Dyslipidemia

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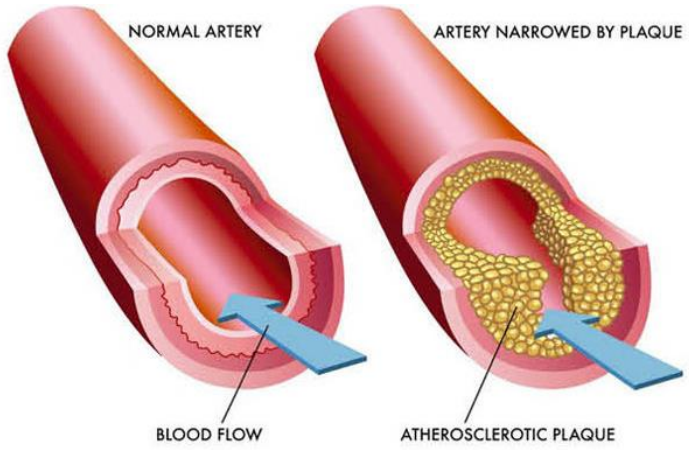
Introduction

Lipid abnormalities increase the risk of coronary, cerebrovascular, and peripheral vascular arterial disease collectively known as *atherosclerotic cardiovascular disease* (**ASCVD**).

Premature coronary atherosclerosis is the most common and significant consequence of dyslipidemia.



Epidemiology

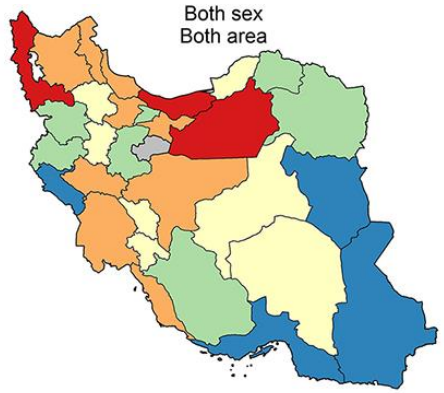
Total cholesterol and LDL-C **increase** *throughout life* in both men and women. According to AHA estimates, approximately 45% of American adults aged 20 or older have total cholesterol levels exceeding 200 mg/dL.

In 2011, CHD caused *one* in every *seven* **deaths** in the United States. More than half of individuals at borderline-high risk remain **unaware** that they have dyslipidemia, and fewer than half of the highest risk persons (those with symptomatic CHD) are receiving lipid-lowering *treatment*.

Epidemiology

Prevalence of dyslipidemia in **Iran**:

- Hypercholesterolemia (≥200 mg/dl): **41.6%**
- Hypertriglyceridemia (≥150 mg/dl): **46.0%**
- High levels of low density lipoprotein cholesterol ([LDL-C] [≥ 130 mg/dl]): **35.5%**
- Low levels of high density lipoprotein cholesterol ([HDL-C] <40 mg/dl in males, <50 mg/dl in females): **43.9%**



Epidemiology

When patients who are at risk but who have not yet experienced initial cardiovascular (eg, myocardial infarction [MI]) or cerebrovascular (eg, ischemic stroke) events are treated, it is termed **primary prevention**. Treatment for those with manifest ASCVD is termed **secondary prevention**.

Etiology

Genetic abnormalities and *environmental factors* are involved in the development of dyslipidemia. The underlying causes of dyslipidemias can be categorized into two types: **primary** or **secondary**.

Genetic factors that increase lipid levels can be inherited and cause *primary or familial* dyslipidemia. By contrast, **lifestyles**, **diseases**, **medications**, and **diet** can all lead to abnormal lipid levels and cause *secondary or "acquired"* dyslipidemia.

Desired Outcomes

Not atherogenic

TABLE 14.6 Classification of Total, LDL, and HDL Cholesterol (mg/dL) and Recommended Levels for Adults

Total Cholesterol	
< 200	Desirable
200–239	Borderline high
≥ 240	High
LDL Cholesterol	
< 100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high
HDL Cholesterol	
< 40	Low
≥ 60	High
Triglycerides	
< 150	Normal
150–199	Borderline high
200–499	High
≥ 500	Very high

SOURCE: National Heart, Lung, and Blood Institute. (2005). *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (NIH Publication No. 05-3290). Online: http://www.nhlbi.nih.gov/health/public/heart/chol/wyntk.htm.

General Approach

A **comprehensive approach** to treating dyslipidemia and all modifiable major risk ASCVD factors is required to significantly reduce the risk of first and recurrent ASCVD events.

Therapeutic lifestyle change

- Reduction in the percent of calories from *saturated* and *trans fats*,
- Increased intake of *soluble fiber*,
- *Weight reduction* if overweight or obese,
- Increased *physical activity* (aerobic activity 3-4 sessions/week each on average 40-minutes), and
- Avoiding or quitting *tobacco use*.

General Approach

Additionally, patients with a diagnosis of **hypertension** should achieve *optimal blood pressure control* based on the ACC/AHA Guidelines for control of hypertension.

Persons with **diabetes mellitus**, especially those with established ASCVD, should receive glucose-lowering therapies that have been shown to *reduce ASCVD risk*.

