continuing education for pharmacists

Volume XXXIV, No. 2

Update on Cholesterol Treatment and Two New Drugs: Praluent and Repatha

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Dr. Mona T. Thompson has no relevant financial relationships to disclose.

Goal. The goals of this lesson are to provide an overview of the 2013 American College of Cardiology/ American Heart Association (ACC/ AHA) Guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, and to discuss the role of PCSK9 inhibitors following the approval of alirocumab (Praluent®) and evolocumab (Repatha™).

Objectives. At the completion of this activity, the participant will be able to:

1) demonstrate an understanding of the use of the newly introduced atherosclerotic cardiovascular disease (ASCVD) risk calculator;

2) identify patients at risk of developing ASCVD who fall into one of the four statin benefit groups;

3) list therapy recommendations for each statin benefit group according to the 2013 ACC/AHA guidelines;

4) demonstrate an understanding of the mechanism of action of proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitor and its role in treating hypercholesterolemia; and

5) identify key prescribing, dispensing and counseling points associated with the new drugs alirocumab (Praluent) and evolocumab (Repatha).

Background

Atherosclerotic cardiovascular disease is the leading cause of death, decreased quality of life, and medical costs in the United States. Commonly called *hardening of the arteries*, arteriosclerosis includes a variety of conditions that cause artery walls to thicken and lose elasticity. It can occur because of fatty deposits on the inner lining of arteries, calcification of the wall of the arteries, or thickening of the muscular wall of the arteries from chronically elevated blood pressure. Atherosclerosis, a specific type of arteriosclerosis, causes coronary artery disease (CAD), the most common form of heart disease in the United States. About 610,000 people die of heart disease in the U.S. every year.

Hypercholesterolemia, the presence of high cholesterol in the blood, doubles the risk of heart disease compared to persons with lower levels. While the body needs some cholesterol, 71 million American adults (33.5 percent) have high low-density lipoprotein cholesterol (LDL), commonly referred to as "bad" cholesterol. Familial hypercholesterolemia is a genetic disorder characterized by very high levels of LDL in the blood and early cardiovascular (CV) disease. Excess blood cholesterol can lead to plaque build-up or atherosclerosis as previously defined. In 2004, the National Cholesterol Education Program (NCEP) recommended an LDL goal of less than 100 mg/ dL in high-risk patients, with an even lower level of <70 mg/dL for very high risk patients including patients with diabetes.

While CAD is preventable by making healthy choices and treating underlying diseases such as hypertension and diabetes, aging and genetics also contribute to the development of CV disease. A heart healthy lifestyle is recognized as the foundation for cardiovascular health. Dietary recommendations include a diet that is low in saturated fat, trans fat, and sodium; and high in vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts. Adults should engage in regular aerobic physical activity, maintain a healthy body weight, avoid smoking, and control hypertension and diabetes when present.

Overview of 2013 ACC/AHA Guidelines for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

The 2013 ACC/AHA guidelines for the treatment of blood cholesterol were developed by a team of experts charged with creating recommendations for the treatment of blood cholesterol levels to specifically reduce ASCVD. The data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs were utilized with an ASCVD definition including coronary heart disease, stroke, and peripheral arterial disease. The systematic review was limited to literature that examined

Table 1
Major statin recommendations for the reduction of ASCVD in adults*

The appropriate intensity of statin therapy should be initiated or continued:

1. Clinical ASCVD^
   - Persons aged ≤75 years with no safety concerns: high-intensity statin
   - Persons aged >75 years or with safety concerns: moderate-intensity statin
2. Primary prevention: persons with primary LDL level ≥190 mg/dL
   - Rule out secondary causes of hypercholesterolemia
   - Persons age ≥21 years: high-intensity statin
   - Achieve ≥50 percent reduction in LDL level
   - May consider LDL lowering nonstatin therapy to further reduce LDL levels
3. Primary prevention: persons with diabetes aged 40-75 years with an LDL level of 70-189 mg/dL
   a. Moderate-intensity statin
   b. Consider high-intensity statin with 10-year ASCVD risk ≥7.5 percent
4. Primary prevention: persons without diabetes aged 40-75 years with an LDL 70-189 mg/dL
   a. Estimate 10-year ASCVD risk (using risk calculator) in those not receiving a statin; estimate risk every 4-6 years
   b. To determine whether to initiate a statin, engage a clinician-patient discussion of potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences. Reemphasize healthy life style habits and address other risk factors. If statin therapy is chosen:
      - Persons with ≥7.5 percent 10-year ASCVD risk: moderate- or high-intensity statin
      - Persons with 5 to <7.5 percent 10-year ASCVD risk: consider moderate-intensity statin
      - Other factors may be considered such as: LDL level ≥160 mg/dL, family history of premature ASCVD and lifetime ASCVD risk
5. Primary prevention when LDL level is <190mg/dL and person is aged <40 years or >75 years or has <5 percent 10-year ASCVD risk
   a. Statin therapy may be considered in selected persons
6. Statin initiation is not routinely recommended for persons with NYHA class II-IV heart failure or those who are receiving maintenance hemodialysis

