
- Colestipol: Complete biliary obstruction, history of serious hypersensitivity to this medication.

Warnings/precautions:

- May increase TG and cause acute pancreatitis, monitor TG, may cause GI obstruction, avoid with gastroparesis, other GI motility disorders, may cause vitamin K or fat-soluble vitamin deficiencies

  Some products contain phenylalanine, which may be harmful to patients with phenylketonuria.

US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Bile Acid Sequestrants

- Adverse effects: Constipation, dyspepsia, and nausea

- Use during pregnancy/lactation: Considered safe to use

- Drug-drug interactions:
  - ✓may decrease absorption of other medications; give other medications ≥4 hours before BAS
  - ✓decrease absorption of cyclosporin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan, phenytoin, sulfonylureas, thyroid replacement therapy, warfarin
  - ✓warfarin, monitor INR frequently during BAS initiation and then periodically
  - ✓Cholestyramine may increase exposure to metformin; monitor glycemic control

US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Bile Acid Sequestrants

Considerations in prescribing:

Pill burden; inconvenience in preparation of oral suspension preparations; drug interactions, GI side effects; exacerbation of hypertriglyceridemia; orally administered, colesevelam lowers HbA1c 0.5% in diabetes

CV outcomes trials:

In LRC-CPPT, 3,806 asymptomatic middle-aged men with primary hypercholesterolemia were randomized to cholestyramine resin vs placebo for an average of 7.4 years. The cholestyramine group experienced a 19% reduction in risk ($P < 0.05$) of the primary endpoint—definite CHD death and/or definite nonfatal MI.

Effects of colesevelam and colestipol on cardiovascular morbidity and mortality have not been determined

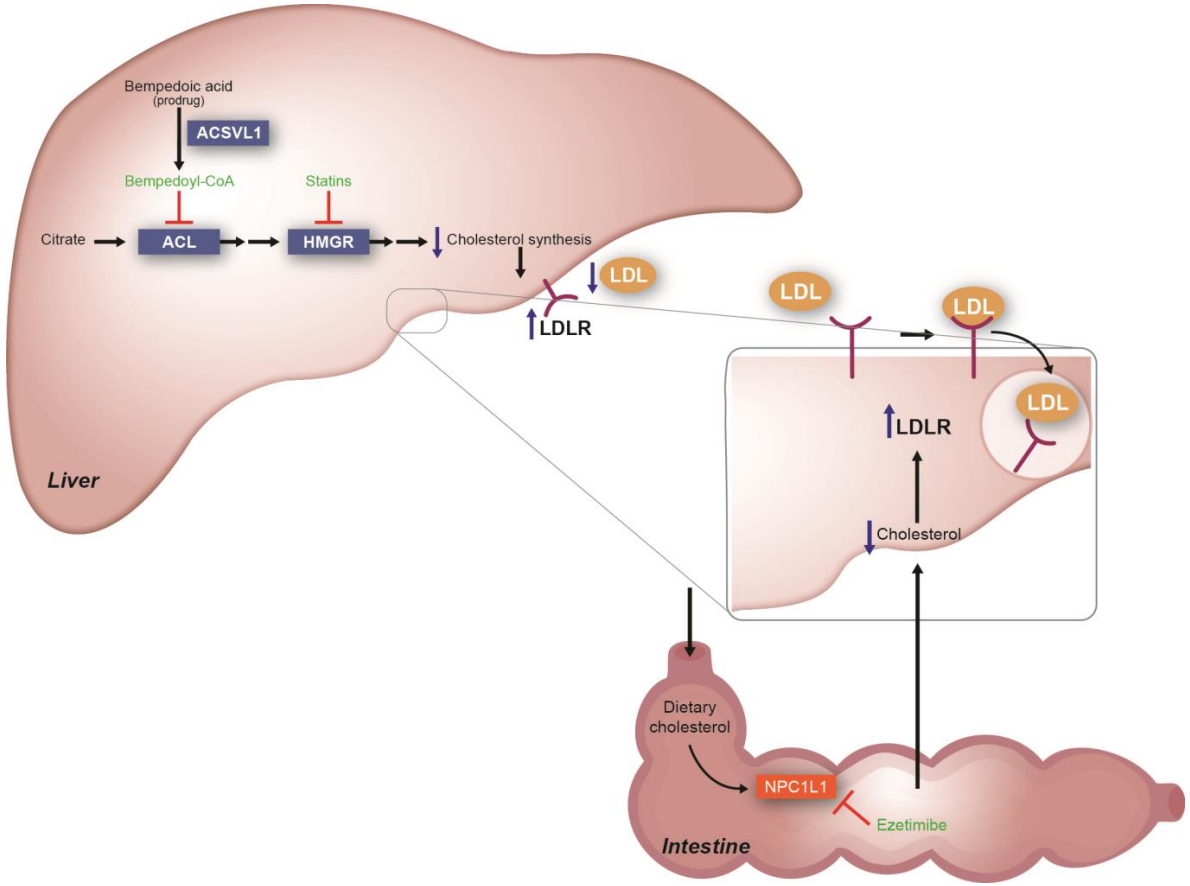
US Food & Drug Administration. Drugs@FDA -Welchol. Accessed December 23, 2021.
US Food & Drug Administration. Drugs@FDA -Colestid. Accessed December 23, 2021.

Cholesterol Absorption Inhibitor - Ezetimibe

MOA

Acts in the small intestine to inhibits NPC1L1 (sterol transporter), inhibits gastrointestinal cholesterol absorption, leads to decreased hepatic cholesterol, resulting in increased LDLR and decreased plasma LDL-C

Upregulates LDL receptors



Efficacy:

- ⬇ LDL-C 18% monotherapy, 25% with statin
- ⬆ HDL by 3 %

ACL = ATP citrate lyase; ACSVL1 = very long-chain acyl-CoA synthetase 1; HMGR = 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase; ATP = adenosine triphosphate; LDL = low-density lipoprotein; LDLR = LDL receptor;
NPC1L1 = Niemann-Pick C1-Like 1; TCA = tricarboxylic acid.

Garcia-Calvo M, et al. *Proc Natl Acad Sci.* 2005;102:8132–8137; Ference BA, et al. *Eur Heart J.* 2017;38:2459–2472.
US Food & Drug Administration. Drugs@FDA - Zetia (ezetimibe). Accessed December 10, 2021.

