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PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9) INHIBITOR ANTIBODIES

PRALUENT™ (alirocumab)
REPATHA (evolocumab)

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Introduction

In July 2015, the FDA approved Praluent™ (alirocumab); the first drug in a new class called the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor(s).[1] In August 2015, the FDA approved another drug in this class; Repatha (evolocumab).[2] These drugs are indicated as an adjunct to maximally tolerated statin therapy in adults with (1) heterozygous familial hypercholesterolemia (HeFH) or (2) clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). (3) Repatha (evolocumab) is also indicated in homozygous familial hypercholesterolemia (HoFH).[1,2]

Shrank et al. raised important questions in a recently published viewpoint/opinion in JAMA[3]:

- "Will clinicians interpret the guidelines to indicate that the highest-risk patients should be prescribed PCSK-9 inhibitors?"[3]
- "Perhaps most concerning from a social cost point of view, will relatively low-risk patients be considered for PCSK-9 inhibitors?"[3]

The authors also comment that "there is likely to be substantial enthusiasm about this class of drugs in the marketplace."[3]

The purpose of this review is to ensure appropriate use of the PCSK9 inhibitors in terms of approved doses and use in patient populations in which alirocumab and evolocumab have been shown to be cost-effective and safe.

Background

The definitive association between elevated levels of low-density lipoprotein (LDL) and the risk of cardiovascular disease has been confirmed in many studies.[4] Elevated LDL-C is a common condition affecting more than 73 million adults (32%) in the United States (US).[3,5] Cardiovascular disease is the leading cause of death in the US (1 out of 7 deaths) and approximately one third of American adults have CVD.[5-7]

Hyperlipidemia can be classified as:

A. Primary: Also known as genetic or familial hyperlipidemia, or
B. Secondary: When it is caused by factors other than genetics e.g. age, diabetes mellitus, hypothyroidism, Cushing's syndrome, chronic kidney disease, cholestatic disorders, or medications (these could include HIV protease inhibitors, atypical antipsychotics, corticosteroids, isotretinoin, beta-blockers, thiazide diuretics, azole antifungals, cyclosporine, tacrolimus, or some oral contraceptives).[4]

Familial hypercholesterolemias (FH)

Familial hypercholesterolemias (FH) are a group of genetic defects characterized by high levels of LDL which leads to a higher risk for cardiovascular disease (CVD).[8,9] FH is caused by a defect on chromosome 19 (condition begins at birth) and the mutations prevent removal of low density lipoprotein (LDL, or "bad") cholesterol from the blood, which can cause heart attacks at an early age.[8] The guidance from the National Lipid Association states that FH has historically referred specifically to LDL receptor defects, but defects in the genes for apolipoprotein (Apo) B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and possibly others have also caused severe hypercholesterolemia.[9]

According to the guidance from the National Lipid Association (2011), there are approximately 620,000 FH patients currently living in the US.[9] Diagnosis of familial hypercholesterolemia is based on physical examination, family and personal medical history, and laboratory testing. Symptoms of FH may include fatty

skin deposits (xanthomas over parts of the hands, elbows, knees, ankles, and around the cornea of the eye), cholesterol deposits (xanthelasmas in the eyelids), and signs of coronary artery disease such as chest pain.[8]

FH can be further classified as homozygous or heterozygous FH.

A. Heterozygous FH (HeFH)
   Patients who have one abnormal copy of the gene (inherited the gene mutation from one parent; heterozygous) have baseline LDL-C levels ranging from 190 to 250 mg/dl (when left untreated levels are typically 200-400 mg/dL which is 2-3 times higher compared with healthy individuals[10]) and may have premature cardiovascular disease at the age of 30 to 50.[10-12]
B. Homozygous FH (HoFH)
   Patients with two abnormal copies (inherited the gene mutation from both parents; homozygous) have baseline LDL-C levels greater than 300 mg/dl (when left untreated levels are typically >600 mg/dL which is 6-10 times higher compared with healthy individuals[10]) and may have severe cardiovascular disease in childhood (mean age at the time of diagnosis of CVD is 20 years[10]).[11,12]

Heterozygous FH (one abnormal copy of gene) is a common genetic disorder that occurs in 1 in 500 people in most countries (may be as high as 1 in 100 in some populations e.g. French Canadians or Dutch Afrikaners due to the founder effect), whereas homozygous FH is much rarer and occurs in 1 in one million births.[10,11,13] According to Joshua Knowles, MD, PhD, the Chief Medical Officer for the Familial Hypercholesterolemia Foundation (the FHF), the exact figure for prevalence of familial hypercholesterolemia in the United States is unknown and there is emerging data that FH is actually more common than the 1 in 500 (perhaps 1 in 200) and it is commonly quoted that less than 10% of familial hypercholesterolemia patients are diagnosed in the US, but it is possible that as little as 1% to 2% are diagnosed.[14] A National registry, CASCADE FH (CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia), was launched in September 2013 to collect current, real-world data on prevalence and treatment of FH.[15]

