New options when statins are not enough

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Abstract Many recent advances in the understanding of lipid management greatly impact the profession of pharmacy and individual pharmacists. Clinical trial evidence has re-established the need to achieve aggressive lipid lowering, including the use of adjunctive therapy when statins are insufficient. Ezetimibe and the PCSK9 inhibitors are some of the most promising agents for adjunctive therapy, although many drugs used for lipid management have their advantages and disadvantages. Pharmacists need to understand why guidelines are evolving and how we can assure that patients reach optimal outcomes.

Introduction

Over the past several years, experts in cardiology and endocrinology have made a major shift in the way that they approach the management of their patients’ lipids. Although statins still rule the initial management of patients with elevated low-density lipoprotein (LDL), the importance of adjunctive therapy is emerging. This article explores the evolution of major clinical guidelines and the literature base that prompted those changes; identifies the most promising adjunctive antihyperlipidemic agents; delineates the pharmacologic and pharmacokinetic advantages and disadvantages of antihyperlipidemic agents; focuses on PCSK9 inhibitors; and defines the role of the pharmacist in the contemporary care of patients with hyperlipidemia.

National guidelines for lipid management

Lipoproteins are defined as very low-density lipoproteins (VLDL), calculated as 20% of triglyceride concentrations, LDL, and high-density lipoprotein (HDL). High native HDL concentrations provide some level of cardioprotection. Total cholesterol (LDL + VLDL...
+ HDL) is not useful clinically, but LDL is very useful and non-HDL cholesterol (LDL + VLDL) might have utility.\(^3\)

**Major national lipid guidelines**

National Cholesterol Education Program (NCEP) adult treatment panel guidelines were published in 2002 and remained in effect through 2013. They recommended achieving an LDL cholesterol level commensurate with the patient’s baseline risk of cardiovascular disease.\(^2\) Those with cardiac disease or the highest risk of cardiac disease had to achieve an LDL less than 100 mg/dL, although a level less than 70 mg/dL was acceptable when those with moderate or low cardiac disease risk had to achieve LDL levels less than 130 mg/dL or less than 160 mg/dL, respectively. The non-HDL cholesterol goals were 30 mg/dL above the LDL goals for each category of cardiac risk. The guidelines did not specify a preferred agent for cholesterol management and advocated for aggressive multidrug therapy if needed to achieve LDL and non-HDL therapy. The authors of the guidelines initially designed the document using epidemiologic data and then assessed clinical trial data to see if it supported their epidemiologic orientation.\(^2\)

In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) took over the role of hypercholesterolemia guideline creation from NCEP. ACC/AHA guidelines stress the pre-eminence of statin therapy with a dosing intensity dictated by a patient’s cardiovascular risk.\(^3\) Patients younger than age 75 years with atherosclerotic cardiovascular disease (ASCVD; history of acute coronary syndromes [unstable angina, myocardial infarction (MI)], stable angina, stroke or transient ischemic attack, peripheral arterial disease of atherosclerotic origin, or arterial revascularization [coronary, cerebrovascular, leg artery]), LDL concentration above 190 mg/dL (which includes most patients with heterozygous and homozygous familial hypercholesterolemia [FH]), and those with a 10-year ASCVD risk more than 7.5% (based on ACC/AHA risk calculator; www.cvriskcalculator.com) should utilize high-intensity statin therapy. Atorvastatin 40–80 mg or rosuvastatin 20–40 mg are considered high-intensity statin therapy because both reduce an average patient’s LDL more than 50%.

