Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

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Cholesterol is a fat-like substance our body needs to build cell membranes, make certain hormones and produce substances that aid in the digestion of fat. Two kinds of lipoproteins carry cholesterol throughout your body: low-density lipoproteins (LDL) and high-density lipoproteins (HDL). LDL cholesterol typically makes up 60-70 percent of the total serum cholesterol in our body and is the primary target of therapy. A high LDL level leads to a buildup of cholesterol in arteries.

Hyperlipidemia occurs when your blood has too many lipids (or fats), such as cholesterol and triglycerides. Hypercholesterolemia means there is too much LDL (bad) cholesterol in your blood, and that increases your risk of developing atherosclerosis, coronary heart disease, stroke, and peripheral vascular disease. LDL-cholesterol levels of <100 mg/dL are considered optimal. At near optimal levels, 100-129 mg/dL, atherogenesis, the formation of abnormal fatty or lipid masses in arterial walls, occurs. At borderline high levels, 130-159 mg/dL, atherogenesis proceeds at a significant rate. At high levels, 160-189 mg/dL, and very high levels, ≥190 mg/dL, atherogenesis is accelerated.

Two main factors causing hyperlipidemia are lifestyle and genetic predispositions. An inherited condition called familial hypercholesterolemia (FH) causes very high LDL cholesterol.

Table 1. Most Commonly Encountered Secondary Causes of Hyperlipidemia in Clinical Practice

| Secondary Cause                  | Elevated LDL-C                                                                 | Elevated Triglycerides                                                                 |
|---------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Diet**                        | Foods high in saturated or trans fats, increased body fat, anorexia            | Increased body fat, very low-fat diet, high intake of refined carbohydrates, excessive alcohol consumption |
| **Drugs**                       | Diuretics, cyclosporine, glucocorticoids, amiodarone                          | Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxefine, tamoxifen, beta-blockers (not carvedilol), thiazide diuretics, atypical antipsychotics |
| **Diseases**                    | Biliary obstruction, nephrotic syndrome, chronic kidney disease               | Nephrotic syndrome, chronic kidney disease, lipodystrophies, acute pancreatitis         |
| **Disorders and altered states of metabolism** | Hypothyroidism, obesity, pregnancy                                           | Inadequately controlled diabetes mellitus, hypothyroidism, obesity, pregnancy          |

Abbreviations: LDL-C: low-density lipoprotein cholesterol
Treatment

Guidelines for the management of hyperlipidemia to reduce atherosclerotic cardiovascular risk in adults have been developed by multiple medical societies, including the American College of Cardiology and the American Heart Association (ACC/AHA), American Association of Clinical Endocrinologists and American College of Endocrinology (AACE), the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), U.S. Preventive Services Task Force (USPSTF), and the National Lipid Association (NLA). This manuscript will focus on the 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, and the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines on the Management of Blood Cholesterol. The biggest changes from the 2013 to the 2018 ACC/AHA Guidelines are more detailed risk assessments and new cholesterol-lowering drug options for people at the highest risk for cardiovascular disease.4,6

Healthy diet or lifestyle modification is critical in health promotion and atherosclerotic cardiovascular disease (ASCVD) risk reduction both prior to and in coordination with cholesterol-lowering drug therapies. Interventions include adhering to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight.6

Statins are the preferred therapy for most patients requiring treatment of hypercholesterolemia, according to the 2013 and 2018 ACC/AHA cholesterol guidelines. Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors (alirocumab and evolocumab).4,6

Primary Prevention

Primary prevention refers to delaying or preventing the onset of ASCVD. Clinical ASCVD is defined as having either acute coronary syndrome, 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.4

Evaluation for primary prevention of ASCVD should include a review of major risk factors (Figure X). Elevated serum cholesterol, usually identified clinically as measured LDL-C, is a major ASCVD risk factor. Drug therapy is only needed in selected patients with moderately high LDL-C levels (≥160 mg/dL) or patients with very high LDL-C levels (≥190 mg/dL). Three major higher risk categories are patients with:

- Severe hypercholesterolemia (LDL-C levels ≥190 mg/dL)
- Adults with diabetes
- Adults 40 to 75 years of age