Ezetimibe

FDA-approved indication(s): As adjunct to diet to:

1. Decrease TC, LDL-C, ApoB, non–HDL-C in patients with primary hyperlipidemia, either alone or in combination with statin therapy;
2. Decrease TC, LDL-C, ApoB, non–HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate
3. Decrease TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin
4. Decrease sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)

Dose: 10 mg orally daily, with/without food. Take either ≥2 h before or ≥4 h after BAS, if used in combination

US Food & Drug Administration. Drugs@FDA - Zetia (ezetimibe). Accessed December 10, 2021.

Ezetimibe

Contraindication: History of hypersensitivity

Warnings/precautions:

1. Not recommended in patients with moderate/severe hepatic impairment.

2. Persistent elevations in hepatic transaminases may occur with concomitant statin therapy. Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy.

3. Cases of myopathy and rhabdomyolysis have been reported when ezetimibe was used alone or in combination with statin therapy.

US Food & Drug Administration. Drugs@FDA - Zetia (ezetimibe). Accessed December 10, 2021.

Ezetimibe

Adverse effects:

- Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities
- In combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea

Use during pregnancy/lactation: No safety data in humans; avoid use

Drug–drug interactions: Cyclosporine, fibrates, BAS

Other prescribing considerations: Generally well tolerated. Generic available

US Food & Drug Administration. Drugs@FDA - Zetia (ezetimibe). Accessed December 10, 2021.

Ezetimibe

CV outcomes trials:

1. IMPROVE-IT (The addition of ezetimibe to moderate-intensity statin therapy in patients with recent ACS resulted in incremental lowering of LDL-C and reduced the primary composite endpoint of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years)

2. SHARP (Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years)

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.
Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet.

PCSK9 inhibitors

Human monoclonal antibody that binds to PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9)

- solution for SC inj
- prefilled pen or syringe

alirocumab (Praluent)

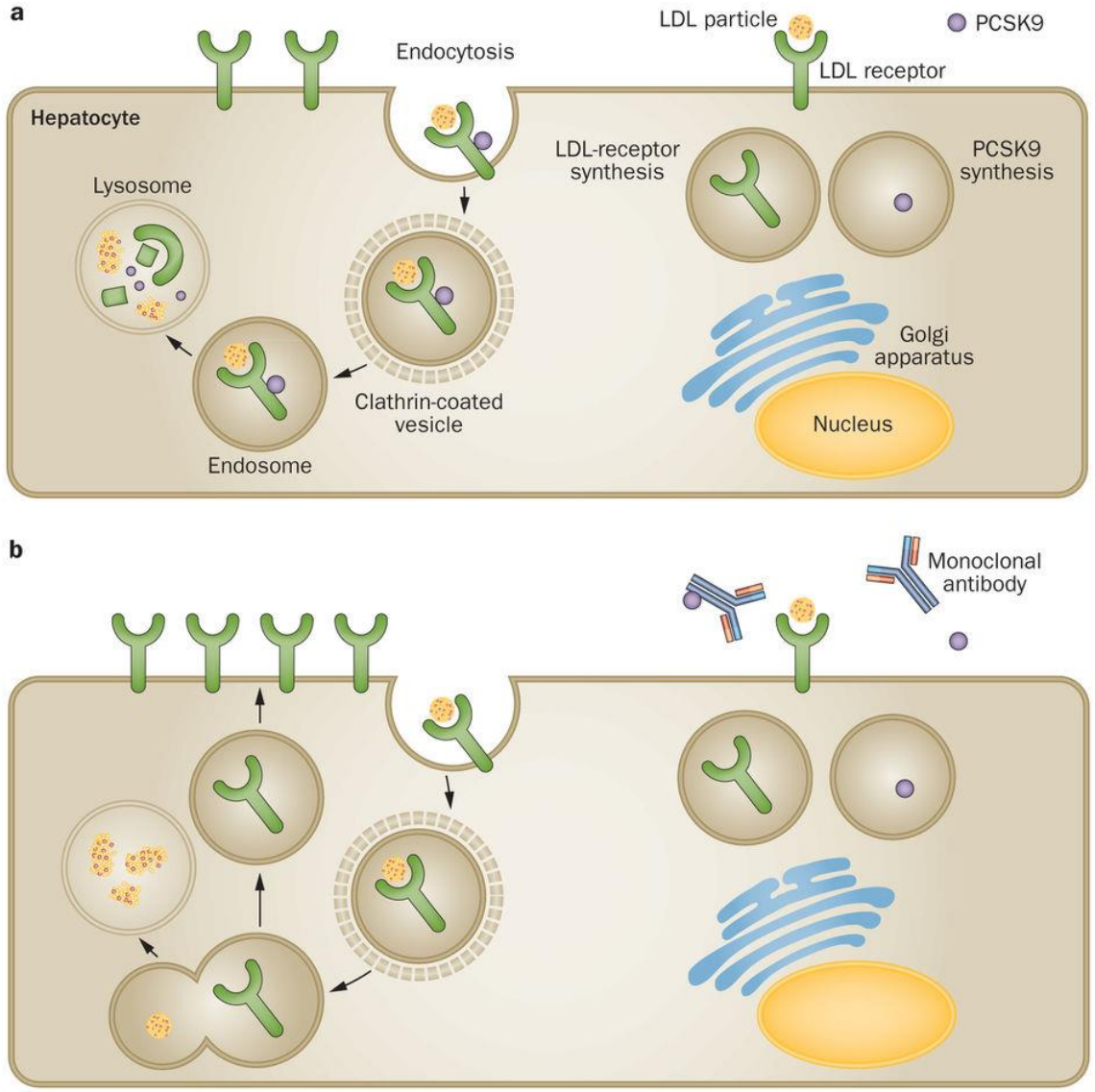
- 75mg/mL
- 150mg/mL

evolocumab (Repatha)

- 140mg/mL

US Food & Drug Administration. Drugs@FDA -Praluent (alirocumab). Accessed December 10, 2021.
US Food & Drug Administration. Drugs@FDA -Repatha (Evolocumab). Accessed December 10, 2021.

PCSK9 inhibitors MOA



MOA: Human mAb to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C

a) PCSK9 is synthesized in the liver. PCSK9 circulates in the plasma. The complex of the PCSK9 molecule and the LDL receptor is internalized and undergoes degradation in endosomal and lysosomal compartments, with few receptors recycled to the cell surface. This leads to fewer LDL receptors on the surface of cells.

b) Human monoclonal antibodies against PCSK9 can bind to the protein adjacent to the region that is required for interaction with LDL receptors. PCSK9 is, therefore, prevented from binding to LDL receptors. After endocytosis, the LDL receptor is recycled back to the surface of the cell, with few receptors degraded in the lysosome.

Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9

Dadu, R. T. & Ballantyne, C. M. Lipid lowering with PCSK9 inhibitors. *Nat. Rev. Cardiol.* **11**, 563–575 (2014).

PCSK9 inhibitors

FDA-approved indication(s): Alirocumab and Evolocumab:

Decrease LDL-C in adults with primary hyperlipidemia (including HeFH) as adjunct to diet, either alone or in combination with other lipid-lowering therapies

Alirocumab:

1. Decrease risk of MI, stroke, and UA requiring hospitalization in adults with ASCVD
2. Decrease LDL-C in adults with HoFH as adjunct to other LDL-C–lowering therapies

Evolocumab:

1. Decrease risk of MI, stroke, and coronary revascularization in adults with ASCVD
2. Decrease LDL-C in pediatric patients (aged ≥10 years) with HeFH as adjunct
3. Decrease LDL-C in adults and pediatric patients (aged ≥10 years) with HoFH as adjunct

US Food & Drug Administration. Drugs@FDA -Praluent (alirocumab). Accessed December 10, 2021.
US Food & Drug Administration. Drugs@FDA -Repatha (Evolocumab). Accessed December 10, 2021.

PCSK9 inhibitors

Dose and route of administration: SC in the thigh, abdomen, or upper arm

Alirocumab:

- In adults with ASCVD or primary hyperlipidemia: initiate **75 mg SC every 2 weeks**. If more LDL-C reduction needed, may increase dose to **150 mg every 2 weeks**.
- Alternative starting dose: **300 mg SC every 4 weeks**. [administer 2 (150-mg) injections consecutively at 2 different injection sites.]

Evolocumab:

- In adults with ASCVD, adults with primary hypercholesterolemia, including with established clinical ASCVD or HeFH, or in pediatric patients (aged ≥10 years) with HeFH, **140 mg SC every 2 weeks or 420 mg SC once monthly**

US Food & Drug Administration. Drugs@FDA -Praluent (alirocumab). Accessed December 10, 2021.
US Food & Drug Administration. Drugs@FDA -Repatha (Evolocumab). Accessed December 10, 2021.

PCSK9 inhibitors

Mean % LDL-C reduction:

- Alirocumab: when **added to maximally tolerated statin** therapy
  - 75 mg every 2 weeks decreased LDL-C by additional 45%
  - 150 mg SC every 2 weeks decrease LDL-C by additional 58%

- Evolocumab:
  - 140 mg every 2 weeks decrease LDL-C by an additional 58%
  - 420 mg SC every 4 weeks, decrease LDL-C by an additional 64%

Contraindication: History of hypersensitivity

Warnings/precautions: If a serious hypersensitivity reaction occurs, DC therapy; treat according to standard of care; monitor until signs and symptoms resolve

US Food & Drug Administration. Drugs@FDA -Praluent (alirocumab). Accessed December 10, 2021.
US Food & Drug Administration. Drugs@FDA -Repatha (Evolocumab). Accessed December 10, 2021.

PCSK9 inhibitors

Adverse effects:

- nasopharyngitis, upper respiratory tract infection, injection site reactions, influenza, noncardiac chest pain, myalgia, back pain

Use during pregnancy/lactation: No safety data in humans; avoid use.

Drug-drug interactions: No clinically significant drug-drug interactions identified for alirocumab or evolocumab

Other prescribing considerations: Robust LDL-C reduction, cost, SC administration at home, may require prior authorization.

- Evolocumab: Advise latex-sensitive patients that the needle covers on the products contain latex

US Food & Drug Administration. Drugs@FDA -Praluent (alirocumab). Accessed December 10, 2021.
US Food & Drug Administration. Drugs@FDA -Repatha (Evolocumab). Accessed December 10, 2021.

PCSK9 inhibitors

CV outcomes trials:

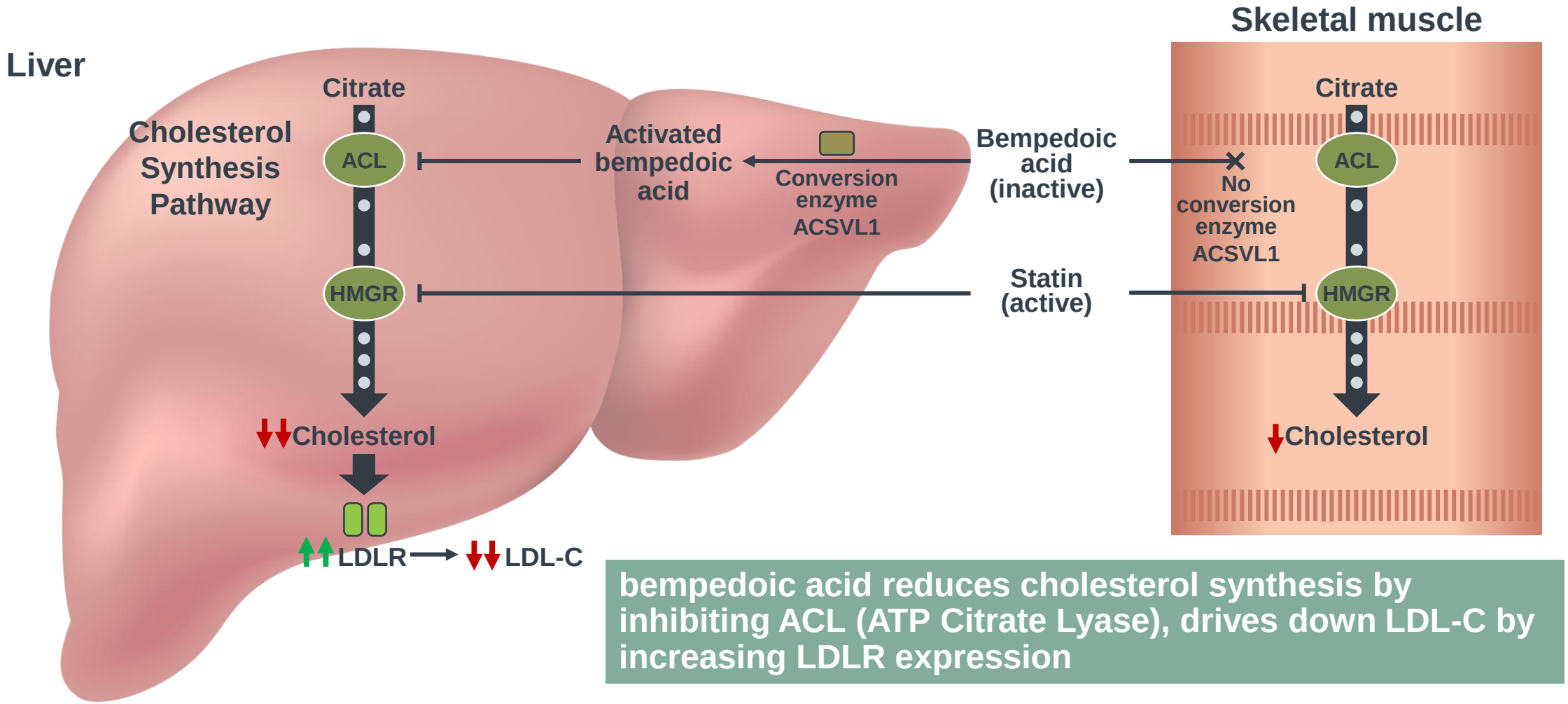
- Alirocumab: ODYSSEY Outcomes in 18,600 post-ACS (4-52 weeks) patients on evidence-based statin therapy; Demonstrated that addition of alirocumab reduced the primary endpoint of CHD death, MI, ischemic stroke, or hospitalization for UA.