Researchers and authorities are faced with many challenges when evaluating new drugs for rare diseases such as homozygous FH and a particular pitfall is the small patient numbers limiting the potential for quantifying clinical outcomes.[16] The treatment goal for patients with FH is reduction of atherosclerotic heart disease risk by aiming for a 50% reduction in LDL through lifestyle changes and pharmacotherapy.[8,9,17] Patients who inherited only one copy of the defective gene (heterozygous FH) may respond well to diet changes combined with statin drugs while those who inherited two copies (homozygous FH) of the defective gene often do not respond well to conventional lipid-lowering drugs due to the genetically impaired LDL receptor functionality (drugs work by upregulating these receptors in the liver). These patients are at increased risk for early heart attacks and are often resistant to treatment.[8] Some patients with receptor-defective HoFH who have some residual LDL receptor activity could benefit from modest reduction in LDL-C with maximal conventional therapy.[18]

Congress passed the Orphan Drug Act in 1983 for rare diseases, because it was not financially viable for pharmaceutical companies to develop treatment options. The legislation created several incentives for pharmaceutical companies to develop drugs for rare diseases ("tax incentives totaling half the development cost, clinical research and development subsides, fast-track development and approval, and enhanced patent protection and marketing rights").[19] "In 2013, the FDA granted evolocumab an orphan drug designation for HoFH."[20]

Clinical atherosclerotic cardiovascular disease (CVD)

As mentioned above, the PCSK9 inhibitors are also indicated as adjunct therapy in patients with clinical atherosclerotic cardiovascular disease (CVD) on maximally tolerated statin therapy who require additional lowering of LDL-C. Clinical ASCVD is defined as acute coronary syndrome, a history of myocardial infarction

(MI), stable or unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, or atherosclerotic peripheral arterial disease.[4,21]

Methodology

The Agency for Healthcare Research and Quality (AHRQ; www.guideline.gov), Cochrane Library, the FDA website (including product labeling information), PubMed, UpToDate, Micromedex, Lexicomp, the National Lipid Association website, the FH foundation website, the Institute for Clinical and Economic Review (ICER) website, Continuing education websites[22-25], and the National Institute for Health and Clinical Excellence (NICE) website, were searched for systematic reviews, clinical trials, guidelines, other reports, reviews, efficacy and safety information. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials.

Treatment options

Appendix 1 contains summary tables of the PCSK9 Inhibitors.

Reduction in cardiovascular events

Statins remain first-line pharmacotherapy for cholesterol reduction and the mainstay of therapy for FH. In clinical trials with statins, significant reductions in major vascular events, including death, myocardial infarction, stroke, and coronary revascularization have been reported, whereas studies of other drugs including niacin, hormone therapy (estrogen plus progestin), torcetrapib, and dalcetrapib, have shown that these did not decrease cardiovascular events.[6,26-34] Torcetrapib and dalcetrapid are cholesteryl ester transfer protein (CETP) inhibitors. Development of torcetrapib was suspended (in 2006) because data showed an increased risk of mortality and cardiovascular events (safety concerns were reported).[28] The development of dalcetrapib was terminated (in 2012) after its Phase III dal-OUTCOMES trial in acute coronary syndrome patients failed to demonstrate a significant reduction in cardiovascular adverse events (no safety concerns were reported).[32,33] According to a joint statement by the European Society of Cardiology (ESC), International Atherosclerosis Society (IAS), and the NLA on CETP Inhibition and HDL, "Several other CETP inhibitors that raise HDL-cholesterol levels to a greater extent than dalcetrapib and also significantly lower LDL cholesterol and novel HDL-raising agents remain under development by both major pharmaceutical manufacturers and biotechnology companies."[32]

In a recent publication (Cannon et al. June 3, 2015. NEJM[35]), of the anticipated final results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), it was reported that a significant reduction in cardiovascular rates was reported in a study of ezetimibe added to simvastatin.[7,35] The National Lipid Association (NLA) issued a statement on the IMPROVE-IT Study Findings: "Results Support the NLA Recommendations that Lower Is Better. The findings are consistent with the NLA's Part 1 Recommendations that treatments associated with lower concentrations of atherogenic lipoproteins are associated with lower ASCVD risk. The data suggest a benefit from additional non-statin therapy to treat to goals for LDL and non-HDL cholesterol, as recently advocated in NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report published in *the Journal of Clinical Lipidology* (JCL) on March 26, 2015."[36] The NLA reported "In the editorial "Proof that lower is better – LDL cholesterol and IMPROVE IT" by John A. Jarcho, MD, and John F. Keany, Jr., MD, that accompanied the article, the results of IMPROVE-IT were summarized"[36]: "In IMPROVE-IT, 18,144 patients who had an acute coronary syndrome were randomly assigned to either simvastatin (40 mg) plus ezetimibe (10 mg) or to simvastatin (40 mg) plus placebo. At 1 year, the mean LDL cholesterol level was 53.2 mg per deciliter (1.4 mmol per liter) in the simvastatin-plus-