Patients with diabetes mellitus who do not meet the criteria for high-intensity therapy, patients with a 10-year risk of ASCVD between 5% and 7.4%, and those not tolerating higher-intensity statin therapy can consider a moderate-intensity statin therapy. Atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2–4 mg are moderate-intensity statins because these reduce LDL by 30% to 49%. If patients do not tolerate or are likely to not tolerate high-intensity statin therapy, moderate-intensity statin therapy should be employed. In persons older than age 75 years, the guideline does not insist on treating it with pharmacotherapy or on any intensity of statin therapy. For all patients, once the maximum tolerated statin dose is achieved, the ACC/AHA 2013 guidelines state that a nonstatin drug may be considered to further reduce LDL, but the benefits and risks, drug interactions, and patient preference should be considered, and the ACC/AHA had no preference about whether or not it should be used.\(^3\)

In August 2016, the European Society of Cardiology (ESC) along with the European Atherosclerosis Society (EAS) developed their guideline. Its recommendations are hybrid of the NCEP and the ACC/AHA 2013 approaches.\(^4\) Patients with ASCVD, diabetes mellitus, or chronic kidney disease are considered high or very high risk. For all other patients, they recommend using the Systematic Coronary Risk Evaluation (SCORE) system, which estimates the 10-year cumulative risk of a first fatal ASCVD event (scoring criteria given in ESC/EAS 2016 guidelines), unlike the ACC/AHA CV risk calculator, which estimates fatal and nonfatal event risk. Low and moderate ASCVD death risk have a 10-year risk of less than 1% and 1% to 5%, while those with risks of 5% to less than 10% and 10% or greater are classified as high or very high risk, respectively. All patients with ASCVD are considered very high risk, as are those with diabetes mellitus who have target organ damage such as retinopathy or nephropathy. Patients with a marked elevation in total cholesterol (>310 mg/dL) or blood pressure (>180/110 mm Hg) would be considered high risk even if the SCORE risk was less than 5%, as would all other patients with diabetes mellitus. In patients at very high ASCVD risk, an LDL goal of less than 70 mg/dL or a 50% or greater reduction from baseline if the LDL is 70 to 135 mg/dL is recommended. In patients at high ASCVD risk, an LDL goal of less than 100 mg/dL or a 50% or greater reduction from baseline if the LDL is 100 to 200 mg/dL is recommended. In subjects at low or moderate risk, a target LDL of less than 115 mg/dL is recommended. Statins are considered the preferred baseline therapy in all patients not achieving their goal, and the dose should be maximized to achieve the LDL goal or to the maximum tolerated dose. Unlike the ACC/AHA guideline, the ESC/EAS 2016 guideline specifically recommends adjunctive therapy if the LDL goals are not achieved and recommends that ezetimibe be the preferred second-line therapy for resistant patients.\(^4\)
**TABLE 1**

<table>
<thead>
<tr>
<th>MECHANISM OF ACTION</th>
<th>USE IN UNPLAQUED ELEVATED LDL</th>
<th>MUSCLE TOXICITY POTENTIAL</th>
<th>USE IN RAISED TRIGLYCERIDES</th>
<th>PREGNANCY/ BREASTFEEDING</th>
<th>DRUG INTERACTIONS</th>
<th>GLADD POTENTIAL</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Blocks PCSK9, extends life of LDL receptors that take LDL out of the circulation</td>
<td>Yes</td>
<td>+/−</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>No known interactions, eliminated by saturable binding to PCSK9 and nonsaturable proteolysis</td>
<td>+</td>
</tr>
<tr>
<td>Statins</td>
<td>- Block HMG CoA, a critical step in cholesterol synthesis</td>
<td>No</td>
<td>Lova, Simva</td>
<td>+++</td>
<td>Yes</td>
<td>Pregnancy Category X</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>Fibrates</td>
<td>- Activates lipoprotein lipase</td>
<td>No</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>Pregnancy Category C</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>Niacin</td>
<td>- Hepatocyte diacylglycerol acyltransferase-2 inhibitor, leads to breakdown of VLDL and LDL particles</td>
<td>No</td>
<td>++</td>
<td>Use with caution</td>
<td>**</td>
<td>Pregnancy Category C</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>- NPC1L1 protein inhibitor, leads to less dietary and biliary cholesterol absorption</td>
<td>Not recommended but not contraindicated</td>
<td>+/−</td>
<td>Yes</td>
<td>Pregnancy Category C</td>
<td>Breastfeeding</td>
<td>Possible use</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>- Microsomal triglyceride transfer protein inhibition, necessary for VLDL assembly and secretion in the liver</td>
<td>No</td>
<td>??</td>
<td>Yes</td>
<td>Pregnancy Category X</td>
<td>Breastfeeding</td>
<td>Don’t use</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>- Antisense oligonucleotide to apo B-100 mRNA, needed to create LDL and VLDL</td>
<td>No</td>
<td>??</td>
<td>Not recommended with severe renal impairment, proteinuria, or dialysis</td>
<td>**</td>
<td>Pregnancy Category B (use only if clearly indicated)</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>BAS</td>
<td>- Binds cholesterol-rich biliary acids, prevents enterohepatic recycling of cholesterol</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Pregnancy Category B (use only if clearly indicated)</td>
<td>Breastfeeding</td>
<td>Safe to use</td>
</tr>
</tbody>
</table>