- Metformin
- SGLT-2 inhibitors: empagliflozin, canagliflozin
- GLP-1 RAs: Liraglutide
- TZDs: Pioglitazone

General Approach

Clinical ASCVD

- Acute Coronary Syndrome
- Those with history of
  - MI,
  - Stable or unstable angina,
  - Coronary and other arterial revascularization,
  - Stroke,
  - Transient ischemic attack (TIA), or
  - Peripheral artery disease (PAD) including aortic aneurysm

"***All of atherosclerotic origin***"

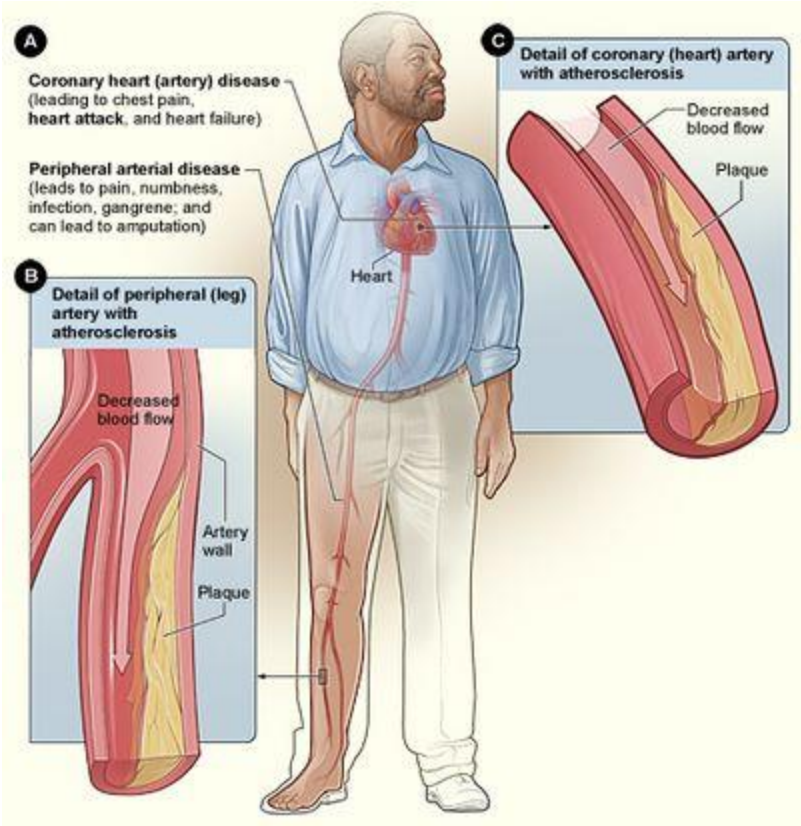
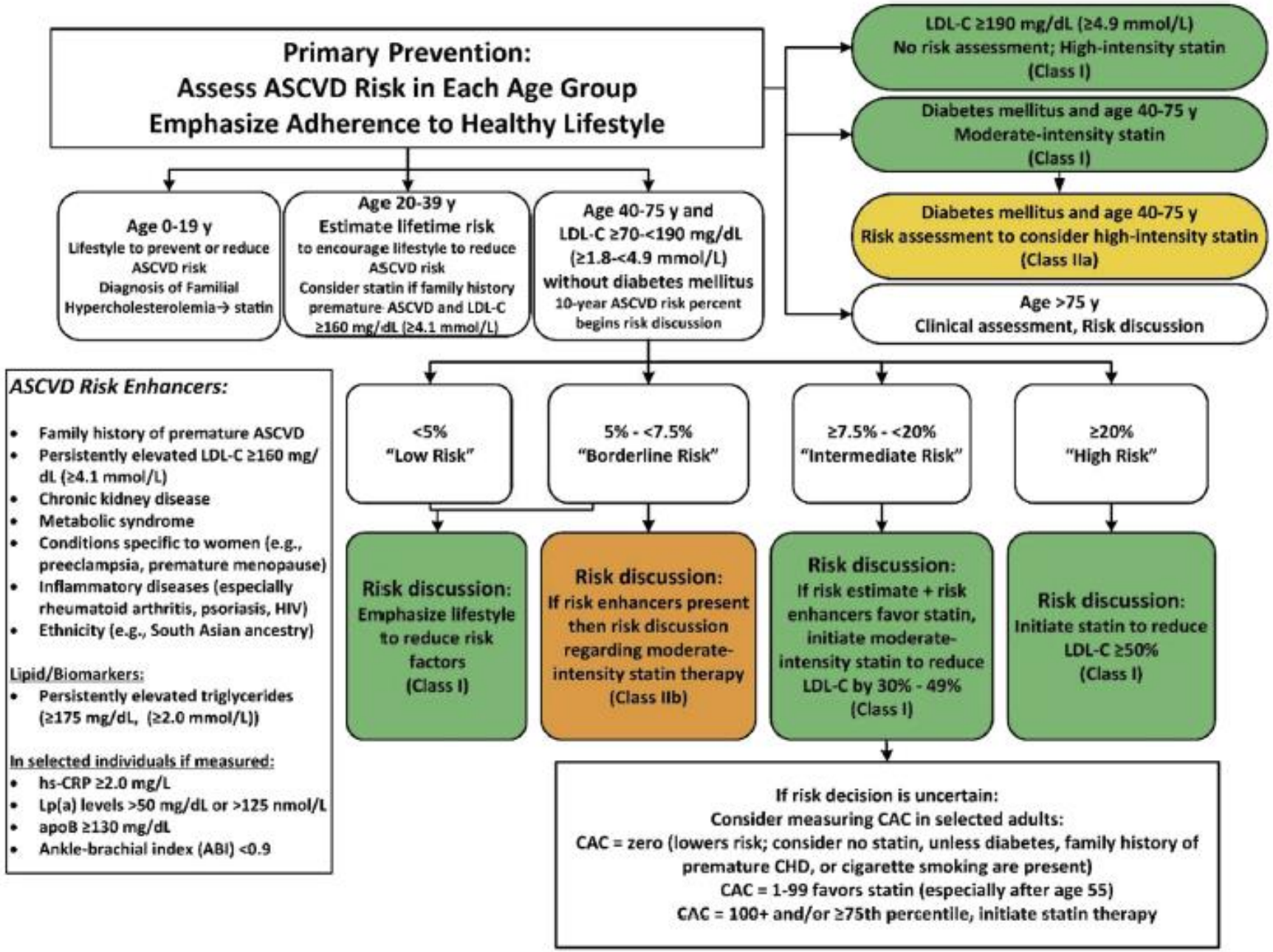


FIGURE 2 Primary Prevention



7.2% Borderline — **Current 10-Year ASCVD Risk****

Lifetime ASCVD Risk: **50%** Optimal ASCVD Risk: **2.1%**

Current Age * 50
Age must be between 20-79

Sex * ✔ Male | Female

Race * White | African American | ✔ Other
⚠ See the Estimate Warning below

Note: These estimates may *underestimate* the 10-year and lifetime risk for persons from some race/ethnic groups, especially American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may *overestimate* the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans). Because the primary use of these risk estimates is to facilitate the very important discussion regarding risk reduction through lifestyle change, the imprecision introduced is small enough to justify proceeding with lifestyle change counseling informed by these results.