*Excerpt from *Ann Intern Med*. 2014; 160:339-343.
^*Clinical ASCVD* is defined as acute coronary syndromes or a history of myocardial infarction, stable angina, coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

ASCVD outcomes. The recommendations, which will be outlined in this lesson, are intended to provide a strong evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD in adults. The recommendations were hence designed to identify patients who would most likely benefit from cholesterol-lowering statin therapy.

It has been noted that while other drug therapy strategies to reduce ASCVD events have been advocated, such as treat-to-cholesterol target or the concept that lower cholesterol is better, only RCTs using fixed-doses of cholesterol-lowering drugs have evaluated this risk reduction. Thus, evidence to support titrated (dose-adjusted) statin treatment to achieve prespecified LDL or non-HDL-C goals is lacking. The Blood Cholesterol Expert Panel considered only RCTs studying medication therapy with statin drugs in these recommendations, due to the substantial amount of evidence associated with these agents. It is noteworthy that the 2013 ACC/AHA Blood Cholesterol Guidelines were not written to serve as a comprehensive document for detection, evaluation, and treatment of lipid disorders as in previous reports. Future updates are anticipated to build upon this foundation.

In summary, the new guidelines answer the following questions: 1) who should be assessed for cardiovascular risk, and how; 2) what lifestyle changes are recommended to reduce the CV risk; 3) who should be treated with a statin; and 4) statin therapy recommendations. Specifically, the 2013 guidelines introduce four major statin benefit groups utilized to identify patients likely to experience a reduction in ASCVD events in secondary and primary prevention. Furthermore, they stratify patients into pharmacologic treatment option groups ranging from no statin therapy to low-, moderate-, and high-dose statin therapy based on risk factors. The addition of a nonstatin has not been proven to further reduce CV risk.

Assessing Patients for ASCVD Risk and the Newly Introduced ASCVD Risk Calculator

In general, patients aged 20 to 79 years without atherosclerotic cardiovascular disease should be assessed for traditional risk factors such as elevated lipids, hypertension, or presence of diabetes every four to six years.

Additionally, in patients aged 40 to 75 years of age for patients not receiving cholesterol lowering therapy and with an LDL 70-189 mg/dL, the patients' 10-year ASCVD risk should be calculated. This is determined by using the newly instituted risk calculator for the estimation of cardiovascular disease. The calculator is intended to identify patients in the primary prevention group who may have previously been overlooked for treatment, but will benefit from statin therapy. The calculator is available at http://my.americanheart.org/cvriskcalculator or through an app from iTunes (for iPhone, iPad, and iPod), or Google Play (for Android). The CardioSource website is a tool from ACC/AHA that offers an interactive reference including the calculator

and appropriate information for both patients and clinicians. This easy-to-use website can be found at http://tools.acc.org/ASCVD-Risk-Estimator/.

The REGARDS trial, published in *JAMA* in 2014, was a large-scale, community-based study that looked at how accurate and discriminatory the risk estimator was. The trial showed that the risk estimator has very good calibration and accuracy. The tool was also successful in correctly ranking individuals from high to low risk. This additional validation allows clinicians to confidently weigh patient characteristics and determine if statin treatment would be of benefit. Providers may find it is helpful in making an informed decision when weighing statin use in patients with a history of myalgias. Additionally, empowering patients to utilize the calculator and references to understand their long-term risks for cardiovascular disease may improve compliance in medication therapy and lifestyle modifications.