Those with severe hypercholesterolemia and adults aged 40-75 with diabetes mellitus are recommended for immediate statin therapy without a further risk assessment. In other adults aged 40-75, 10-year ASCVD risk guides therapy.5

In addition to these traditional risk factors, the 2018 ACC/AHA Guidelines suggest looking at “risk-enhancing factors” (Table 2) to favor initiation or intensification of statin therapy. Guidelines also recommend measuring the coronary artery calcium (CAC) score when risk is uncertain in order to refine risk assessment. A CAC score predicts ASCVD events in a graded fashion and is independent of other risk factor (e.g., age, sex, ethnicity). Patients >75 years of age are recommended to engage in a clinician/patient risk discussion for deciding whether to continue or initiate statin treatment.6

Table 2. Risk-Enhancing Factors for Clinician – Patient Risk Discussion6

| ASCVD Risk-Enhancing Factors |
|-------------------------------|
| **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) |
| **Primary hypercholesterolemia** (LDL-C 160–189 mg/dL; non-HDL-C 190–219 mg/dL) |
| **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes diagnosis) |
| **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m2 with or without albuminuria; not treated with dialysis or kidney transplantation) |
| **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS |
| **History of premature menopause (before age 40 y) and history of pregnancy associated conditions that increase later ASCVD risk such as preeclampsia** |
| **High-risk race/ethnicities** (e.g., South Asian ancestry) |

**Lipid/biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL)

**In selected individuals if measured:**
- Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
- Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a)
- Elevated apo B ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
- **ABI** <0.9
In order to estimate 10-year ASCVD risk (defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke), it is recommended to use the Pooled Cohort Risk Assessment Equations CV Calculator (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk). Initial evaluation prior to statin initiation should include a fasting lipid panel, alanine aminotransferase (ALT), creatinine kinase, and hemoglobin A1C in those without clinical ASCVD (if diabetes status unknown). Evaluation for other secondary causes should be considered (see Table 1).

Patients with severe hypercholesterolemia (LDL-C >190 mg/dL) have a high lifetime risk and do not require ASCVD risk scoring. In patients 20 to 75 years of age with severe hypercholesterolemia, maximally tolerated statin therapy is recommended. In these patients who achieve less than a 50 percent reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. In patients that have fasting triglycerides ≤300 mg/dL while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.

| Drug Name and Dose | Average LDL-C Reduction (%) | Relative CV Risk Reduction (p-value) | Study |
|--------------------|----------------------------|------------------------------------|-------|
| **High-Intensity Statin Therapy** |
| Atorvastatin 40-80 mg | ≥50 | | |
| Rosuvastatin 20-40 mg | 44% (<0.00001) | JUPITER |
| **Moderate-Intensity Statin Therapy** |
| Atorvastatin 10-20 mg | 36% (0.0005) | ASCOT-LLA |
| Rosuvastatin 5-10 mg | 24% (not reported) | HOPE-3 |
| Simvastatin 20-40 mg | 34% (0.00001) | 4S |
| Pravastatin 40-80 mg | 31% (<0.001) | WOSCOPS |
| Lovastatin 40 mg | 37% (<0.001) | AFCAPS/TexCAPS |
| Fluvastatin XL 80 mg | 22% (0.01) | LIPS |
| Fluvastatin 40 mg bid | | |
| **Low-Intensity Statin Therapy** |
| Simvastatin 10 mg | <30 | 33% (0.01) | MEGA |
| Pravastatin 10-20 mg | | 37% (<0.001) | AFCAPS/TexCAPS |
| Lovastatin 20 mg | | |
| Fluvastatin 20-40 mg | | |
| Pitavastatin 1 mg | | |
Figure 1. Primary Prevention (2018)
Adapted from Grundy SM, et al.