Systolic Blood Pressure (mm Hg) * 150
Value must be between 90-200

Diastolic Blood Pressure (mm Hg) * 85
Value must be between 60-130

Total Cholesterol (mg/dL) * 190
Value must be between 130 - 320

HDL Cholesterol (mg/dL) * 35
Value must be between 20 - 100

LDL Cholesterol (mg/dL) 110
Value must be between 30-300

History of Diabetes? * Yes | ✔ No

Smoker? * Current | Former | ✔ Never

On Hypertension Treatment? * ✔ Yes | No

On a Statin? Yes | ✔ No

On Aspirin Therapy? ✔ Yes | No

General Approach

TABLE 3 High-, Moderate-, and Low-Intensity Statin Therapy*

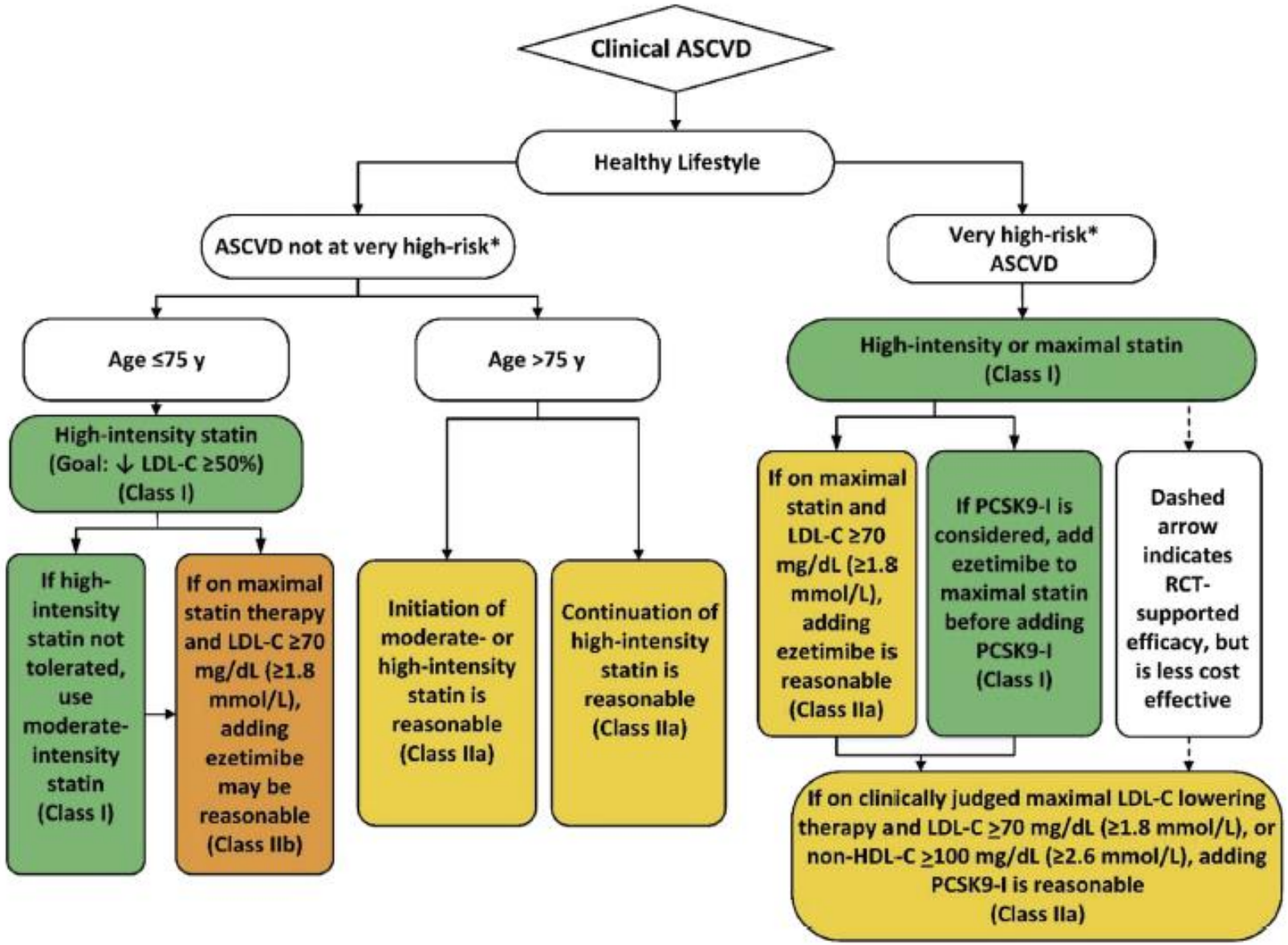
	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin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

TABLE 4 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 peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation [S4.1-40])
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) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

FIGURE 1 Secondary Prevention in Patients With Clinical ASCVD



General Approach

Recommendation for Monitoring
Referenced studies that support the recommendation are summarized in Online Data Supplement 17.

COR	LOE	RECOMMENDATION
I	A	1. Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety (S4.4.3-1–S4.4.3-3).

General Approach

Recommendations for Hypertriglyceridemia
Referenced studies that support recommendations are summarized in Online Data Supplements 31 and 32.

RECOMMENDATIONS
1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [2.0 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides (S4.5.2-1).
2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).
3. In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy (S4.5.2-3–S4.5.2-5, S4.5.2-7, S4.5.2-8).
4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1,000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (S4.5.2-7, S4.5.2-9).

Statins

These agents are competitive inhibitors of HMG-CoA reductase, the rate-limiting step in **cholesterol biosynthesis**.