- Evolocumab: FOURIER in 27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization, or hospitalization for unstable angina.

Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097–2107.
Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376: 1713–1722.

ATP Citrate lyase inhibitor - Bempedoic acid

BEMPEDOIC ACID AND STATINS WORK IN THE SAME CHOLESTEROL SYNTHESIS PATHWAY[1,2]



bempedoic acid reduces cholesterol synthesis by inhibiting ACL (ATP Citrate Lyase), drives down LDL-C by increasing LDLR expression

ACL=ATP citrate lyase; ACSVL1=very long-chain acyl-CoA synthease-1; HMGR=3-hydroxy-3-methylglutarate-CoA reductase; LDLR=low-density lipoprotein receptor.

1. NEXLETOL Prescribing Information. Ann Arbor, MI: ESPERION Therapeutics, Inc.; February 2020.
2. Pinkosky SL, et al. *Nat Commun*. 2016;7:13457.

ATP Citrate lyase inhibitor - Bempedoic Acid

FDA-approved indication(s): decreases LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy.

Dose: 180 mg orally once daily, with or without food.

Mean % reduction in LDL-C (per PI): Combination therapy with statin therapy (placebo-corrected incremental reduction) **17%-18%.**

Its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver.

US Food & Drug Administration. Drugs@FDA -Nexletol (bempedoic acid). Accessed December 10, 2021.

Bempedoic Acid

Contraindication: none

Warnings/precautions:

1. May increase serum uric acid

- Advise patients to contact clinician if symptoms of hyperuricemia occur.
- Assess serum uric acid when clinically indicated.
- Monitor for signs and symptoms of hyperuricemia, initiate treatment with urate-lowering drugs, as appropriate.
- Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur

2. Discontinue immediately if the patient experiences rupture of a tendon.

- Consider discontinuing if the patient experiences joint pain, swelling, or inflammation.
- Advise to rest at the first sign of tendinitis or tendon rupture and to contact health care provider if tendinitis or tendon rupture symptoms occur.
- Consider alternative therapy if hx of tendon disorders or tendon rupture.

NEXLETOL Prescribing Information. Ann Arbor, MI: ESPERION Therapeutics, Inc.; February 2020.

Bempedoic Acid

Adverse effects: Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes.

Use during pregnancy/lactation: Discontinue if pregnant. There are no available data on use in pregnant women.

Drug–drug interactions: Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily.

NEXLETOL Prescribing Information. Ann Arbor, MI: ESPERION Therapeutics, Inc.; February 2020.

Bempedoic Acid

CV outcomes trials:

CLEAR Outcomes trial: 13,970 statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).

NEXLETOL Prescribing Information. Ann Arbor, MI: ESPERION Therapeutics, Inc.; February 2020.