USE IN: Apo B-100, LDL, VLDL, HDL, Lp(a), cholesterol, triglycerides.

MUSCLE TOXICITY: Myalgia, myositis, rhabdomyolysis.

PREGNANCY/BREASTFEEDING: Category X, contraindicated; Category C, use with caution.

DRUG INTERACTIONS: Azole antifungals, cyclosporine, statins, niacin, ezetimibe, gemfibrozil, warfarin, olmesartan, dabigatran, daptomycin, combined with statins, gemfibrate, fibrates; Gem increases repaglinide conc greatly, contraindicated; Gem increases statin conc more than Feno (both increase risk of myopathy when combined); Feno+colchicine=increased myopathy risk; Feno+Ezet=increased gallbladder risk.

GLADD POTENTIAL: +, no known interactions; ++, increased risk of myopathy; ++++, increased risk of rhabdomyolysis.

NOTES: Space ezetimibe from fibrates; space fibrates from warfarin; space niacin from BAS; space Lomit from BAS; Space Ezet from BAS; Ezet+cyclosporine=higher INR; Ezet+Feno=increased gallbladder risk; Gem +++, (erythema, diaphoresis, flushing) Feno +; No use in gallbladder disease pts; Use only 1 dose (10mg).

* Allergic reaction (anaphylactic). ** Hypersensitivity reaction. --- No evidence for benefit.
Clinical trials driving differences in the guidelines

Although the NCEP guidelines were driven by epidemiologic associations, the ACC/AHA and the ESC/EAS 2016 guidelines are driven primarily by randomized, controlled trials. The results of major placebo-controlled trials in patients with ASCVD (CARE, LIPID, HPS, GREACE) show that set doses of statins reduce the occurrence of subsequent coronary events and mortality versus placebo. In patients with elevated LDL levels but no ASCVD, major placebo-controlled trials (WOSCOPS, AFCAPS/TexCAPS, ASCOT-LLA) show that set doses of statins reduce ASCVD events and may also reduce mortality versus placebo. In 2 clinical trials of patients with ASCVD and 1 trial of patients without ASCVD, using higher-intensity statin therapy (secondary prevention: PROVE-IT, TNT; primary prevention: JUPITER) was associated with better outcomes than those seen with the use of moderate-intensity statin therapy. At the time that the ACC/AHA guidelines were being constructed, however, major clinical trials demonstrated no additional benefits when fenofibrate, niacin, or the experimental cholesteryl ester transfer protein inhibitors were used with statins versus statins alone (AIM-HIGH, HPS2-THRIVE, ACCORD, ILLUMINATE). This lack of literature support for achieving better results when such adjunctive therapy was added to a statin was the reason the ACC/AHA guidelines abandoned the specific target LDL goals of the NCEP, which had advocated for multidrug therapy if needed to achieve them.