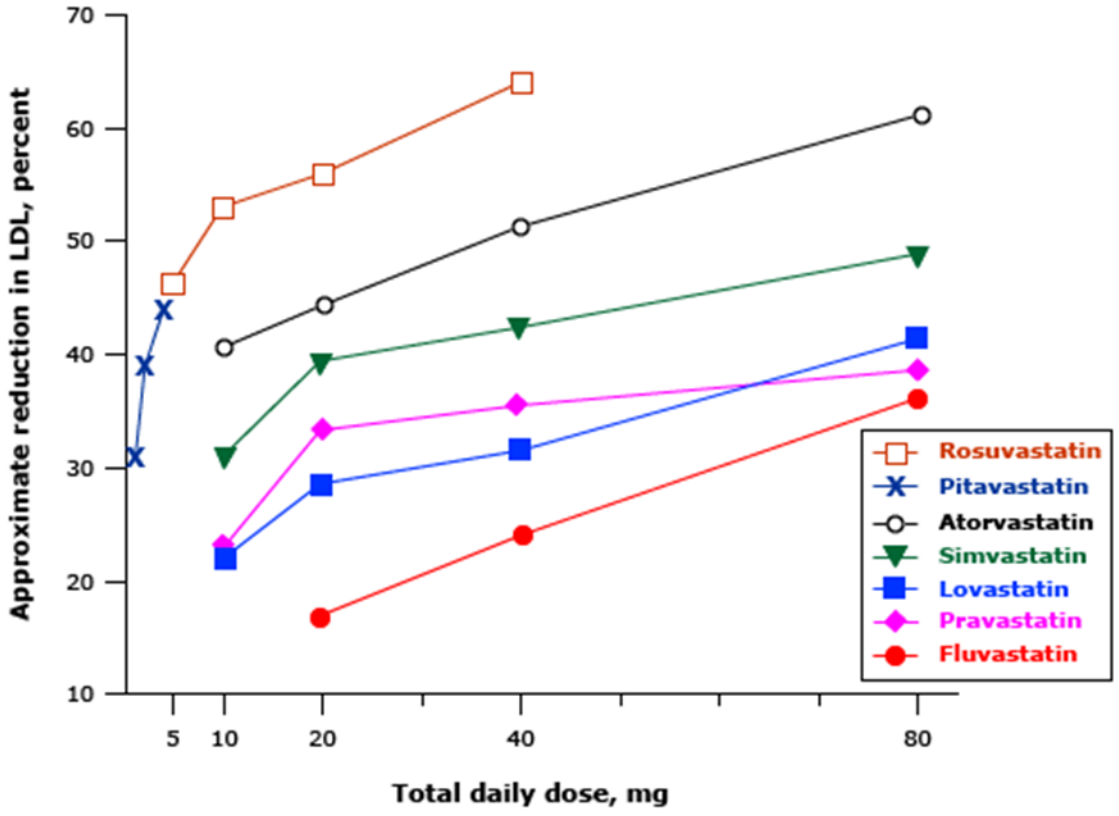
Most of the statins have modest high-density lipoprotein (**HDL**) cholesterol raising properties (about 5 percent), although rosuvastatin has a *larger effect*. **Triglyceride** concentrations fall by an average of 20 to 40 percent depending upon the statin and dose used.

Statins

Effect on LDL cholesterol

At maximal prescribed doses, LDL cholesterol reduction is greater with **rosuvastatin** and **atorvastatin** than with the other available statins

Comparison of the efficacy of statin drugs



Comparison of the percent reduction in serum LDL cholesterol with various statin drugs.

LDL: low-density lipoprotein.

UpToDate®

Statins

Side Effects

- Only a *slight increased risk* of side effects compared with **placebo** in randomized trials.
- More **lipophilic** statins (simvastatin, lovastatin, atorvastatin, and fluvastatin) may be associated with *more adverse events* than the more **hydrophilic** statins (pravastatin and rosuvastatin).

Statins

Statin muscle-related adverse events

Myalgia: A symptom of muscle-discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level.

Myonecrosis: Elevation in muscle enzymes

Mild – Three- to 10-fold elevation in CK

Moderate – 10- to 50-fold elevation in CK

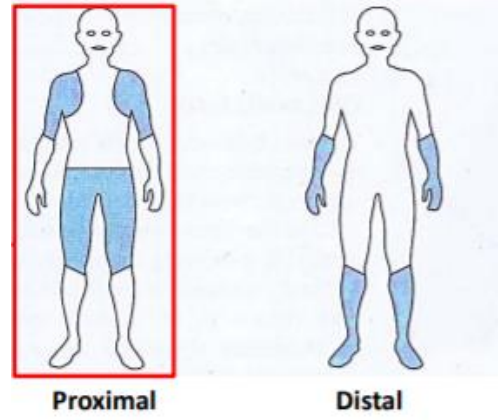
Severe – 50-fold or greater elevation in CK

Clinical rhabdomyolysis: myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 0.5 mg/dL).

Statins

Symptoms

- Typically present as *proximal*, **symmetric** muscle weakness and/or soreness.
- May be muscle *tenderness*.
- May be functional impairments such as *difficulty raising the arms* above the head, *arising from a seated position*, or *climbing stairs*.
- These symptoms are often *described as* **fatigue** or **tiredness** by the patient.
- Other reported symptoms include cramping (including nocturnal cramping), stiffness, and tendon pain.