Four Major Statin Benefit Groups

Statin therapy is recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects relative to the potential benefit. The four major statin benefit groups that were established are intended to treat the following patients: 1) with clinical ASCVD for secondary prevention; 2) with primary elevations in LDL ≥190 mg/dL; 3) with diabetes aged 40 to 75 years with LDL 70 to 189 mg/dL and without clinical ASCVD; and 4) without clinical ASCVD or diabetes with LDL 70 to 189 mg/dL and estimated 10-year ASCVD risk ≥7.5 percent (i.e., primary prevention). These groups are outlined in Table 1.

Moderate evidence supports the use of statin therapy for primary prevention in individuals with a 10-year ASCVD risk of 5 to <7.5 percent. For patients who do not fit into one of the four statin benefit groups, yet have a 10-year ASCVD risk of 5 to 7.5 percent, additional factors may be taken into consideration if there is clinical suspicion that a patient may benefit. These include: 1) LDL ≥160 mg/dL or other evidence of genetic hyperlipidemia; 2) CV disease onset in a first degree male relative before age 55 or in a first degree female relative before age 65; 3) elevated lifetime risk of ASCVD (risk calculator also displays this); and 4) other clinical markers. Additionally, clinicians and patients should discuss statin adverse effects, statin drug interactions, and patient preferences.

The definition used for clinical ASCVD in this guideline is consistent with the inclusion criteria for secondary prevention trials. It is defined as acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin.

Table 2
High-, moderate-, and low-intensity statin therapy^

	High-Intensity	Moderate-Intensity	Low-Intensity
Atorvastatin (Lipitor)	**40*-80 mg**	**10**-20 mg	–
Rosuvastatin (Crestor)	**20**-40 mg	5-**10 mg**	–
Simvastatin (Zocor)	–	**20-40 mg****	10 mg
Pravastatin (Pravachol)	–	**40**-80 mg	**10-20 mg**
Lovastatin (Mevacor)	–	**40 mg**	**20 mg**
Fluvastatin (Lescol XL)	–	80 mg XL	–
Fluvastatin (Lescol)	–	**40 mg twice daily**	20-40 mg
Pitavastatin (Livalo)	–	2-4 mg	1 mg

^Statins and doses in bold reduced major CV events in RCTs
*40 mg may be used if patient can't tolerate 80 mg dose
** 80 mg was the evaluated dose in RCTs, however, FDA now recommends against the initiation of simvastatin 80 mg due increased risk for myopathy and rhabdomyolysis

Appropriate Intensity of Statin Therapy

Once a clinician identifies that a patient falls into one of the statin benefit groups (or additional clinical suspicion leads to a decision to start statin therapy), the guidelines next suggest that the appropriate intensity of statin therapy should be initiated. These recommendations are based on doses utilized in RCTs.

In summary, high-intensity statin therapy, therapy intended to decrease LDL levels by ≥50 percent, is recommended for adults ≤75 years of age who have clinical ASCVD and no safety concerns. High-intensity statins are limited to atorvastatin 80 mg once daily (or 40 mg if 80 mg is not tolerated) and rosuvastatin 20 to 40 mg once daily. Moderate-intensity statin therapy, therapy intended to decrease LDL levels by 30 to 50 percent, is recommended for adults ≤75 years of age who have clinical ASCVD and safety concerns, and in those >75 years with clinical ASCVD. Low-intensity statin therapy may be used when high- or moderate-intensity statins are not tolerated. All statin agents may be dosed to meet moderate-intensity recommendations. However, atorvastatin and rosuvastatin are too potent for utilization of low-intensity doses.

Table 1 lists the full recommendations and considerations for high-, moderate-, and low-intensity statin treatment for each statin benefit group. Table 2 lists the recommended statin doses by intensity.

Monitoring Adherence and Safety with Statin Therapy

Regular monitoring for adherence to drug therapy along with safety assessments continue to be recommended. Routine monitoring

of hepatic function with alanine aminotransferase (ALT) levels or muscle injury with creatine kinase (CK) levels is not recommended. ALT should be checked at baseline only, and then repeated only if symptoms of hepatotoxicity occur. Clinicians may choose to obtain a baseline CK in patients at risk of myopathy (i.e., drug interactions). Otherwise, CK levels should be checked if a patient is experiencing severe muscle symptoms or fatigue of unknown cause. In these instances, the statin should be held followed by a CK level check and urinalysis to rule out rhabdomyolysis.

A fasting lipid panel is recommended four to 12 weeks after statin initiation or change in therapy, then every three to 12 months thereafter. Patients should also be monitored for new-onset diabetes according to the diabetes screening guidelines.