Until June 2015, we lacked data from randomized, controlled trials suggesting that adding a drug to a statin for further lowering of LDL reduced the occurrence of ASCVD events more than using a statin alone. This changed with the publication of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). Patients (n=18,144; median follow-up, 6 years) within 10 days of a recent MI or unstable angina event were randomized to receive ezetimibe 10 mg daily plus simvastatin 40 mg or simvastatin 40 mg alone. The primary endpoint was a composite of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke. Those receiving ezetimibe plus simvastatin had a lower on-treatment LDL (53.7 mg/dL vs 69.5 mg/dL, P<.001) and fewer ASCVD events (32.7% vs 34.7%, P=.16) than those receiving simvastatin alone. Rates of muscle, gallbladder, and hepatic adverse effects and cancer were similar between the groups, making the balance of benefit to harm very favorable. Although this is the first and most compelling data that lowering LDL levels with adjunctive therapy is better than using a statin alone, there are some limitations. First, the group was very high risk for recurrent ASCVD events, having just experienced one within the past 10 days, and they compared adjunctive therapy with ezetimibe on top of moderate-rather than high-intensity statin therapy.

None of the PCSK9 inhibitor trials completed to date assessed mortality or cardiovascular events as a prespecified primary outcome. In a meta-analysis, however, PCSK9 monoclonal antibodies reduced the odds of experiencing all-cause mortality by 55% (P=.015) and MI by 51% (P=.03). It should be noted that the researchers used a fixed-effect model to pool these studies, while a random-effects model might have been more prudent given the clinical and methodologic heterogeneity in the constituent studies. The ODYSSEY LONG TERM trial had 49% and 84% of the weight for the all-cause mortality and MI outcomes, respectively, and warrants separate discussion. Patients (n=2341) at high risk for cardiovascular events with LDL concentrations 70 mg/dL or higher despite maximum tolerated statins received alirocumab 150 mg or placebo subcutaneous injection every other week. The patient’s LDL was reduced from 123 mg/dL to 48 mg/dL in the alirocumab group. In a post-hoc analysis, the alirocumab group had a lower occurrence of major adverse cardiac events (MACE; death from coronary disease, nonfatal MI, nonfatal ischemic stroke, or unstable angina requiring hospitalization) than placebo (1.7% vs 3.3%; P=.02) but was driven primarily by reductions in nonfatal MI (0.9% vs 2.3%; P=.01).

When the data from adjunctive ezetimibe and PCSK9 inhibitor therapy versus statin alone trials are viewed along with the higher-versus lower-intensity statin therapy trials, the most likely assumption is that lowering LDL to a greater extent further reduces ASCVD events, a conclusion built into the ESC/EAS 2016 guidelines but not able to be incorporated in the ACC/AHA 2013 guidelines.

Comparing pharmacologic agents that lower LDL

Table 1 compares and contrasts the pharmacologic and safety features of the main antihyperlipidemic agents being used in the United States. Some agents have advantages in patients with liver or renal disease, in pregnancy or lactation, and in terms of gastrointestinal tolerability, muscle symptomatology, and drug interactions. The agents also differ in terms of the expected range of LDL reductions that can be expected as denoted in Figure 1. Lipid apheresis (in which a dialysis-like machine is used to extract lipoproteins from the bloodstream) PCSK9 inhibitors, and high-intensity statin therapy have the greatest ability to reduce LDL, with the first 2 options being markedly expensive. Lipid apheresis is also inconvenient, however, because a patient has to go to a health system and be hooked up to the machine. Lomitapide and mipomersen are options in patients with homozygous FH, but are
expensive options with important safety and tolerability drawbacks. As identified in the ESC/EAS 2016 lipid guidelines, statins are first-line agents followed by adjunctive ezetimibe. A case could be made for several options to be the second adjunctive agent added to a patient’s regimen, but the PCSK9 inhibitors have the most potent LDL lowering in general patients, patients with hetero- and homozygous hypercholesterolemia, and the strongest evidence of reducing ASCVD events.

**Spotlight on PCSK9 inhibitors**

LDL receptors are expressed on the surface of hepatocytes. The receptor binds LDL and is internalized, the therapies such as statins, ezetimibe, or LDL apheresis who require additional lowering of LDL.

The impact of these agents on efficacy, safety, and tolerability endpoints in patients without homozygous FH is displayed in Table 1 and Figure 1. This data was derived from numerous well-conducted trials in patients with heterozygous FH or a high risk of cardiovascular disease. In patients with homozygous FH, only evolocumab has been assessed. In the TESLA-B trial, the use of adjunctive injectable evolocumab reduced LDL by 31% (P<.001) versus placebo, which is in line with that seen with other drugs approved for homozygous FH such as lomitapide and mipomersen.