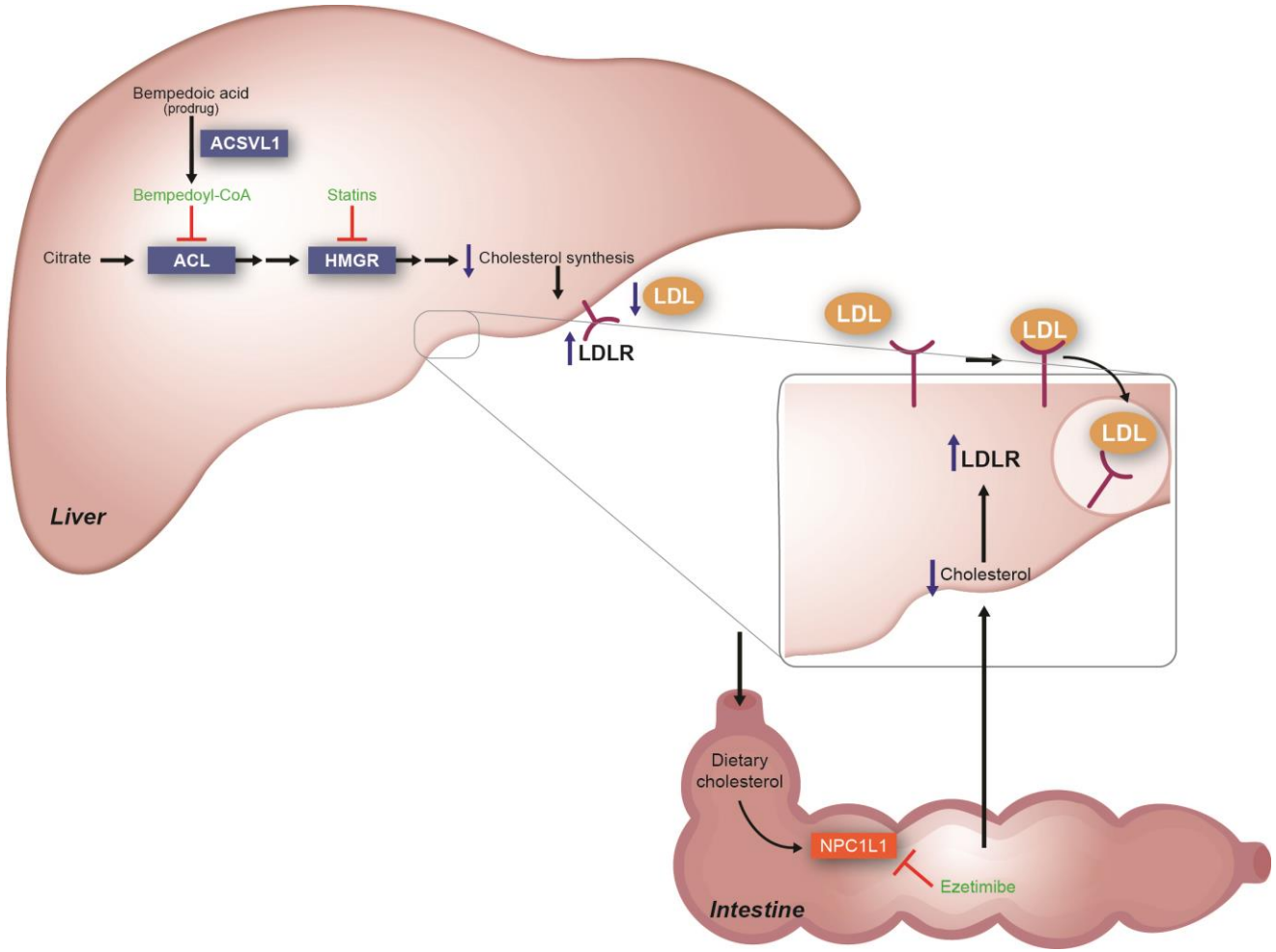
NEXLIZET: Complementary Non-Statin MOA

Bempedoic Acid[1]

- Inhibits ATP citrate lyase (ACL)
  - *Active primarily in liver cells*
- Acts in the same cholesterol biosynthesis pathway as statins
- Upregulates LDL receptors

Ezetimibe[2,3]

- Inhibits NPC1L1 (sterol transporter)
- Inhibits gastrointestinal cholesterol absorption, which leads to decreased hepatic cholesterol, resulting in increased LDLR and decreased plasma LDL-C
- Upregulates LDL receptors



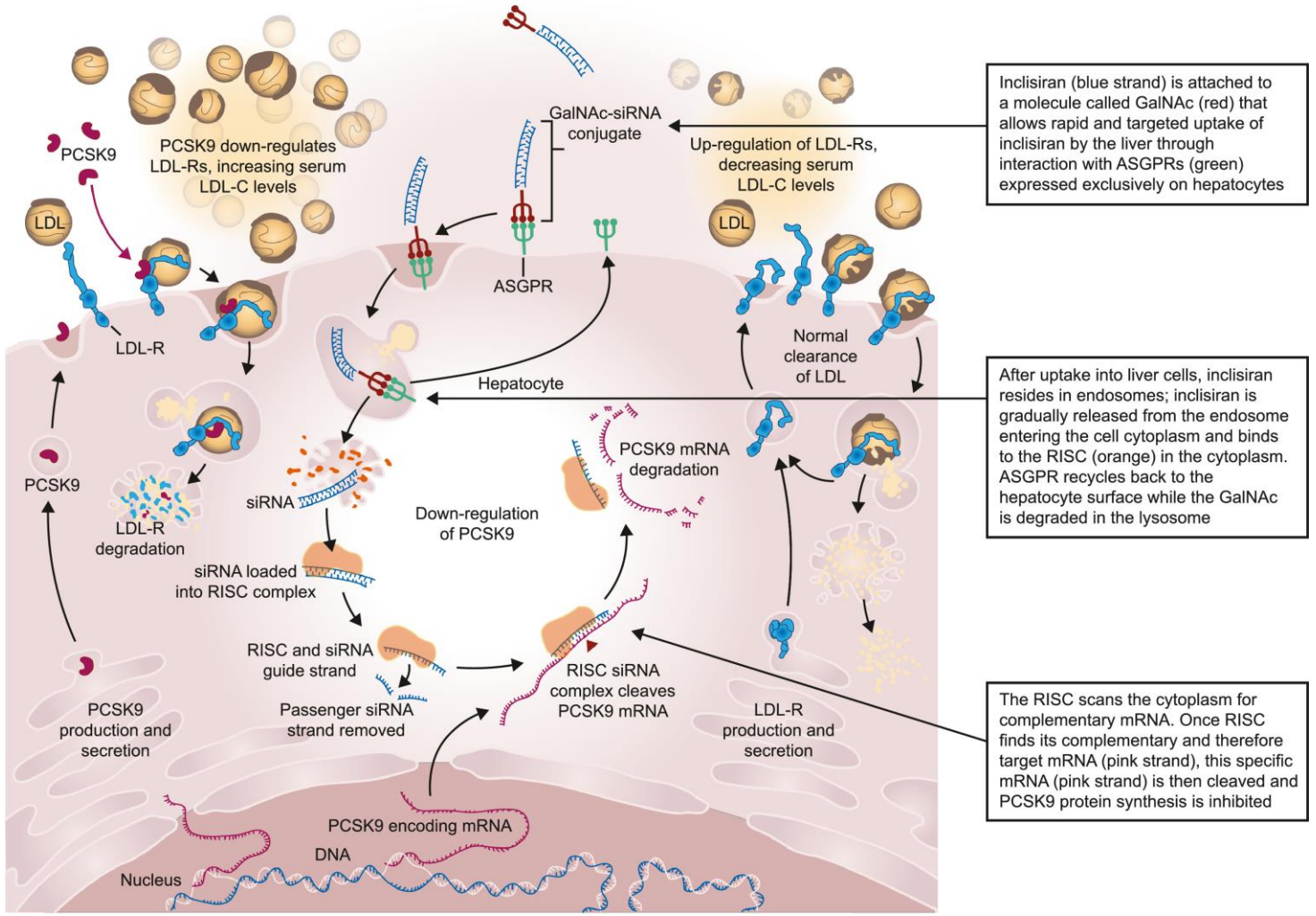
ACL = ATP citrate lyase; ACSVL1 = very long-chain acyl-CoA synthetase 1; HMGR = 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase; ATP = adenosine triphosphate; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDLR = LDL receptor; NPC1L1 = Niemann-Pick C1-Like 1.

1. Pinkosky SL, et al. *Nat Commun.* 2016;7:13457; 2. Garcia-Calvo M, et al. *Proc Natl Acad Sci.* 2005;102:8132–8137; 3. Ference BA, et al. *Eur Heart J.* 2017;38:2459–2472.