Statins

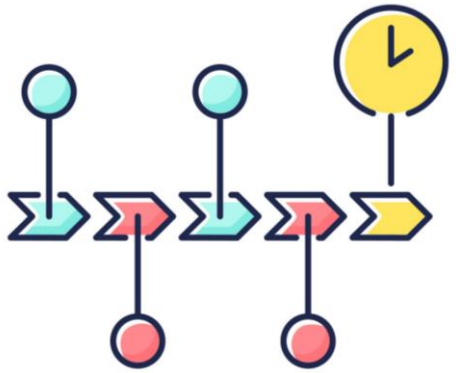
Risk Factors

- **Statin characteristics**: more common with lovastatin, simvastatin, and atorvastatin
- **Preexisting neuromuscular disorders**: ALS, myasthenia gravis
- **Patient characteristics**: genetic factors, advanced age (greater than 80 years), frailty, female sex, small body frame, acute or decompensated liver disease, and severe renal disease
- **Hypovitaminosis D**
- **Hypothyroidism**

Statins

Time course of muscle events

- Usually within **weeks to months** after the initiation of statin therapy.
- May occur at **any time** during treatment.
- Myalgias and weakness usually resolve and serum CK concentrations return to normal over **days to weeks** *after discontinuation* of the drug.



Statins

Monitoring

- *Routine monitoring* of serum creatine kinase (CK) levels is **not recommended.**
- It is useful to obtain a **baseline serum CK** before initiation of statin therapy.

Statins

Management

- Discontinue statin therapy.
- After resolution of symptoms, initiate a **different** statin at a **lower dose**.
- Hydrophilic statins (such as atorvastatin and rosuvastatin) may be better tolerated than lipophilic statins (such as simvastatin).
- Treat *potential causes* before statin rechallenge.
- *Every other day* dosing using statins with *long half-lives* (atorvastatin, rosuvastatin) may also be considered.
- Nonstatin therapies may be considered in patients who fail multiple statins.

Statins

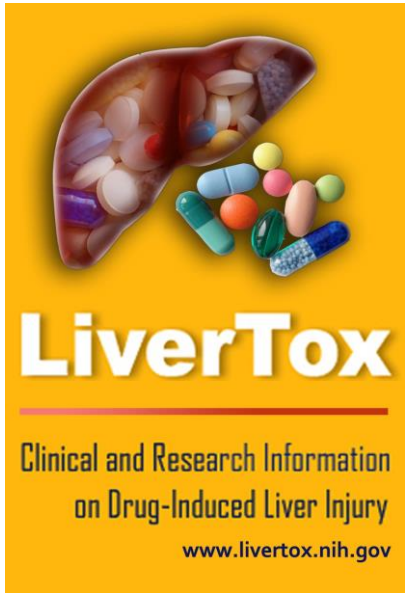
Therapies of uncertain benefit

- CoQ10 **depletion** that reduces skeletal muscle ubiquinone concentrations may play a role in statin myopathy.
- **Coenzyme Q10** is **not recommended** to improve or prevent SAMS.

Statins

Hepatic dysfunction

- 0.5 to 3.0 percent occurrence of persistent elevations in aminotransferases.
- Primarily occurred during the **first three months** of therapy.
- Is *dose-dependent*.
- FDA in 2012: **only** recommend liver function testing *prior to initiation* of statin therapy and to only repeat such testing for clinical indications.
- **Changing medications** or **lowering the statin dose** in patients who are found to have an *ALT level more than three times* the upper limit of normal that is confirmed on a second occasion.



Statins

Renal dysfunction

- Statins are able to cause proteinuria.
- Particularly in patients receiving rosuvastatin or simvastatin
- Proteinuria with statins is a **benign** finding.

Statins

Behavioral and cognitive

- **Case reports** of patients developing *severe irritability* and *aggression* (causality not confirmed)
- Cognitive dysfunction and *memory loss*

Diabetes mellitus

- **Small** increased risk of developing *diabetes*
- The risk is slightly greater with **intensive statin** therapy than moderate statin therapy.
- Beneficial effects of statins on *cardiovascular events* and mortality **outweigh** any increased risk.

Statins

Risks in pregnancy and breastfeeding

- FDA has recommended that statins be **discontinued** in most *pregnant patients*.
- Clinicians may consider their use in patients at *very high risk* of cardiovascular events.
- *Breastfeeding* is still **not recommended**.
- If a statin is to be discontinued during *pregnancy*, it is recommended, based on the drug half-life, withdrawal a minimum of **6 weeks** and preferably **12 weeks** before planned conception.

Statins

Administration

- Timing of administration
- Alternative dosing regimens
  - on average nearly **twice** that of the daily dose
  - with rosuvastatin and atorvastatin
  - only based on the effect on *lipid profile*
  - no data on clinical outcomes
- Interchange
  - equipotent doses with regard to LDL cholesterol reduction
- Drug interactions