**Primary Prevention:**
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- LDL-C levels > 190 mg/dL
  No risk assessment
- Diabetes mellitus and age 40-75 y
  Moderate-intensity statin
- Age > 75 y
  Clinical assessment, risk discussions
- Risk assessment to consider high-intensity statin

**Age 0-19 y**
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of FH initiate statin

- <5% "Low Risk"
  Risk discussion: Emphasize lifestyle risk factors
- 5% - <7.5% "Borderline Risk"
  Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity therapy
- >7.5% - <20% "Intermediate Risk"
  Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
- >20% "High Risk"
  Risk discussion: Initiate statin to reduce LDL-C ≥ 50%

**Age 20-39 y**
Consider statin if family history of premature ASCVD and LDL-C ≥ 160 mg/dL

**Age 40-75 y and LDL-C > 70-<190 mg/dL w/o diabetes mellitus**
10-year ASCVD risk % begins risk discussion

Abbreviations: ASCVD- atherosclerotic cardiovascular disease; LDL-C- low-density lipoprotein cholesterol; FH- familial hypercholesterolemia
Statins are listed as pregnancy category X and therefore should not be used in women of childbearing age unless these women are using effective contraception and not nursing. The potential for ASCVD risk reduction benefit, adverse effects, and drug-drug interactions along with other cautions and contraindications to statin therapy and choice of statin dose must be considered by the treating clinician.⁴

### Table 4. Differentiated Statin Therapy¹⁷-²⁰

| Statin Therapy | Adverse Reactions                                                                 | Prescribing Considerations                                                                                     | AWP (30-day supply)* |
|----------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------|
| **Atorvastatin** | Diarrhea (up to 14.1%), Arthralgia (up to 11.7%), Myalgia (up to 8.4%), Urinary tract infectious disease (up to 8%), Nasopharyngitis (8.3%), Pain, In extremity (up to 9.3%) | • Preferred in those with severe renal impairment  
• Metabolized by CYP3A4 | $59 |
| **Rosuvastatin** | Abdominal pain (2.4%), Nausea (Up to 6.3%), Myalgia (1.9% to 12.7%), Asthenia (0.9% to 4.7%), Headache (3.1% to 8.5%) | | $268 |
| **Simvastatin** | Abdominal pain (7.3%), Constipation (6.6%), Nausea (5.4%), Headache (2.5% to 7.4%), Upper respiratory infection (9%) | • Prodrug  
• Dose reduction should be considered in patients with severe renal impairment  
• Metabolized by CYP3A4  
• Administer in the evening | $147 |
| **Pravastatin** | Rash (1.2% to 7.2%), Diarrhea (4.7% to 8.5%), Nausea and vomiting (4% to 10.5%), Musculo-skeletal pain (3.9% to 24.9%), Headache (3.5% to 7.5%), Cough (1.2% to 8.2%), Rhinitis (1.2% to 7%), Upper respiratory infection (4.1% to 21.2%) | • Preferred in those with chronic liver disease  
• Dose reduction should be considered in patients with moderate to severe renal impairment  
• Causes less insomnia  
• Not metabolized by the cytochrome P450 enzymatic pathway, therefore have a low chance for drug interactions | $144 |
Monitoring Statin Therapy

An initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C) followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy should be completed to determine adherence and assess response to therapy. Thereafter, assessments should be done every 3 to 12 months as clinically indicated. A baseline serum creatinine kinase level and aminotransferase levels may be useful for reference purposes prior to starting statin therapy, but routine monitoring is not recommended. Although muscle-related side effects may occur while on a statin therapy, many patients will be able to tolerate the same statin or a different statin when restarting. To determine true statin intolerance, most experts recommend that patients are documented to have unacceptable muscle-related symptoms that resolve with discontinuation of therapy and occur after re-challenging on at least 2 to 3 statins.

LDL-C lowering has been shown to reduce the risk of cardiovascular disease events. The amount of LDL-C lowering achieved as a percentage of baseline with statins is directly related to the amount of ASCVD risk reduction. Updated 2018 AHA/ACC Guidelines define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. Generally, a lowering of LDL-C levels of 1% gives an approximate 1% reduction in the risk of ASCVD.