Small Interfering Ribonucleic Acid-Inclisiran

MOA: siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors - mimicks the body's natural pathway of RNA interference to specifically prevent PCSK9 synthesis

Abbreviations:
ASGPR: asialoglycoprotein receptor
DNA: deoxyribonucleic acid
GalNAc: N-acetylgalactosamine
LDL: low-density lipoprotein
LDL-C: LDL cholesterol
LDL-R: LDL receptor
mRNA: messenger RNA
PCSK9: proprotein convertase subtilisin/kexin type 9
RISC, RNA-induced silencing complex siRNA, small interfering RNA.



Khvorova A. *N Engl J Med*. 2017;376(1):4-7

Inclisiran

FDA-approved indication(s): decrease LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy.

Dose: Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician.

Mean % reduction in LDL-C: 48%-52%

Contraindications: None

Warnings/precautions: None

US Food & Drug Administration. Drugs@FDA -Leqvio (inclisiran). Accessed December 10, 2021.

Inclisiran

Adverse effects: Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea

Use during pregnancy/lactation: No safety data in humans; avoid use

Drug–drug interactions: None

Other prescribing considerations: robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization

US Food & Drug Administration. Drugs@FDA -Leqvio (inclisiran). Accessed December 10, 2021.

Inclisiran

CV outcomes trials: CV outcomes trials not yet completed

1. ORION-4 currently in progress with estimated completion in 2026

2. VICTORION-2P currently in progress with estimated completion in 2027

US Food & Drug Administration. Drugs@FDA -Leqvio (inclisiran). Accessed December 10, 2021.

What do the Guidelines Say?

As LDL-C guideline recommendations evolve, lower targeted LDL-C levels and use of adjunct nonstatin therapy have been included

	2001 NCEP ATP III[1]	2004 NCEP ATP III Update[2]	2013 ACC/AHA Guidelines[3]	2017 AACE/ACE Guidelines[4]	2018 ACC/AHA Guidelines[5]	2019 ESC/EAS Guidelines[6]	2020 AACE/ACE Consensus Statement[7]
LDL-C goal or threshold	<100 mg/dL for patients with CHD and CHD risk equivalents	<100 mg/dL for high risk Optional goal of <70 mg/dL for very high risk	No LDL-C goals • 4 statin benefit groups defined • Statin therapy recommendations for each group	<70 mg/dL for very high risk <55 mg/dL for extreme risk	Intensify therapy if ≥70 mg/dL for high risk	<70 mg/dL for high risk <55 mg/dL for very high risk <40 mg/dL if second CVD event within 2 years	<70 mg/dL for very high risk <55 mg/dL for extreme risk
Nonstatin add-on therapy recommended	✓	✓	✓	✓	✓	✓	✓

NCEP-ATP=National Cholesterol Education Program–Adult Treatment Panel; ACC/AHA=American College of Cardiology/ American Heart Association; AACE/ACE=American Association of Clinical Endocrinologists/American College of Endocrinology; ESC/EAS=European Society of Cardiology/European Atherosclerosis Society.

1. NCEP Expert Panel. *Circulation.* 2002;106(25):3143-3421; 2. Grundy SM, et al. *J Am Coll Cardiol.* 2004;44(3):720-732; 3. Stone NJ, et al. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934; 4. Jellinger PS, et al. *Endocr Pract.* 2017;23(Suppl 2):1-87; 5. Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24):e285-e350; 6. Mach F, et al. *Eur Heart J.* 2020;41(1):111-188; 7. Handelsman Y, Jellinger PS, Guerin CK, et al. *Endocr Pract.* 2020;26(10):1196-1224.

2018
AHA/ACC/AACVPR/
AAPA/ABC/ACPM/
ADA/AGS/APhA/
ASPC/NLA/PCNA

Guideline on the Management of Blood Cholesterol

The full-text guidelines are available on the following web sites:
www.acc.org or professional.heart.org

2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

SECONDARY PREVENTION

Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85, or previous revascularization or amputation)

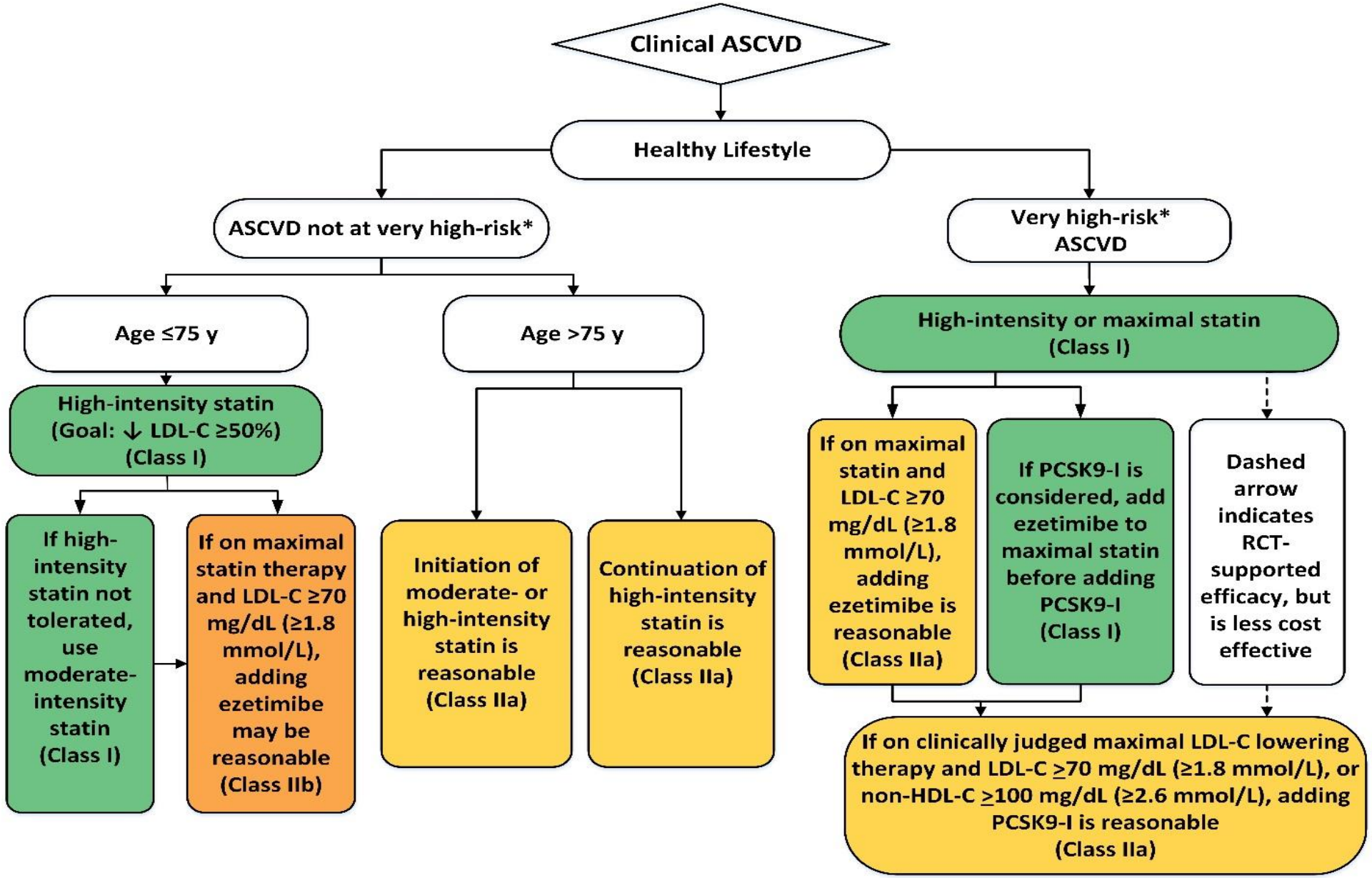
Grundy SM, Stone NJ, et al 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Journal of the American college of Cardiology (2018),