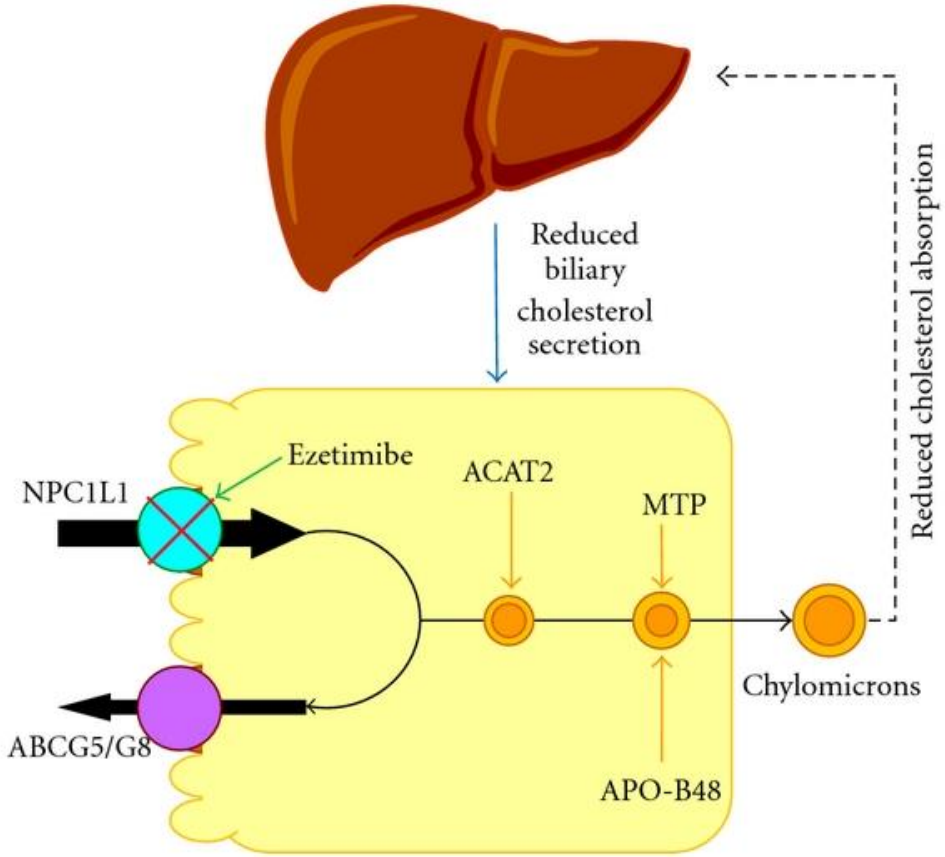
Statins

Table S5. Common Medications That May Potentially Interact With Statins

Can Be Used With a Statin Using a Risk-Mitigation Strategy*		Do Not Use With Any Statin
• Amiodarone • Amlodipine • Atazanavir plus ritonavir • Boceprevir • Clarithromycin • Cobicistat-containing products • Colchicine • Cyclosporine • Danazol • Darunavir plus ritonavir • Diltiazem • Dronedarone • Erythromycin • Fenofibrate • Fenofibric acid • Fluconazole • Fosamprenavir (with or without ritonavir)	• Itraconazole • Ketoconazole • Lomitapide • Lopinavir plus ritonavir • Nefazodone • Nelfinavir • Niacin (≥1 g/d) • Posaconazole • Ranolazine • Rifampin • Saquinavir plus ritonavir • Telaprevir • Telithromycin • Tipranavir plus ritonavir • Verapamil • Voriconazole • Warfarin	Gemfibrozil

Cholesterol Absorption Inhibitors

- Ezetimibe is a preferred **adjunct** therapy when used in combination with *statins*.
- The primary lipid lowering effect: a modest reduction in LDL-C of 15% to 24%
- Higher reductions achievable when used in combination with statin therapy.
- Ezetimibe reduces LDL-C by inhibiting the *NPC1L1 protein*.

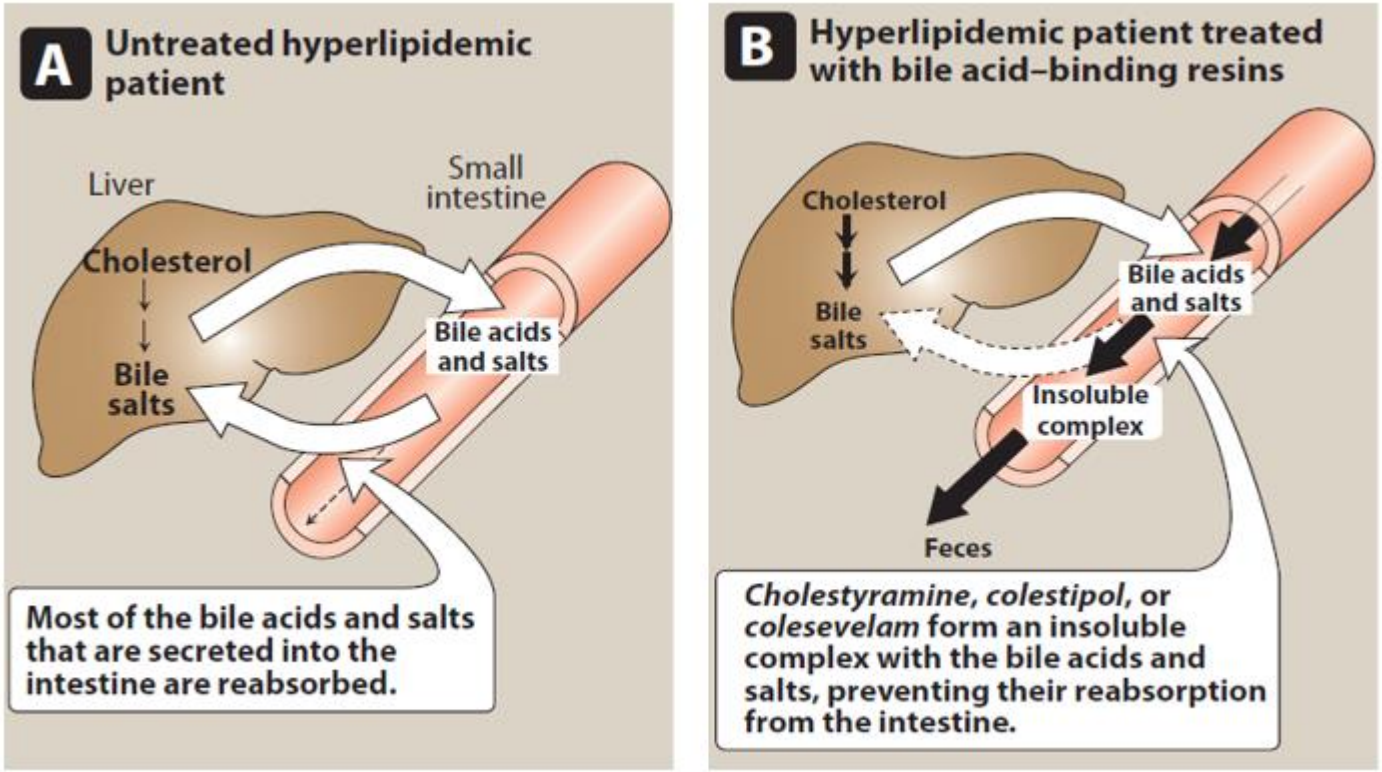


Cholesterol Absorption Inhibitors

- Adverse effects: mild gastrointestinal complaints, post-marketing reports of *myalgia* and *mild ALT elevations (in combination with statins)*.
- Previous concerns over a potential increased risk of **cancer** have been **nullified** given recent prospective clinical trial data.
- No effects on the CYP450 enzyme system.