### Table: Adverse Reactions and Prescribing Considerations for Statins

| Statin Therapy | Adverse Reactions | Prescribing Considerations | AWP (30-day supply)* |
|----------------|-------------------|----------------------------|----------------------|
| Lovastatin     | Abdominal pain (up to 2.5%), Constipation (up to 3.5%), Arthralgia (5% to 6%) | • Prodrug  
• Dose reduction should be considered in patients with severe renal impairment  
• Metabolized by CYP3A4  
• Food increases bioavailability | $50 |
| Fluvastatin    | Indigestion (3.5% to 7.9%), Nausea (2.5% to 3.2%), Headache (4.7% to 8.9%) | • Preferred in those with severe renal impairment  
• Metabolized by the CYP2C9 isoenzyme  
• Causes less insomnia | $252 |
| Pitavastatin   | Headache (2%), Constipation (4%), Diarrhea (3%), Back pain (4%), Myalgia (2% to 3%) | • Brand name only  
• Not metabolized by the cytochrome P450 enzymatic pathway, therefore have a low chance for drug interactions  
• Marginally metabolized by CYP2C9 isoenzyme  
• Taken any part of the day, with or without food  
• Lower dose required for renal impairment | $309.90 |

* For lowest effective dose

Abbreviations: AWP- Average wholesale price; CYP3A4- Cytochrome P450 3A4; CYP2C9- Cytochrome P450 2C9
Secondary ASCVD Prevention

In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%. Patients may need additional non-statin medications (ezetimibe, bile acid sequestrants, PCSK9 inhibitors) in combination with statin therapy under certain circumstances.\(^6\)

Table 5. Defining Very High Risk of Future ASCVD Events\(^6\)

| **Major ASCVD Events** | **High-Risk Conditions** |
|------------------------|--------------------------|
| Recent ACS (within the past 12 months) | Age ≥ 65 y |
| History of MI (other than recent ACS listed above) | Heterozygous FH |
| History of ischemic stroke | History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) |
| Symptomatic peripheral arterial disease (history of claudication with amputation) | 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 |

Abbreviations: ASCVD- atherosclerotic cardiovascular disease; ACS- acute coronary syndrome; MI- myocardial infarction; FH- familial hypercholesterolemia; CKD- chronic kidney disease; eGFR- estimated glomerular filtration; LDL-C- low-density lipoprotein cholesterol; HF- heart failure

If LDL-C levels remain ≥70 mg/dL on maximally tolerated statin therapy, adding ezetimibe may be reasonable. In very high-risk patients (Table 5) with multiple high-risk clinical factors, ezetimibe can be added to maximally tolerated statin therapy. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. If LDL-C levels remain ≥70 mg/dL, adding a PCSK9 inhibitor is reasonable if the cost-benefit ratio is favorable. Potential benefits versus adverse effects of statin therapy should be considered in patients >75 years of age with clinical ASCVD. In patients with HF due to ischemic heart disease, moderate-intensity statins may be considered.\(^6\)
Figure 2. Secondary Prevention in Patients with Clinical ASCVD

*Adapted from Grundy SM, et al.

Clinical ASCVD

ASCVD not at very high-risk

Age ≤ 75 y

High-intensity statin (moderate-intensity if not tolerated)

Goal: ↓ LDL-C ≥50%

If on maximal statin therapy and LDL-C ≥70 mg/dL, adding ezetimibe may be reasonable

ASCVD not at very high-risk

Age > 75 y

Initiation or continuation of moderate- or high-intensity statin is reasonable

If on maximal statin and LDL-C ≥70 mg/dL, adding ezetimibe is reasonable

High-intensity or maximal statin

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL, or non-HDL-C ≥100 mg/dL, adding a PCSK9-I is reasonable

*Less cost-effective

Abbreviations: ASCVD- atherosclerotic cardiovascular disease; LDL-C- low-density lipoprotein cholesterol; PCSK9-I – PCSk9-inhibitor
### Table 6: Differentiated Non-Statin Drug Therapy