At the European Atherosclerosis Society meeting in June 2016, researchers presented the results of the open-label and single-blinded TAUSSIG trial. In patients with homozygous FH, adjunctive evolocumab reduced LDL by 23%, and over 1.7 years of follow-up, there were no deaths and the annualized cardiac event rate was 2.1%. This is less than the 3.5% estimated annual event rate in other trials conducted in homozygous FH patients receiving statin plus ezetimibe.

**Role of pharmacists in contemporary practice**

Changing back from a statin-driven guideline to an LDL goal-derived guideline is very important for the practicing pharmacist. Technicians could refer patients with known genetic predilection to hypercholesterolemia, those complaining of a family history of premature MI or ischemic strokes, or patients with cardiac disease currently to the pharmacist for a more in-depth assessment of the adequacy of their lipid-lowering therapy. Pharmacists should start with statins and try to maximize the dose before seeking adjunctive therapy. Ezetimibe has stronger outcome data than the PCSK9 inhibitors, with a lower drug acquisition cost and more-convenient oral dosing making it the first adjunctive treatment of choice. Data show that niasin and fibrac acid derivatives lack additional final health outcome benefits when added to statins and have a less favorable safety profile than the PCSK9 inhibitors. This makes the PCSK9 inhibitors the preferable second-line adjunctive therapy.

Although these are evidence-based standard recommendations for the average patient, many patients have coexisting diseases and disorders, drug intolerances, and adverse events and use concomitant drugs, making standard recommendations implausible. For example, patients resisting self-injection or the high drug acquisition cost could lead the pharmacist.
Drug counseling on signs and symptoms of adverse effects, expected benefits when the patients are compliant, and proper administration times and approaches are critical. Spacing bile acid sequestrants from drugs like statins (giving the bile acid sequestrant 3–4 hours apart from statins, levotyrox-ine, warfarin, and digoxin), using pravastatin and fluvastatin at bedtime, and taking niacin with food to avoid stomach upset are all useful tips. Patients starting on PCSK9 inhibitors will need to understand how to administer a subcutaneous injection, and pharmacists, with their certifications for immunizations, are increasingly prepared to counsel them on safe use. PCSK9 inhibitors are refrigerated and must be warmed to room temperature for 30 to 40 minutes before use, but discarded if at room temperature for 24 hours or longer. The drug product should be inspected visually and if the solution is discolored or contains visible particulate matter, it should not be used. Standard aseptic injection technique is required for every injection. Subcutaneous injections into the thigh, abdomen, or upper arm area are advisable but not if those areas are burned, inflamed, infected, or if a rash is noted. Patients should rotate injection sites, and PCSK9 inhibitors should not be injected into the same site as other injectable medication. Some fine tuning of this counseling based on whether the injections come in a syringe, pen, or autoinjector will be needed.

**Conclusion**

There is a new shift in the paradigm of lipid management. The resumption of LDL goals provides great opportunities for pharmacists to have an important impact on the healthcare team and in patients’ lives, but it requires knowledge of the guidelines themselves, the clinical trials that underlie them, and unique pharmacologic and pharmacokinetic properties of the drugs that are available for use.

**REFERENCES**


TEST QUESTIONS

FOR PHARMACISTS

1. What type of data did NCEP guidelines primarily use when defining the LDL goals of individual patients?
   a. Randomized controlled trials
   b. Uncontrolled clinical trials
   c. Epidemiologic studies
   d. Case reports

2. Why did ACC/AHA 2013 guidelines not recommend LDL goals like the NCEP guidelines and instead strongly advocate for different intensities of statin therapy with no position on use of adjunctive therapy?
   a. Because clinical trials conducted to that point assessed set doses of statins of different intensities to reduce ASCVD risk, not statin therapy linked to specific target LDL goals, and found no additional benefits from using adjunctive therapy
   b. Because no studies were conducted adding another lipid-altering drug to statins versus a statin alone
   c. Because the ACC/AHA as a rule does not publish guidelines with target goals for diseases
   d. Because statins were so widely used it would make it easier for clinicians to adopt their guidelines

3. According to ACC/AHA 2013 guidelines, what type of statin therapy is recommended for use in those >75 years with or without ASCVD?
   a. High intensity
   b. Low intensity
   c. Moderate intensity
   d. They do not insist on the use of statins or a statin dose intensity.