For patients who experience a less than anticipated therapeutic response, adherence to lifestyle and drug therapy should be reinforced. An increase in statin intensity or addition of nonstatin therapy shown to reduce ASCVD events may be considered in high risk patients including those with genetic hypercholesterolemia.

In the event that a patient is not able to tolerate the recommended intensity of statin therapy, it is suggested to use the maximally tolerated intensity of statin. If muscle symptoms occur, the statin may be discontinued until symptoms resolve. Clinicians may then consider re-challenging the patient with the same or lower dose of statin. If muscle symptoms recur, the statin should be discontinued followed by a re-challenge of progressively lower doses of the same statin or a different statin.

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibition and Role in Hypercholesterolemia

Since the discovery of the low density lipoprotein cholesterol receptor over 40 years ago, many randomized studies have supported the causal relationship between LDL and cardiovascular disease. The use of HMG-CoA reductase inhibitors or statins to reduce major cardiovascular events and mortality has been substantiated and has already been reviewed in this lesson. While statins have been the first-line therapy for cholesterol reduction since the late 1980s, it is estimated that for one in five individuals, statin therapy does not sufficiently lower cholesterol. As previously discussed, some patients are intolerant to statin therapy due to muscle pain, liver damage, or the development of diabetes. With the approval of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, patients may benefit from an alternate and powerful mechanism to reducing cholesterol. The remainder of this lesson will review the basic research supporting use of PCSK9 inhibitors and the potential role of recently approved agents in the treatment of hypercholesterolemia.

PCSK9 is a serine protease that plays an important role in modulating LDL levels by targeting LDL receptors (LDLR) for lysosomal degradation. It has been established that PCSK9 acts as a chaperone protein. It binds to LDL receptors creating a PCSK9-LDLR complex that is moved from the plasma membrane to the lysosome where it is degraded. PCSK9 is also thought to degrade LDLR intracellularly. Since the LDLR is not recycled to the cell surface, the number of LDL receptors expressed on the surface is reduced. This is significant as it leads to a reduction in the clearance of LDL or, stated otherwise, an increase in unbound, circulating blood cholesterol.

Therefore, inhibiting PCSK9 increases the number of LDL-receptors on the hepatocyte surface, resulting in lower LDL plasma concentrations. The effect of PCSK9 on LDL cholesterol appears to be mediated exclusively through LDL receptors.

Intracellular cholesterol content is the principal factor controlling PCSK9 gene expression. PCSK9 gene transcription is regulated by a detailed process in the body taking into account fatty acid synthesis and cholesterol metabolism. Interestingly, because cholesterol levels in the liver mediate PCSK9 expression, pharmacotherapy that results in cholesterol depletion will lead to up-regulation of PCSK9. This has been observed following treatment with statins, ezetimibe and bile acid-binding resins. Therefore, therapeutic synergy has been suggested for PCSK9 inhibition and statin therapy on LDL lowering.

Additionally, genetic association studies have demonstrated that loss-of-function mutations in PCSK9 are associated with low plasma LDL levels and a reduction in the incidence of adverse cardiovascular events. Individuals with total PCSK9 deficiency have very low plasma levels of LDL, such as 10-20 mg/dL without any apparent adverse clinical consequence.

The findings related to PCSK9 have sparked investigation of multiple approaches to PCSK9 inhibition. At the time of publication, two PCSK9 inhibitors, alirocumab (Praluent) and evolocumab (Repatha), both human monoclonal antibodies, had been recently approved. A third monoclonal antibody, bococizumab, was currently in phase 3 trials and expected to be presented for FDA approval.

Alirocumab (Praluent)

The PCSK9 inhibitor alirocumab [PRAHL-u-ent] was approved by FDA in July 2015. It is a monoclonal antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol.

The recommended starting dose is 75 mg administered subcutaneously once every two weeks. In clinical trials, the majority of patients achieved sufficient LDL

reduction with this dose. However, if the LDL response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered subcutaneously every two weeks. It is recommended to measure LDL levels within four to eight weeks of initiating or titrating Praluent to allow for assessment of the response and adjustment of dose. Advise the patient that if a dose is missed and it is within seven days from the missed dose, the patient can still administer the dose and resume original schedule. However, if the missed dose is not administered within seven days, the patient should be instructed to wait until the next dose on the original schedule.