ezetimibe group, and 69.9 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group. The primary end point was a composite of cardiovascular death, major coronary event (nonfatal myocardial infarction, unstable angina, or coronary revascularization), or nonfatal stroke. At 7 years, the rate of the primary end point was significantly lower, by 2.0 percentage points, in the simvastatin-plus-ezetimibe group than in the simvastatin-monotherapy group (32.7% vs. 34.7%) [HR 0.936; CI 0.89 to 0.99; P=0.016]. No significant differences in rates of adverse events were seen between the two study groups."

Problem with Statins/Unmet Need

Some patients do not tolerate statins (approximately 10-20%) or have inadequate reductions in LDL-C.[6,7,26] Other lipid-lowering agents provide only modest LDL-C reduction.[7]

LDL Apheresis

LDL apheresis is sometimes considered in patients who do not respond to or are intolerant to drug therapy. This is an expensive treatment option. LDL-C is removed from the circulation by circulating a portion of the blood outside the body, passing it through a special adsorber column to remove the LDL cholesterol and then return the treated blood back to the patient (similar to dialysis, but the treatment involves placing two needles into your veins for removing the blood and returning the treated blood).[37]

Novel Agents: lomitapide and mipomersen

In May 2014, the Utah Medicaid DUR Board reviewed two orphan drugs indicated as adjunctive treatment of homozygous familial hypercholesterolemia (HoFH)[38,39]; lomitapide (Juxtapid) oral capsules (approved by FDA in December 2012; launched May 2013[40,41]) and mipomersen (Kynamro) subcutaneous injection (approved by the FDA in January 2013[42,43]). Lomitapide (Juxtapid); a microsomal triglyceride transfer protein (MTP) Inhibitor; is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including low-density lipoprotein (LDL) apheresis where available, to reduce LDL cholesterol, total cholesterol, apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)[41,44] Mipomersen (Kynamro); an apolipoprotein B antisense oligonucleotide; is indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).[43,45] Both medications have black box warnings, REMS, and Medication guides limiting their utility. The Utah Medicaid DUR Board did not place a prior authorization on lomitapide and mipomersen.[46]

Novel agents: PCSK9 Inhibitors

Praluent™ (alirocumab) and Repatha (evolocumab) are human monoclonal antibodies (alirocumab: IgG1 isotype; evolocumab: IgG2 isotype) that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). "PCSK9 binds to the low-density lipoprotein receptors (LDLR) on hepatocyte surfaces to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL; therefore, the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-cholesterol (LDL-C). By inhibiting the binding of PCSK9 to LDLR, alirocumab (or evolocumab) increase the number of LDLRs available to clear LDL, thereby lowering LDL-C levels."[47]

As mentioned in the introduction, these drugs are indicated as an adjunct to maximally tolerated statin therapy in adults with (1) heterozygous familial hypercholesterolemia (HeFH) or (2) clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).[1,2] (3) Repatha (evolocumab) is also indicated in homozygous familial hypercholesterolemia (HoFH).[2]

Other agents in this class include Bococizumab (PF0490615, RN316) in phase III development, and others in earlier development.[7]

Cost
The estimated annual cost of LDL apheresis ranges from $45,000 to $100,000.[10,48] Approximate annual wholesale costs of lomitapide (Juxtapid) and mipomersen (Kynamro) are $210,000-$350,000 per patient.[16] Approximate costs of Praluent™ (alirocumab) and Repatha (evolocumab) are $14,600 and $14,100 a year.[3,49] Interestingly, Repatha was launched at a much lower monthly cost of £340 in the UK (~$6,780 a year).[50] Cardiovascular events due to FH (primary hyperlipidemia) or secondary hyperlipidemia place a huge burden on the health care system related to both acute and long-term costs.[10,14,50-53] FH accounts for a sizable proportion of very early-onset cardiac events[14], and in HoFH the severity of hypercholesterolemia usually results in severe atherosclerosis and cardiovascular disease during childhood and adolescence.[9]

An important note is that these are long-term use, expensive agents that target a common condition and are not curative.[3] Statins are available generically with lower costs. Shrank et al. report that "The cost implications for payers and society could be extraordinary; if used broadly, PCSK-9 inhibitors would likely be the most costly class of medications marketed thus far."[3]

FDA Advisory Panels

"The FDA advisory panels noted the lack of outcomes data and the need for more broad evaluation to assess potential adverse effects of the PCSK-9 inhibitors; the panels suggested that use for those who do not have a diagnosis of familial hypercholesterolemia should be limited."[3]