4. What is the major difference between the ACC/AHA 2013 CV risk calculator and the ESC/EAS 2016 SCORE risk system?
   a. ACC/AHA 2013 calculator uses risk over 20 years instead of 10 years.
   b. ACC/AHA 2013 calculator uses risk over 10 years instead of 20 years.
   c. ACC/AHA 2013 calculator determines risk of all ASCVD events, while ESC/EAS 2016 SCORE only determines fatal ASCVD events.
   d. There is no difference, they calculate the same type of risk over the same time period.

5. What LDL goals are recommended by ESC/EAS 2016 guidelines?
   a. Very high risk = LDL <30 mg/dL; high risk = LDL <110 mg/dL; low-to-moderate risk = LDL <130 mg/dL
   b. Very high risk = LDL <70 mg/dL; high risk = LDL <100 mg/dL; low-to-moderate risk = LDL <115 mg/dL
   c. Very high risk = LDL <40 mg/dL; high risk = LDL <70 mg/dL; low-to-moderate risk = LDL <100 mg/dL
   d. Very high risk = LDL <100 mg/dL; high risk = LDL <130 mg/dL; low-to-moderate risk = LDL <160 mg/dL

6. According to ESC/EAS 2016 guidelines, which adjunctive agent is preferred when statins are insufficient to achieve LDL goals?
   a. Ezetimibe
   b. Niacin
   c. Fenofibrate
   d. Evolocumab

7. What did the PROVE-IT, TNT, and JUPITER trials show?
   a. That higher-intensity statin therapy was not better than moderate-intensity statin therapy at reducing ASCVD events
   b. That higher-intensity statin therapy was the same as moderate-intensity statin therapy at reducing ASCVD events
   c. That higher-intensity statin therapy was better than moderate-intensity statin therapy at reducing ASCVD events
   d. That statins were better than other lipid-lowering drugs at reducing ASCVD events

8. Why was the IMPROVE-IT trial so impactful on the ESC/EAS 2016 guidelines and clinical care?
   a. It showed for the first time that bile acid sequestrants provided the same ASCVD event reductions as statins.
   b. It showed for the first time that bile acid sequestrants provided better ASCVD event reductions than statins.
   c. It showed for the first time that bile acid sequestrants provided inferior ASCVD event reductions than statins.
   d. It showed for the first time that adding ezetimibe to a statin was better at reducing ASCVD events than using a statin alone.

9. Which of the following drugs are known to be harmful to the developing fetus as designated by a Category X status?
   a. Statins, lomitapide
   b. Lomitapide, mipomersen
   c. Fibrates, ezetimibe
   d. Statins, fibrates

10. Which of the following statins would have the lowest risk of drug interactions when combined with CYP3A4 inhibitors?
    a. Simvastatin
    b. Lovastatin
    c. Rosuvastatin
    d. Atorvastatin

11. Which of the following drugs do not have a high risk of GI effects such as nausea or diarrhea?
    a. PCSK9 inhibitors
    b. Niacin
    c. Lomitapide
    d. Fibrates

12. Which of the following drugs can raise serum uric acid concentrations making it riskier in patients with gout?
    a. Fibrates
    b. Bile acid sequestrants
    c. Mipomersen
    d. Niacin

13. Which of the following can decrease absorption of fat-soluble vitamins?
    a. Bile acid sequestrants, lomitapide
    b. Ezetimibe, statins
    c. Statins, mipomersen
    d. Mipomersen, lomitapide

14. Which of the following drugs have the greatest ability to reduce LDL cholesterol?
    a. Low-intensity statins
    b. PCSK9 inhibitors
    c. Niacin
    d. Fibrates