Cholesterol Absorption Inhibitors

- The bile acid sequestrants (BAS), such as colesevelam, modestly reduce LDL-C (13%-20%).
- Generally used as **adjunct** therapy with *statins*.
- *First line* during **pregnancy** since they are not systemically absorbed and pose no risk to the fetus.
- Bind bile acids in the intestinal lumen, with a concurrent interruption of *enterohepatic circulation* of bile acids.



Cholesterol Absorption Inhibitors

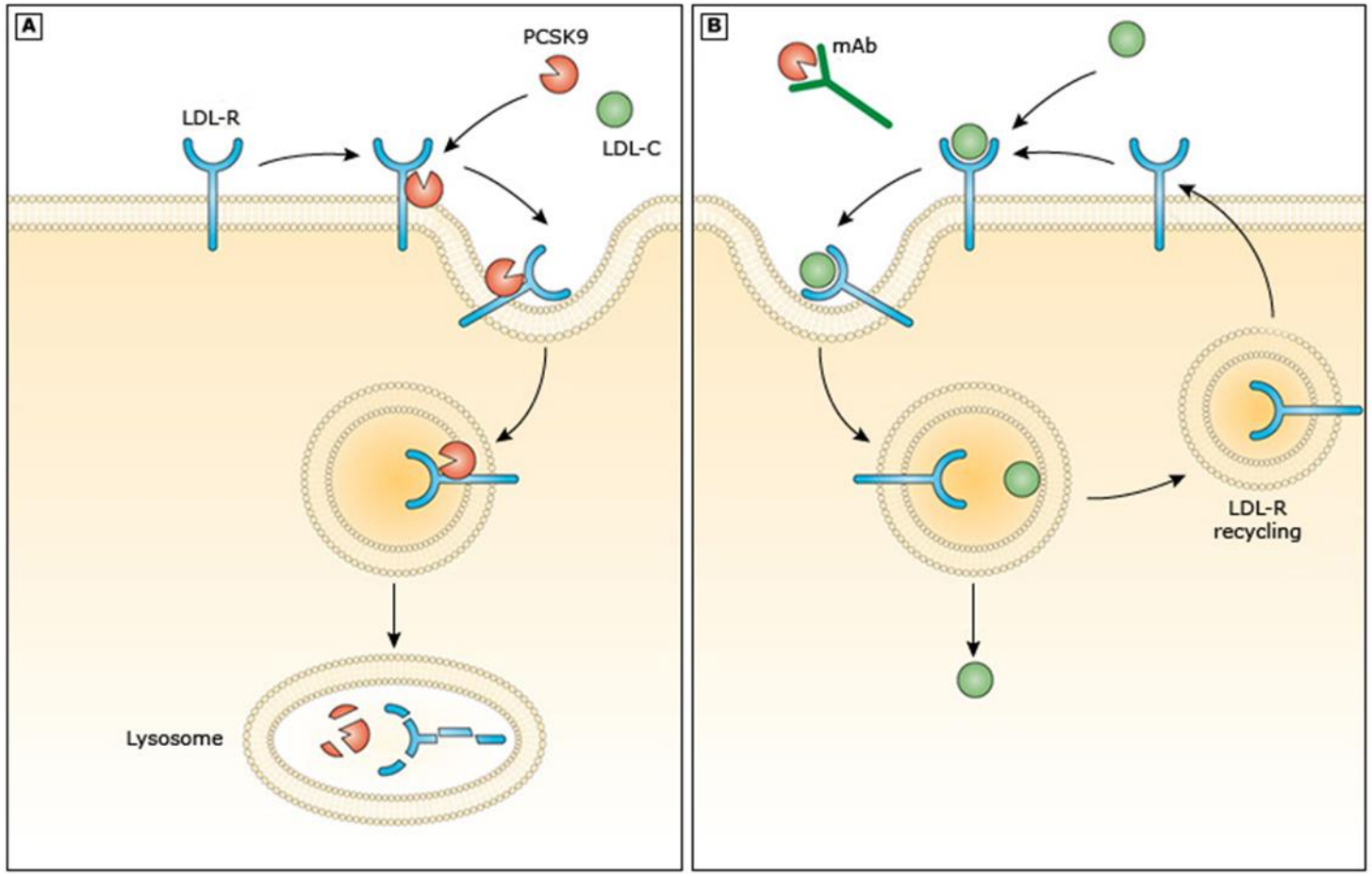
- Main barriers to BAS use: <u>poor tolerability profile</u>
  - **Gastrointestinal** complaints of constipation, bloating, epigastric fullness, nausea, and flatulence;
  - Impaired absorption of fat-soluble *vitamins* A, D, E, and K;
  - Gastrointestinal **obstruction**; and
  - Reduced bioavailability of *other drugs* such as warfarin, levothyroxine, and phenytoin.

- BAS should be **reserved** only for those patients unable to tolerate *ezetimibe* who need additional LDL-C lowering despite maximally tolerated *statin* therapy.

PCSK9 inhibitors

Alirocumab and evolocumab are fully humanized monoclonal antibodies that bind free plasma PCSK9, promoting degradation of this enzyme.

PCSK9 pathway and effect of PCSK9 antibody on LDL-R



LDL-R: low density lipoprotein cholesterol receptor.