| **Adverse Effects** | **CV Outcomes Trials** | **Prescribing Considerations** | **AWP (30-day supply)** |
|---------------------|------------------------|-------------------------------|-------------------------|
| **Ezetimibe**       |                        |                               |                         |
| Diarrhea (2.5% to 4.1%), Arthralgia (2.6% to 3%), Myalgia (3.2%), Nasopharyngitis (3.7%), Sinusitis (2.8%), Upper respiratory infection (2.9% to 4.3%) | IMPROVE-IT: Addition to moderate-intensity statin in patients with recent ACS resulted in incremental lowering of LDL-C and reduced primary composite endpoint of CV death, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke. | Generally well tolerated, taken orally with or without food, generic available. | $377 |
| **Alirocumab**      |                        |                               |                         |
| Injection site reaction (7.2% to 16.6%), Nasopharyngitis (11.3%), Influenza (5.7%), allergic reaction (8.6%) | ODYSSEY Outcomes: Demonstrated that addition of alirocumab reduced the primary endpoint of time to first occurrence of either CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke or hospitalization for unstable angina. | Cost, SQ administration, robust LDL-C reduction, burdensome prior authorization process. | $1,344 |
| **Evolocumab**      |                        |                               |                         |
| Injection site reaction, Influenza (7.5% to 9.1%), Nasopharyngitis (6.1% to 10.5%), Upper respiratory infection (9.1% to 9.3%), back pain | FOURIER: Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization or hospitalization for unstable angina. | Cost, SQ administration, robust LDL-C reduction, burdensome prior authorization process. | $1,953 |
| **Bile Acid Sequestrants** |                       |                               |                         |
| Colesevelam: Constipation (3.4% to 11%), Indigestion (2.8% to 8.3%), Nausea (2.6% to 4.2%), Nasopharyngitis (4.1% to 6.2%) Cholestyramine: Abdominal discomfort, Constipation, Flatulence, Nausea and vomiting Colestipol: Constipation (10%), Vomiting (5%) | CV outcomes data not available | Pill burden, GI side effects, exacerbation of hypertriglyceridemia, CV outcomes data not available | Cholestyramine: $42 |

*Pricing is based on AWP Unit Price of all generic/brand (B) formulations available for a 30-day supply of initial daily dose

**Abbreviations:** CV- cardiovascular; AWP- Average wholesale price; ACS- acute coronary syndrome; LDL-C- low-density lipoprotein cholesterol; MI- myocardial infarction; SQ- subcutaneous; GI- gastrointestinal
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References

1. National Institutes of Health. Hypercholesterolemia. September 25, 2018. https://ghr.nlm.nih.gov/condition/hypercholesterolemia#synonyms. Accessed October 1, 2018.

2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-3421.

3. American Heart Association. Prevention and Treatment of High Cholesterol (Hyperlipidemia). 2018. http://www.heart.org/en/health-topics/cholesterol/prevention-and-treatment-of-high-cholesterol-hyperlipidemia. Accessed October 1, 2018.

4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-2934.

5. Rosenson R. Secondary causes of dyslipidemia. In: Saperia G, ed. UpToDate. Waltham, Mass.: UpToDate, 2018. Accessed May 25, 2018.

6. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASP/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. Circulation. 2018 Nov 10:CIR00000000000000624. doi: 10.1161/CIR.00000000000000624.

7. ASCVD Risk Calculator. American Heart Association. https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp. Published 2018. Accessed October 1, 2018.

8. Cholesterol Treatment Trials’ (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 17,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681.

9. Hsia J, MacFadyen JG, Monyak J, et al. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57:1666-1675.

10. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Swedish Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Drugs. 2004;64 Suppl 2:43-60.

11. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016;374(21):2021-2031.

12. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation. 1998;97(15):1453-1460.

13. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-1307.

14. Downs JR, Cleftield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615-1622.

15. Serruys PWJC, de Feyter P, Macaya C, et al. Fluvasatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;287(24):3215-3222.

16. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155-1163.

17. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. http://www.micromedexsolutions.com. Accessed 2017 April 25.

18. Jones P, Kafonek S, Laurora I, Hunninghade D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvasatin in patients with hypercholesterolemia (the CURVES study). Am J Cardiol. 1998;81(5):582-587.

19. Rosenson R, Statins: Actions, side effects, and administration. In: Saperia G, ed. UpToDate. Waltham, Mass.: UpToDate, 2018. Accessed May 25, 2018.

20. Red Book Online. Micromedex. www.micromedexsolutions.com. Accessed February 24, 2017.

21. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-2397.

22. Schwartz GG, Szarek M, Bhatt DL, et al. The ODYSSEY OUTCOMES Trial: Topline Results: Alirocumab in Patients After Acute Coronary Syndrome. Presented at: American College of Cardiology Annual Scientific Session; March 10, 2018; Orlando, FL.

23. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722.

24. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePolma SM, Minihan MB, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2017 Oct 3;70(14):1785-1822. doi: 10.1016/j.jacc.2017.07.745.