Clinical Guidelines and related evidence

Familial Hypercholesterolemia (HoFH and HeFH)

The treatment goal for patients with FH is a 50% reduction in LDL through lifestyle changes and pharmacotherapy.[9] The goal for patients with FH with additional CHD risk factors (e.g. smoking, diabetes) is a LDL-C level <100 mg/dL.[17] The National Lipid Association (NLA) Expert Panel on Familial hypercholesterolemia and the National Institute for Health and Clinical Excellence guidelines consider statins the mainstay of treatment for FH.[9,51] These guidelines recommend a high-intensity statin (e.g. simvastatin, atorvastatin, or rosuvastatin[17,52]) titrated to the maximum recommended or tolerated dose in order to achieve a 50% LDL-C reduction from baseline. Some patients do not tolerate high-dose statin therapy because of muscle-related side-effects and/or elevated hepatic transaminases and would therefore need to consider low-dose statin therapy in combination with non-statin lipid-lowering treatments (e.g. bile acid sequestrants, ezetimibe, or niacin).[17] Ezetimibe, niacin, and colesevelam are indicated for intensified drug treatment as well as monotherapy in the case of contraindications to statin therapy[9].

Not all patients reach a 50% reduction of LDL with the approved pharmacotherapy alone even at maximum doses. The majority of patients with HoFH will not achieve sufficient reductions.[10] The National Lipid Association recommends LDL apheresis for patients without an adequate response to maximally tolerated drug therapy.[9] Neither of the above-mentioned guidelines recommend the use of lomitapide, mipomersen, or the PCSK9 inhibitors (alirocumab or evolocumab) because the guidelines have not be reviewed since these agents came to market.

The 2014 NLA recommendations for patient-centered management of dyslipidemia (Part 1) include a section on treatment of patients with severe hypercholesterolemia phenotype (LDL-C ≥190 mg/dL). Many of these patients have FH and it may not be possible to achieve goal levels of atherogenic cholesterol even with combination drug therapy resulting a recommendation for an alternative goal of lowering levels by at least

50% (similar to treatment goal above). PCSK9 inhibitors under investigation are mentioned as potential treatment but not currently approved (at that time). Mipomersen is mentioned as a treatment option that can reduce LDL-C by an additional 25% (when given in combination with maximum tolerated doses of lipid-lowering therapy) in HoFH, but the vast majority of patients still do not achieve recommended targets, and injection site reactions, hepatic fat, and liver enzyme elevations are common. Lomitapide is also mentioned as an option that can reduce LDL-C levels up to 50% in HoFH patients on maximum tolerated lipid-lowering therapy and LDL apheresis, but gastrointestinal side effects, elevations in liver enzymes and hepatic fat are common.[53]

The 2014 NLA guidelines (part 1) include criteria from the expert panel on FH of when LDL apheresis may be considered (selected patients with severe hypercholesterolemia). According to the FDA indication, "LDL apheresis is considered medically necessary when patients have failed diet and maximum drug therapy from at least 2 separate classes of hypolipidemic drugs for at least 6 months in addition to any 1 of the following criteria:

- HoFH with LDL-C ≥500 mg/dL
- HeFH with LDL-C ≥300 mg/dL
- Functional HeFH with LDL-C ≥200 mg/dL in patients with coronary artery disease."[53] (note the NLA criteria are more inclusive)

According to a recent review[10], the use of apheresis is limited by high cost ($45,000 to $100,000[48]), limited access (not everywhere available in the US), and the inconvenience of treatment (it involves considerable time commitment of 2-4 hours every 1-2 weeks because LDL-C levels rebound after the procedure[17,18], and it requires frequent repetitive intravenous (IV) access or creation of an arteriovenous fistula[18]).

The NLA guidance (FH) states that HoFH should always be managed by a lipid specialist.[9] The guidelines include guidance on screening and diagnosis.[9] An important part of the recommendations include cascade screening once an index case has been identified. Genetic or DNA testing is not required by the NLA guidelines as it is generally not needed but may be useful when diagnosis is uncertain.[9] It is important to note that some patients with clinically definite FH (about 20%) may have a negative genetic test.[9]

<u>Clinical atherosclerotic cardiovascular disease (CVD)</u>

The 2013 American College of Cardiology and the American Heart Association Prevention Guidelines (ACC/AHA) identified four groups of patients that would benefit from statin therapy including secondary prevention in patients with *clinical* ASCVD.[7,21]

1) Secondary prevention in patients with clinical ASCVD
    - Age ≤75: High intensity statin
    - Age >75: Moderate intensity statin

2) Primary prevention in patients with primary LDL-C ≥190 mg/dL
    - High intensity statin

3) Primary prevention in patients with type 1 or type 2 diabetes aged 40 to 75 years with an LDL-C 70-189 mg/dL without clinical ASCVD
    - Low risk (10-year risk <7.5%): Moderate intensity statin
    - High risk (10-year risk ≥7.5%): High intensity statin

4) Primary prevention in patients without diabetes with a 10-year ASCVD risk of ≥7.5% and age 40-75 years with an LDL-C 70-189 mg/dL

- Consider moderate or high intensity statin

Appendix 3 contains a table of statin intensity classification from the 2013 ACC/AHA guidelines.