15. How does blocking PCSK9 help reduce LDL cholesterol from the circulation?
    a. It reduces LDL receptor manufacture.
    b. It enhances LDL receptor manufacture.
    c. It reduces LDL receptor destruction.
    d. It enhances LDL receptor destruction.
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16. Which of the following drugs is linked appropriately with an important potential drawback?
   a. Ezetimibe = subcutaneous dosing only
   b. Fibrates = contraindicated in gallbladder disease
   c. PCSK9 inhibitors = serious drug interactions
   d. Mipomersen = contraindicated with active peptic ulcer disease

17. If there is a patient who cannot use a statin, what is a limitation of ezetimibe monotherapy?
   a. It only reduces LDL by an average of 18% and patients are unlikely to achieve their ESC/EAS 2016 LDL goal.
   b. It reduces LDL by an average of 60% and patients are likely to have an LDL that is too low and require discontinuation of therapy.
   c. Ezetimibe only reduces cholesterol in patients with high PCSK9 concentrations.
   d. Ezetimibe does not reduce LDL cholesterol unless it is combined with another lipid-lowering drug.

18. When counseling a patient on alirocumab administration, what of the following points should be stressed?
   a. Swallow the tablet and stay upright for 30 minutes.
   b. Premedicate with aspirin to prevent the flushing response.
   c. Inject into the thigh, abdomen, or upper arm and rotate the site.
   d. Inject into the buttocks or thigh and rotate the site.

19. Why should a patient look at their PCSK9 injection before injecting it?
   a. To be sure it contains the right volume
   b. To be sure it is free of particulate matter
   c. To be sure it is not discolored
   d. B and C are both correct

20. How long should evolocumab be left out of the refrigerator before injecting?
   a. 10 min
   b. 20 min
   c. 30 min
   d. 24 hr

FOR PHARMACY TECHNICIANS

1. Which of the following drugs is a PCSK9 inhibitor?
   a. Evolocumab
   b. Ezetimibe
   c. Niacin
   d. Lovastatin

2. If you see someone buying over-the-counter niacin, which of the following is a reason to have the patient consult the pharmacist before letting them purchase it?
   a. It can raise uric acid levels.
   b. Should not be used in people with active peptic ulcer disease.
   c. It can have drug interactions with other medications like statins and bile acid sequestrants.
   d. All of the above

3. PCSK9 inhibitors can only be injected into the following type of skin:
   a. Inflamed
   b. Freckled
   c. Skin with a rash
   d. Burned

4. Which of the following 2 lipoproteins are both associated with ASCVD when their concentrations are too high?
   a. HDL, LDL
   b. VLDL, HDL
   c. LDL, VLDL
   d. PBL, HDL

5. Why should statins be avoided in patients receiving colchicine or daptomycin?
   a. Increased risk of liver disease
   b. Increased risk of kidney disease
   c. Increased risk of myopathy
   d. Decreased ability to lower LDL

6. What drug should be used first for most patients with elevated LDL cholesterol?
   a. Fibrates
   b. Statins
   c. Bile acid sequestrants
   d. Lomitapide

7. Which of the following drugs is the least expensive?
   a. Lomitapide
   b. Mipomersen
   c. PCSK9 inhibitor
   d. Ezetimibe

8. How many times is an LDL receptor usually recycled before it is broken down by the body?
   a. 10
   b. 15
   c. 100
   d. 150

9. According to the ESC/EAS 2016 guidelines, what is the LDL goal for someone with the highest risk of ASCVD?
   a. <30 mg/dL
   b. <70 mg/dL
   c. <90 mg/dL
   d. <120 mg/dL

10. Which statin can increase the risk of spilling a protein in the urine?
    a. Lovastatin
    b. Simvastatin
    c. Pitavastatin
    d. Rosuvastatin
Overset page

Do you feel that bile acid sequestrants will reduce ASCVD events as well as ezetimibe given that these reduce LDL to the same extent?

PCS9 inhibitors are monoclonal antibodies that prevent PCS9 from binding LDL receptors and therefore prolong their effective life.

Changing back from a statin-driven guideline to an LDL goal-derived guideline is very important for the practicing pharmacist.