Because alirocumab is a human monoclonal antibody, the potential for immunogenicity exists. Hypersensitivity reactions such as pruritus, rash, urticaria including serious events such as hypersensitivity vasculitis, and hypersensitivity reactions requiring hospitalization have been reported. If signs or symptoms of allergic reactions occur, treatment with alirocumab should be discontinued and the patient should be treated according to the standard of care.

The most commonly occurring adverse reactions are nasopharyngitis, injection site reactions, and influenza. Other reported adverse reactions (2 to 5 percent of Praluent-treated patients and more frequently than placebo) include urinary tract infections, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, confusion, musculoskeletal pain. Additionally, neurocognitive events, such as confusion or memory impairment, and liver-related disorders related to abnormalities in liver enzymes, were reported more frequently in the Praluent group compared to the placebo group. The most common adverse reactions leading to treatment discontinuation were allergic reactions (0.6 percent for Praluent versus 0.2 percent for placebo) and elevated liver enzymes (0.3 percent versus <0.1 percent).

There is no available data on the use of Praluent in pregnant women. No dosage adjustment is required for patients with mild or moderately impaired renal or hepatic function. No data is available for patients with severe renal or hepatic impairment. The median half-life of alirocumab at steady state was 17 to 20 days.

Alirocumab was investigated in five double-blind, placebo-controlled trials. A total of 3,499 patients were enrolled, of which 36 percent had heterozygous familial hypercholesterolemia (HeFH) and 54 percent non-FH patents with clinical ASCVD. All patients were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapies (LMTs). Three studies utilized the 75 mg every two weeks as the initial dose as part of an up-titration regimen, while the other two studies treated patients with the 150 mg every two weeks dose only. All trials were at least 52 weeks in duration, with the primary efficacy endpoint defined as mean percentage change in LDL from baseline measured at week 24. Clinical trials have proven that alirocumab has a significant effect on LDL reduction. Each of the studies was designed differently in terms of dose and patient population investigated, and the mean LDL percent change ranged from –36 percent to –58 percent at week 24. However, a limitation of its use is that the impact on cardiovascular morbidity and mortality has not yet been established. The ODYSSEY outcomes trial is an ongoing trial that is intended to provide an assessment of the cardiovascular benefit in approximately 18,000 patients treated with alirocumab over a five-year period.

Evolocumab (Repatha)

Evolocumab, the second PCSK9 inhibitor and monoclonal antibody, was approved by FDA in August 2015. Similar to alirocumab, Repatha [ri-PATH-ah] is indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or clinical ASCVD who require additional lowering of LDL. It is also indicated as an adjunct to diet and other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH), the more severe form of FH, who require additional lowering of LDL.

All doses are administered by subcutaneous injection. For primary hyperlipidemia with clinical ASCVD or HeFH, the dose is 140 mg every two weeks or 420 mg once monthly. If a regimen is switched, it is advised that the first dose of the new regimen be administered on the next scheduled date of the prior regimen. When treating patients with homozygous familial hypercholesterolemia, the dose is 420 mg once monthly. In order to achieve the 420 mg dose, three Repatha injections (each 140 mg) should be administered consecutively within 30 minutes. It is recommended that the LDL levels are measured four to eight weeks after starting Repatha, as therapy will depend on the degree of LDLR function. In the event that a dose is missed (for either dosing regimen), patients should be advised to administer Repatha as soon as possible if there are more than seven days until the next dose, or omit the missed dose and administer the next dose according to the original schedule.

Evolocumab is contraindicated in patients with a history of serious hypersensitivity reactions to the entity. Hypersensitivity reactions such as rash and urticaria have been reported. If signs or symptoms of a serious allergic reaction occur, evolocumab treatment should be discontinued followed by standard medical treatment. Other common adverse reactions reported in clinical trials (>5 percent of patients treated with Repatha and occurred more frequently than placebo) included nasopharyngitis, upper respiratory tract infections, influenza, back pain, and injection site reactions. Other less commonly reported adverse reactions reported in the 52-week clinical trial included cough, urinary tract