Specific LDL-C target levels are not recommended in the current guidelines.
Prior guidelines (2001) (National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) guideline) recommended statin therapy to specified LDL-C target levels[34,54]:

- Individuals with cardiovascular disease and those with a 10-year risk ≥20%: <100 mg/dL
- Individuals with multiple risk factors and a 10-year risk <20%: <130 mg/dL

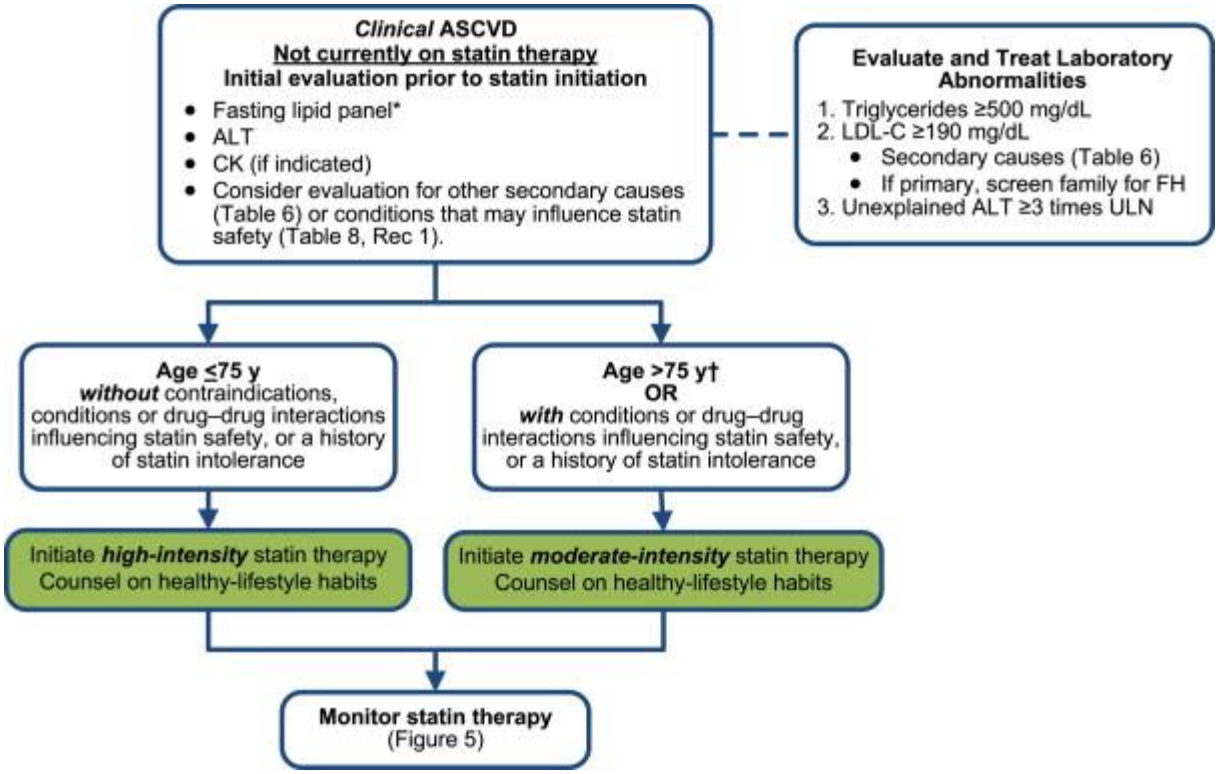

Figure 3. Initiating statin therapy in Individuals with clinical ASCVD – direct excerpt from the 2013 ACC/AHA Blood Cholesterol Guideline.[21]

"*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL could indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences, in initiating or continuing a moderate- or high-intensity statin in individuals with ASCVD who are >75 years of age.
ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and ULN, upper limit of normal."[21]

The PCSK9 inhibitors are indicated as adjunct therapy in patients with *clinical* ACVD on maximally tolerated statin therapy who require additional lowering of LDL-C. Clinical ASCVD is defined as acute coronary syndrome, a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, or atherosclerotic peripheral arterial disease.[4,21]

Adjunct therapy of statin with non-statin agents (e.g. bile acid sequestrants, nicotinic acid derivatives, fibric acid derivatives, ezetimibe, or omega-3 fatty acids) is not recommended per the 2013 ACC/AHA guidelines due to a lack of supporting evidence.[4]

Two main groups of patients with ACVD on maximally tolerated statin doses qualify for the addition of PCSK9 inhibitors to their therapy:

- **Lack of anticipated therapeutic response**
  It is important to assess medication and lifestyle adherence when evaluating lack of anticipated therapeutic response.