High-Risk of Future ASCVD Events

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Grundy SM, Stone NJ, 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),

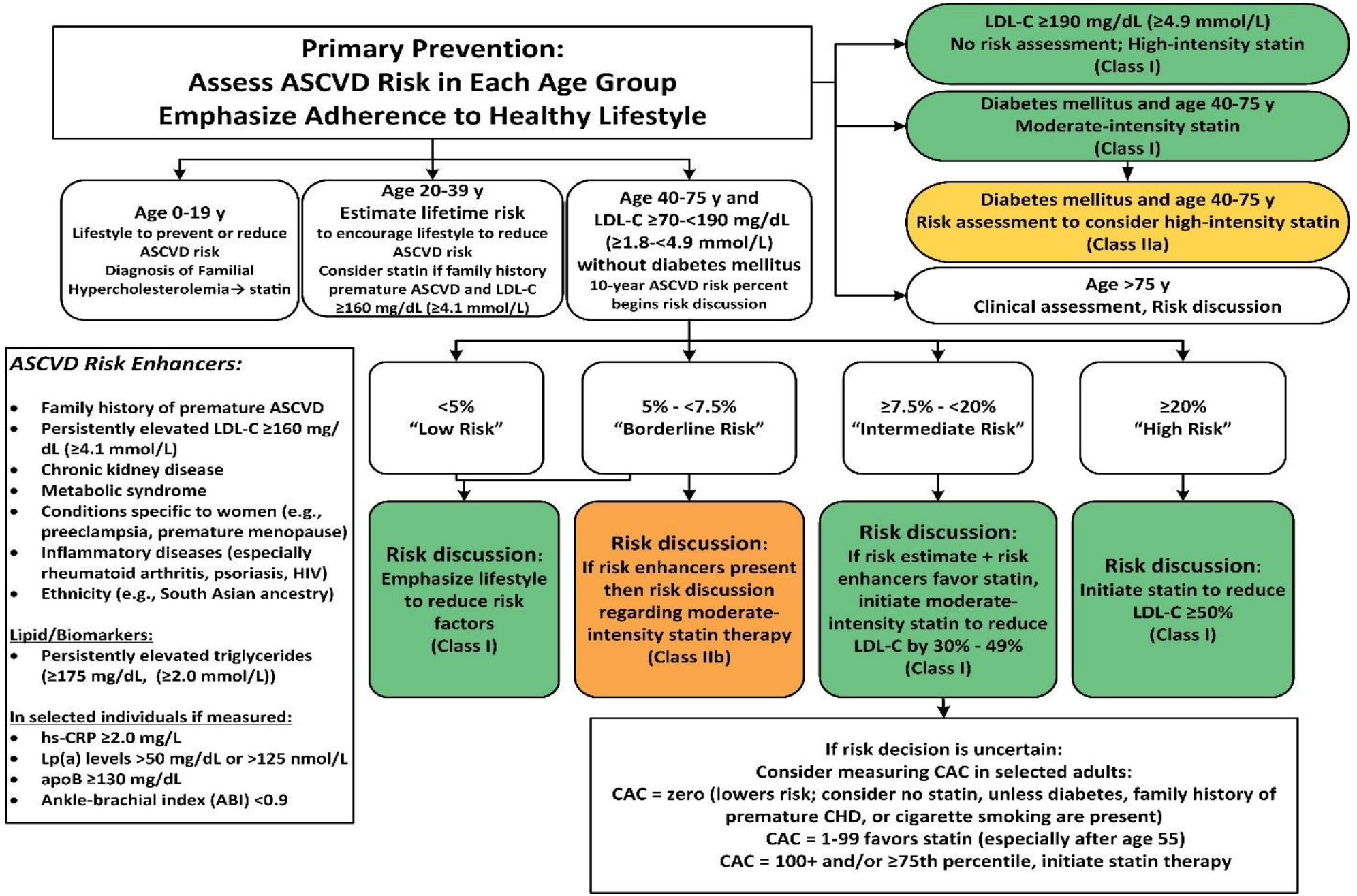
Secondary Prevention



Grundy SM, Stone NJ, 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),

2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

PRIMARY PREVENTION



Grundy SM, Stone NJ, 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),

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk

Since the publication of the 2018 AHA/ACC/Multisociety cholesterol guideline, 2 additional nonstatin therapies received FDA approval for the management of hypercholesterolemia