Table 3
Key prescribing and counseling points for PCSK9 inhibitors

	Alirocumab (Praluent)	Evolocumab (Repatha)
Indications	· Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical ASCVD who require additional lowering of LDL	
		· Adjunct to diet and other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL · May be used in pediatric patients aged 13-17 with primary dyslipidemia or HeFH
Dosing	· Initial dose is 75 mg SC every 2 weeks · After checking LDL 4-8 weeks after initiating, may increase to 150 mg SC every 2 weeks if needed	· ASCVD or HeFH: 140 mg SC every 2 weeks or 420 mg SC once monthly · HoFH: 420 mg SC once monthly
Storage	· Refrigerate at 36-46 F° in outer carton to protect from light · Time out of refrigerator should not exceed 24 hours	· Refrigerate at 36-46 F° · Can be stored at room temperature in original carton for up to 30 days prior to use
Administration	· Allow to warm to room temp for approximately 30-40 minutes · Administer subcutaneously using proper aseptic technique into thigh, abdomen, or upper arm · Single dose; do not reuse · Rotate injection sites; do not inject in sites that are infected or inflamed	
	· May take up to 20 seconds to inject	· To administer 420 mg dose, give 3 consecutive injections of 140 mg within 30 minutes
Allergic Reactions	Advise patients to discontinue and seek prompt medical attention if any signs or symptoms of serious allergic reactions occur	
Product Availability	· Single dose 75 mg/mL pre-filled syringe and pre-filled pen · Single dose 150 mg/mL pre-filled syringe and pre-filled pen	· Single dose 140 mg/mL pre-filled syringe · Single dose 140 mg/mL SureClick® autoinjector

infection, sinusitis, headache, myalgia, dizziness, musculoskeletal pain, hypertension, diarrhea and gastroenteritis. Of these, the most common adverse reaction that led to discontinuation was myalgia (0.3 percent versus 0 percent for Repatha and placebo, respectively).

Among the patients included in the Repatha trials, over 1600 in the treatment arm had at least one LDL value <25 mg/dL. There were no changes to background lipid-altering therapy or evolocumab dosing on this basis. There were no adverse consequences of very low LDL identified in the trials. However, the long-term effects of very low LDL due to Repatha treatment are unknown.

There are no data available on the use of Repatha in pregnant women to indicate a drug-associated risk. The product insert also states that there is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. Repatha's estimated effective half-life is 11 to 17 days.

The safety and effectiveness has been established in adolescent patients aged 13 to17 years with HoFH only. In total, 14 adolescents have been treated with evolocumab with a median exposure of nine months resulting in a similar safety profile as described in adults.

No dosage adjustment is required for patients with mild or moderately impaired renal or hepatic function. No data is available for patients with severe renal or hepatic impairment.

Evolocumab was investigated in four double-blind, placebo-controlled trials, of which three lasted 12 weeks and the fourth lasted 52 weeks. A total of 813 patients were included, all of which received maximally tolerated doses of statin, with or without other lipid-modifying therapies (LMTs). Each of the studies was designed differently in terms of dose and patient population investigated. The mean LDL percent change ranged from –31 percent to –71 percent at study

completion, with the least percent change noted in the HoFH trial.

Counseling Patients on Alirocumab or Evolocumab

When counseling patients on the use of either of these agents, it is important to offer guidance on proper subcutaneous injection technique, including aseptic technique. Praluent is available as a single-dose pre-filled pen (75 mg/mL or 150 mg/mL) or single-dose pre-filled syringe (75 mg/mL or 150 mg/mL). Repatha is available as a 140 mg/mL single-use pre-filled syringe or pre-filled SureClick® autoinjector.

Both products should be stored in the refrigerator. Alirocumab must be maintained in the outer carton to protect it from light until the dose is required. Prior to administration, advise the patient to allow each product to warm to room temperature (30 to 40 minutes) and to inspect it for particulate matter and discoloration. Solutions that contain visible particulate matter or discoloration should not be used. The time out of refrigerator should not exceed 24 hours at 77 F° for alirocumab. If desired, evolocumab may be kept at room temperature in the original carton for up to 30 days. Both products should be administered into the thigh, abdomen, or upper arm, and should not be co-administered with other injectable drugs at the same injection site. Advise patients to rotate injection sites with each injection and to not inject in skin areas with active skin disease or injury or that are bruised, indurated, or inflamed. Table 3 summarizes key prescribing and counseling points for the two agents.

Summary

Adherence to healthy lifestyle behaviors, control of blood pressure and diabetes, and avoidance of smoking are recommended for all adults. Statin therapy should be used to reduce ASCVD risk in individuals who have a clear net benefit with the recommended intensity level (or highest that the patient can tolerate). Five of the seven statins marketed in the United States, including a high-intensity statin, are available as low-cost generics. Pharmacists can help patients understand the role statin therapy can have in reducing their risk of primary and secondary ASCVD. Counseling patients on drug-drug interactions and myalgias may improve compliance and tolerability.