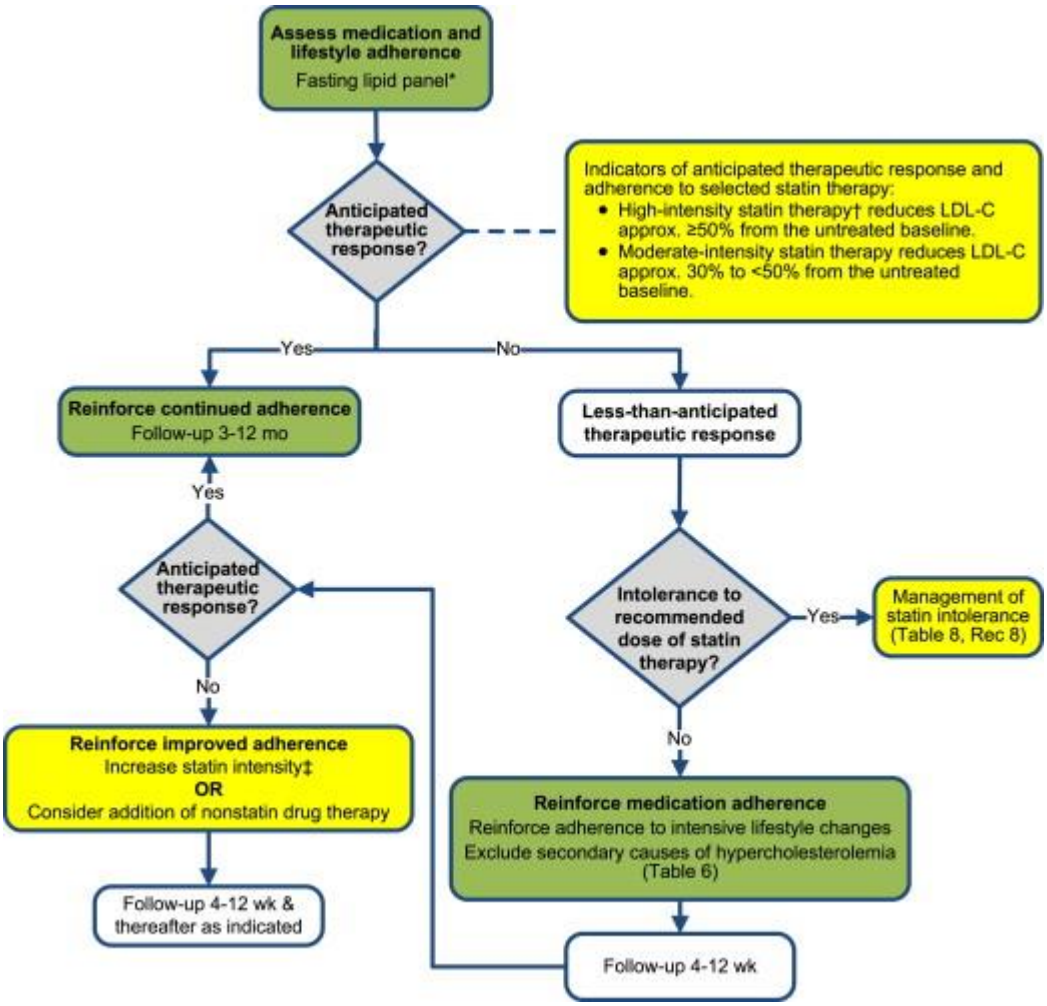

Figure 5. Statin Therapy: Monitoring Therapeutic Response and Adherence - direct excerpt from the 2013 ACC/AHA Blood Cholesterol Guideline.[21]

*Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
‡See Section 6.3.1.

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized clinical trials.

If the statin does not achieve the desired response:

- Clinicians should use their professional judgment and consider increasing the dosage.[47]
- Add another lipid-lowering medication from another class:
  - Adherence and lifestyle modifications should be reinforced with the patient first.[47]
  - "Since there is no evidence of additional reduction in ASCVD events when adding a non-statin medication to a statin, no recommendations for a specific lipid-lowering medication is offered. If a high-risk individual (patients with ASCVD, LDL-C ≥190 mg/dL, or diabetes) has a less-than-anticipated response to therapy, is unable to tolerate a less-than-recommended intensity of statin, or cannot tolerate statin therapy altogether, a non-statin lipid-lowering medication, preferably one of those shown to reduce ASCVD events, may be considered."[47]
  - "If combining lipid-lowering therapies, consideration should be given to drug-drug interactions and additional adverse events (eg, myopathy)."[47]
  - "The PCSK9 inhibitors (alirocumab and evolocumab) may also be used in combination with standard lipid-lowering therapy (eg, statins) in patients who cannot achieve adequate LDL-C reduction with standard therapy alone or in patients who are statin-intolerant or in whom the use of stains is contraindicated."[47]