New FDA approvals for hypercholesterolemia

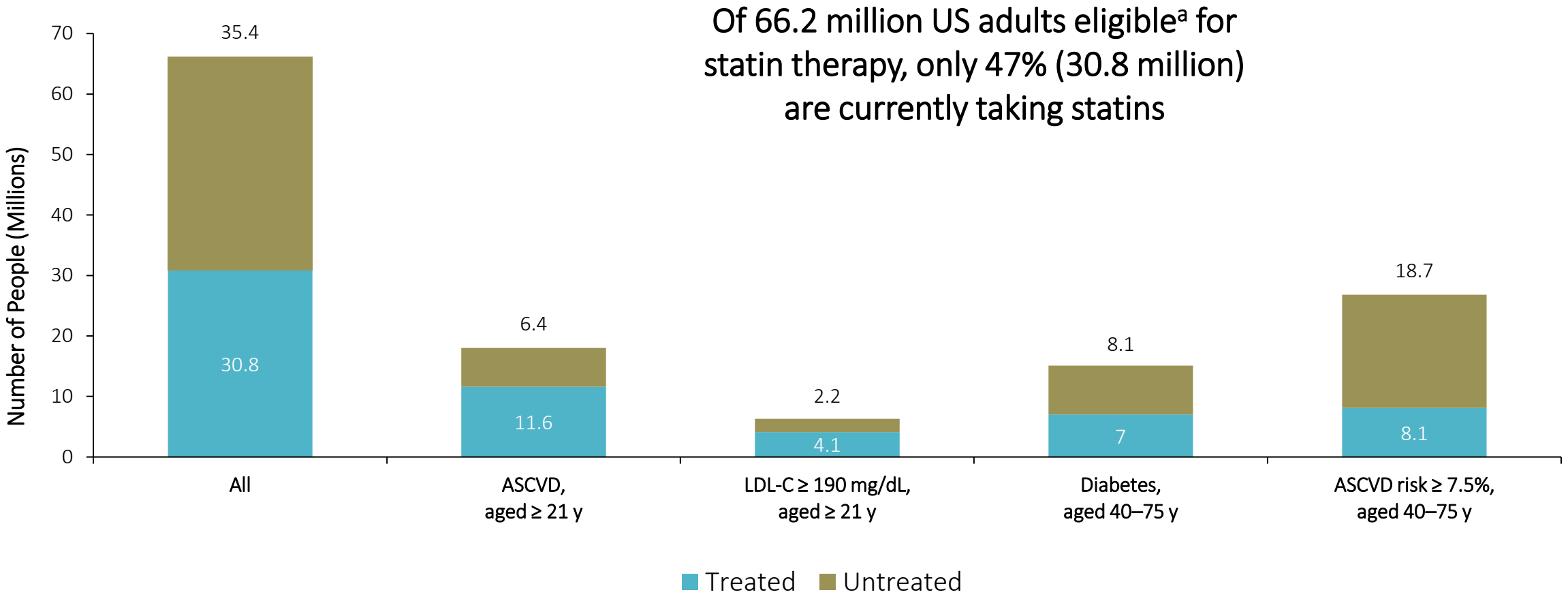
- Bempedoic Acid
- Inclisiran

Awaiting ongoing CV outcomes trials and subsequent revision of evidence based-guidelines

Recommend to use newer nonstatin therapies if the response to statin therapy, ezetimibe, and/or PCSK9-i is deemed inadequate

Lloyd-Jones DM et al, J Am Joll Cardiol 2022

Number of US Adults Eligible for and Currently Taking Statins

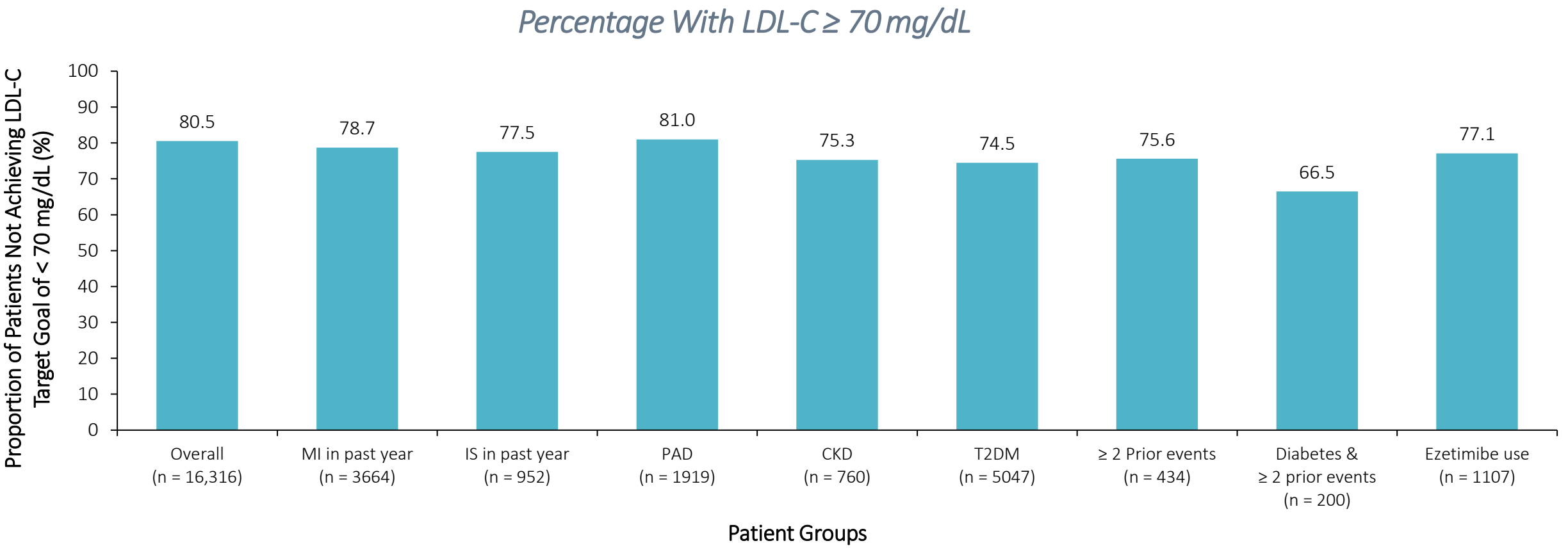


[a]Eligibility groups outlined in the 2018 ACC/AHA Guideline on the Treatment of Blood Cholesterol in Adults.

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

American Heart Association. Centers for Health Metrics and Evaluation (CHME). Data visualization. https://healthmetrics.heart.org/data-visualization /. Accessed January 28, 2021.

Most Patients with High CV Risk Receiving Moderate- or High-Intensity Statins Do Not Achieve a Treatment Goal of LDL-C < 70 mg/dL



CKD = chronic kidney disease; CV = cardiovascular; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral arterial disease; T2DM = type 2 diabetes mellitus.

Fox KM, et al. *Clin Res Cardiol.* 2018;107:380–388. Image adapted from *Clin Res Cardiol*, Copyright © 2018 with permission per terms of the Creative Commons Attribution 4.0 International License, CC-BY-4.0 from Fox et al.

Take away message

Important to lower LDL-C

The lower the LDL-C the greater regression of atherosclerosis

The greater the risk reduction

Time is also important

The longer the sustained reduction the greater the benefits

Let’s check our knowledge

Thank you!