Recently approved PSCK9 inhibitors, Praluent and Repatha, now offer a powerful and synergistic method of lowering LDL in patients for whom it is indicated. Pharmacists can help patients understand that these agents have been associated with significant reductions in LDL. While the available data appears promising, long-term data regarding their impact on cardiovascular health has not been defined. Because these agents were approved by FDA following the release of the 2013 AHA/ACC guidelines, they are not included in the review. At the time of publication, pricing for these products was estimated at roughly $14,000 per year.

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Release date: 2-15-16
Expiration date: 2-15-19
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Update on Cholesterol Treatment and Two New Drugs: Praluent and Repatha

1. What percentage of American adults have high LDL?
   a. 33.5 percent c. 40.5 percent
   b. 50.5 percent d. 60.5 percent

2. Clinical ASCVD is defined as all of the following EXCEPT:
   a. hypertension.
   b. acute coronary syndrome or history of myocardial infarction.
   c. stroke.
   d. coronary or arterial revascularization.

3. Patients aged 20-79 years, without ASCVD, should be assessed for traditional risk factors:
   a. every year. c. every 4-6 years.
   b. every other year. d. every 10 years.

4. Which of the following drugs is too potent to be used for low-intensity statin dosing?
   a. Simvastatin c. Atorvastatin
   b. Pravastatin d. Pitavastatin

5. All of the following are true about high-intensity statin therapy EXCEPT:
   a. it is recommended for adults >75 years who have clinical ASCVD.
   b. it is recommended for adults ≤75 years who have clinical ASCVD and no safety concerns.
   c. atorvastatin 40 to 80 mg is recommended.
   d. rosuvastatin 20-40 mg is recommended.

6. Monitoring of hepatic function with ALT levels is recommended:
   a. at baseline only and repeated if hepatotoxicity symptoms occur.
   b. at baseline, then every 3-12 months thereafter.
   c. at baseline, then annually.

7. If muscle symptoms occur, the statin may be discontinued until symptoms resolve, and then the patient may be rechallenged with the same or lower dose.
   a. True b. False

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]	[d]	6.	[a]	[b]	[c]		11.	[a]	[b]	[c]	[d]
2.	[a]	[b]	[c]	[d]	7.	[a]	[b]			12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	8.	[a]	[b]	[c]		13.	[a]	[b]		
4.	[a]	[b]	[c]	[d]	9.	[a]	[b]	[c]		14.	[a]	[b]	[c]	[d]
5.	[a]	[b]	[c]	[d]	10.	[a]	[b]	[c]	[d]	15.	[a]	[b]		

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8. PCSK9 inhibition leads to:
   a. increased number of LDL receptors on the hepatocyte resulting in decreased clearance of LDL from the blood.
   b. decreased number of LDL receptors on the hepatocyte resulting in increased clearance of LDL from the blood.
   c. increased number of LDL receptors on the hepatocyte resulting in an increased clearance of LDL from the blood.

9. The two new PCSK9 inhibitors recently approved are both:
   a. enzymes. c. human monoclonal antibodies.
   b. inactive vaccines.

10. The starting dose for alirocumab is:
   a. 150 mg SC every 2 weeks. c. 420 mg SC once monthly.
   b. 140 mg SC every 2 weeks. d. 75 mg SC every 2 weeks.

11. The most commonly occurring adverse reaction for alirocumab leading to treatment discontinuation is:
   a. nasopharyngitis. c. allergic reaction.
   b. influenza. d. back pain.

12. The starting dose for evolocumab when treating patients with homozygous familial hypercholesterolemia is:
   a. 140 mg SC every 2 weeks. c. 150 mg SC once monthly.
   b. 150 mg SC every 2 weeks. d. 420 mg SC once monthly.

13. Dosage adjustments are required for evolocumab for patients with mild or mildly impaired renal or hepatic function.
   a. True b. False

14. All of the following are important counseling points for both PCSK9 inhibitors EXCEPT:
   a. inject SC into thigh, abdomen, or upper arm.
   b. they may be administered IM.
   c. allow the solution to warm to room temperature before injection.
   d. syringes are for single-dose only.

15. Which of the following can be stored at room temperature for up to 30 days prior to use?
   a. Alirocumab b. Evolocumab

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