- **Those intolerant to statins due to allergies or adverse effects: statin-related myopathy (SRM).** Statin intolerance is mainly due to muscle-related adverse effects. It is unclear if this indication is covered in the FDA approval indications. The ACC/AHA guidelines recommend that patients be treated with the maximum-appropriate intensity statin that does not cause side effects. The ACC/AHA guideline committee states that SRM is rare (0.01 excess case per 100 statin-treated individuals per year), but according to Rallidis et al. this is an underestimation.[55] It is reported that the incidence of SRM ranges between 5-10% based on their clinical practice experience and observational studies.[55-57] They also report, "In most cases, myalgias are mild, and after careful clinical evaluation, discussion with the patient, and weighing benefits and risk, it is likely that the patient will remain on statin therapy, probably at lower dose, and have all the clinical benefits associated with statin treatment."[55] The authors of a recently published study of the effect of statins on skeletal muscle function and performance (STOMP; blinded, controlled trial) concluded that high-dose atorvastatin for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects, but that statins increase muscle complaints (9.4% in atorvastatin 80 mg vs. 4.6% in placebo) and atorvastatin increased average creatine kinase ("suggesting that statins produce mild muscle injury even among asymptomatic subjects"). [58]

  - Muscle-related adverse effects of statins include muscle aches (myalgias) and/or elevations in the muscle enzyme creatinine kinase (CK). More severe effects include myositis where CK levels are elevated ≥4 times.[34]

According to the ACC/AHA guidelines, in patients with clear indications for statin therapy, the benefits of therapy outweigh the risks of developing myopathy (and diabetes).[21,59]

  - In individuals experiencing unacceptable adverse effects when taking the recommended intensity statin, the guidelines recommend, "once severity and association of adverse effects with statin therapy has been established, and once factors potentially contributing to statin therapy are resolved, the patient should be given lower doses of the same statin or an

alternative appropriate statin, until a statin and dose that have no adverse effects have been identified."[21]

The risk for myalgia may be increased with low muscle mass, hypothyroidism, advanced age, reduced renal function, vitamin D deficiency, abnormalities in serum electrolytes, drug interactions or reduced hepatic function (causing reduced metabolism of the statins that result in accumulation and toxicity).[60]

- Patients **who cannot tolerate 2–3 different statins are empirically diagnosed as statin intolerant**, although there is no generally agreed to definition.[60-62]

Martin et al. report in their critical appraisal report of the 2013 ACC/AHA Cholesterol Treatment Guideline that the National Lipid Association (NLA) and the American Association of Clinical Endocrinologist (AACE) provided input to the National Heart, Lung, and Blood Institute and ACC/AHA during the development of the 2013 guidelines but did not endorse it due to "the highly restrictive consideration of evidence, removal of lipid targets, too little guidance on non-statin options, and insufficient consideration of special populations of patients."[63,64]

National Lipid Association (NLA) Guidelines[53]

NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 1

The major conclusions include:

"(1) an elevated level of cholesterol carried by circulating apolipoprotein B-containing lipoproteins (non–high-density lipoprotein cholesterol and low-density lipoprotein cholesterol [LDL-C], termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying process contributing to most clinical atherosclerotic cardiovascular disease (ASCVD) events;

(2) reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies;

(3) the intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event;

(4) atherosclerosis is a process that often begins early in life and progresses for decades before resulting a clinical ASCVD event. Therefore, both intermediate-term and long-term or lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies;

(5) for patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk;

(6) nonlipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus; and

(7) the measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy."[53]

Stepwise Approach to Risk Assessment

1. "Identify highest ASCVD risk category that applies to the patient
2. If very high risk, begin with high-intensity statin. For high risk (FH, CKD. Or diabetes), consider intensity of statin (moderate or high)
3. In remaining patients, count number of major risk factors: ≥3 moves to high risk, and 2 is moderate risk
4. Treat to goals for non-HDL-C and LDL-C"[7,53]

Treatment goals are useful

- "…means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event."
- "facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives, thus supporting efforts to maximize long-term adherence to the treatment plan."[53]

According to the NLA recommendations (part 1), the strategy of treating patients to a specific cholesterol level (LDL-C or non-HDL-C) has not been evaluated in large ASCVD trials (assessing morbidity or mortality), but that results from RCTs have indicated that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event.
Please refer to appendix 3 for information from the NLA (part 1) recommendations.
The NLA recommendations for patient-centered management of dyslipidemia (Part 1) state that "desirable levels of atherogenic cholesterol for primary prevention (those without evidence of ASCVD or other very high-risk conditions) are <130 mg/dL for non-HDL and <100 mg/dL for LDL-C" whereas patients in higher risk categories have lower non-HDL (i.e. very high risk: <100 mg/dL) and LDL-C (e.g. very high risk: <70 mg/dL) treatment goals.[53]

Confirmation of continued treatment success (maintenance of goal levels) and adherence
Monitoring of response to therapy (after goal levels have been achieved) periodically (within 4-12 months) is recommended.