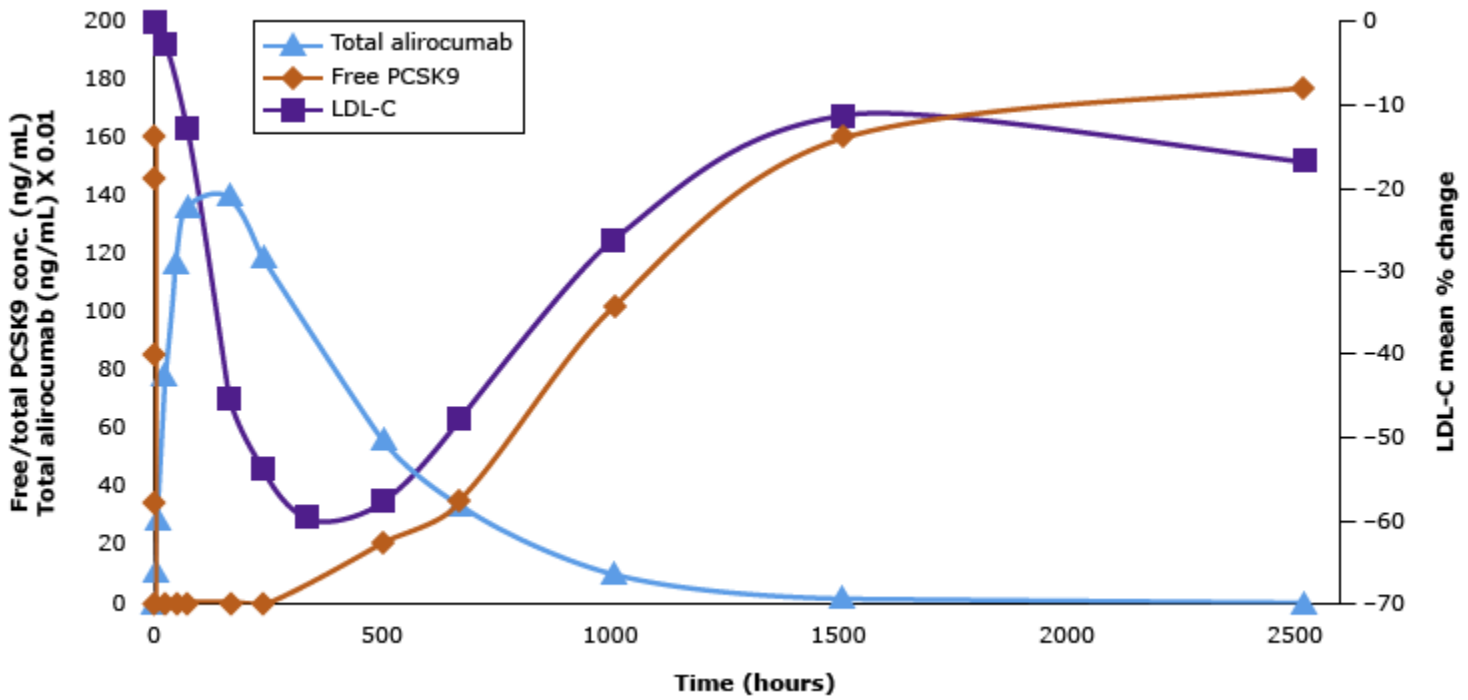
PCSK9 inhibitors

PCSK9 monoclonal antibodies are approved for use in many areas of the world. They are **highly effective** at lowering LDL-C but have the **drawbacks** of requiring frequent (once or twice a month) *subcutaneous injection* and high *cost*.

Patient surveys indicated a high rate of **satisfaction** with PCSK9 injection therapy, with very *few injection site reactions* and a willingness to *self-inject* using the subcutaneous pen injection device.

PCSK9 inhibitors

PCSK9 antibodies bind free (ie, unbound to other proteins) PCSK9 rapidly, resulting in no free PCSK9 availability for *two to three weeks* after antibody administration.



PCSK9 inhibitors

Administration

- Available in a sterile, single-use, preservative-free solution for subcutaneous injection in a *prefilled* syringe or pen.
- Can be injected in the *upper arm* or *leg* or in the *abdomen*.
- For primary hyperlipidemia or secondary prevention of cardiovascular events, the recommended dosage of *evolocumab* is **140 mg** subcutaneously *every two weeks* or **420 mg** *once monthly*.

Fibric Acid Derivatives (Fibrates)

- Fibrates are primarily used in patients with TG levels that **exceed 500 mg/dL** to reduce the risk of **acute pancreatitis**.
- May cause a modest reciprocal *rise in LDL-C* in patients with severely elevated TG levels.
- *HDL-C* concentrations may rise 10% to 15% or more.
- Generally well tolerated, but *gastrointestinal complaints* and transient *elevations in transaminase levels* have been reported.

Fibric Acid Derivatives (Fibrates)

- **Muscle-related adverse effects** can occur with both gemfibrozil and fenofibrate *alone* but is more common when used in *combination with statins*.
- Gemfibrozil has potent effects on CYP450 enzymes (such as CYP3A4) making it highly prone to significantly increase serum *statin* concentrations.
- Fenofibrate and gemfibrozil and may enhance the formation of *gallstones*.

Omega-3 Polyunsaturated Fatty Acids (PUFA)

- 2-4 g/day of EPA/DHA significantly reduce **TG** and VLDL cholesterol levels (20%-50%) with *lesser* effects on *other lipoproteins.*
- DHA and EPA effect on LDL-C
- Prescription omega-3 PUFA products (1 g of EPA/DHA per capsule) and OTC "fish oil" supplements

Omega-3 Polyunsaturated Fatty Acids (PUFA)

Cautions

- *Gastrointestinal complaints* (such as abdominal pain and "fishy burps"), minimized by refrigeration
- Caution in in patients with known *sensitivities* or allergies to fish or shellfish
- Caution is advised when used concomitantly with **antiplatelet** agents or **anticoagulants**.

Niacin

- Niacin (nicotinic acid) increases HDL-C (5%-30%), and lowers TG (20%-50%) and LDL-C (5%-20%).
- Niacin has **not** been shown to improve *cardiovascular outcomes* in patients on background *statin* therapy.
- Niacin has **many adverse drug reactions** that frequently limit its use.

Niacin

- Cutaneous *flushing* and *itching* (aspirin, taking with meal, and titrating the dose upward)
- *Extended- or sustained-release* products may minimize these complaints.
- Potentially important **laboratory abnormalities**: elevated liver function tests, hyperuricemia, and hyperglycemia.
- *Exacerbation* of pre-existing gout and diabetes
- **Contraindicated** in patients with active liver disease and active peptic ulcer disease