Contraindications or intolerance to statin therapy
The guidelines state that it is important to consider other possible causes of musculoskeletal complaints (e.g. elderly patients often complain of such symptoms without statin therapy), and other drugs that could increase the risk of muscle-related adverse effects.
Strategies suggested for patients with statin intolerance:

- Switch to a different statin
- Limit the daily dosage
- Modify regimens (every other day or weekly dosing with statins which have a long half-life)
- Where and if possible, switch to alternative concomitant therapy to enhance statin tolerance

These guidelines state that non-statin drug therapy alone or in combination with another cholesterol-lowering agent may be considered for patients that have contraindications for or intolerance to statins (if above-mentioned strategies failed/not appropriate). They mention all the other lipid-lowering drugs (apart from these newer PCSK9 inhibitors), and state that bile acid sequestrants, fibric acid, and nicotinic acid have been shown to reduce CHD or ASCVD event rates.[53,65-70]

Failure of treatment/Goal levels of atherogenic cholesterol not achieved

- Increase dose of statin

  or
- Consider* combination therapy with agents that further lower non-HDL-C and LDL-C (including non-statin drug therapies alone or in combination)

  or
- Switch to a more efficacious agent

  or
- If adequate trial on highest tolerated statin dose fail (did not achieve goal levels): Consider referral to lipid specialist

*It is stated that the maximum-tolerated statin dose should generally be used first before add-on therapy is considered. It is reported that limited RCT evidence is available to guide therapy in patients on the highest tolerated statin dosage whose level of atherogenic cholesterol remain above treatment goals, and the NLA

Expert Panel recommends that consideration be given to the use of combination therapy until further data is available.

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The following guidelines were reviewed specifically to find additional information or recommendations with regards to the PCSK9 inhibitors.

2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult[71]

- No recommendations for PCSK9 inhibitors

2014 National Institute for Health and Care Excellence (NICE guidelines [CG181]) - Lipid modification: cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular disease.[72]

- No recommendations for PCSK9 inhibitors

2011 ESC/EAS Guidelines for the management of dyslipidaemias (The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)[73])

- No recommendations for PCSK9 inhibitors

Statin therapy to reach target LDL-C level[34,73]:

- Individuals with cardiovascular disease or diabetes: <70 mg/dL
- Primary prevention in high risk individuals: <100 mg/dL

2014 An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report.[74]

- No information for PCSK9 inhibitors
- If optimal LDL-C concentrations with the combination of lifestyle and statin therapies is not achieved (in some patients with severe hypercholesterolemia): Combination drug therapy (eg, statins 1 ezetimibe and/or bile acid resins and/or niacin) is suggested as potentially efficacious.
- Extremely high LDL-C (eg, homozygous FH): LDL apheresis may be required to retard atherogenesis; lomitapide and mipomersen are mentioned as adjunct to diet and drugs in severe familial hypercholesterolemia.

*****

Specific Populations

A. <u>Lipid-lowering medications for children and adolescents</u>

In a recent publication (June 2015), Miller et al. discuss the guidelines and treatment options for this population and how further management with pharmacotherapy has changed. Please refer to appendix 2 for abstract information from this publication. The table below contains summarized information (adapted from highlights and information in publication).

Medication	FDA-approval/Use/Recommendation	Challenges/Disadvantages
Statins	First-line pharmacologic therapy for youth with severe dyslipidemias failing adequate diet and lifestyle modification.	Some patients may not tolerate statins
Bile acid sequestrants	Typically used as adjunctive therapy or for patients not able to tolerate statins	Unpalatability is a challenge
Fibric acid derivatives	Colesevelam FDA-approved* age 10-17 y; heterozygous FH; may be used as monotherapy or in combination with a statin	Colestipol and cholestyramine not FDA-approved. Lack significant pediatric safety and efficacy data.
Niacin	Unlikely therapy option	Lacks FDA approval for youth and is plagued by adverse effects
Ezetimibe	Age ≥10 y; HeFH Alternative adjunct therapy option with statin or monotherapy for patients intolerant to statins or bile acid sequestrants	-
Omega-3 fish oil	-	Lack FDA approval in pediatric patients & limited data in this population. Failed to show significant improvements in lipids.

*"Colesevelam is approved as an adjunct to a diet that is low in cholesterol and saturated fat. Colesevelam is approved for both males and females (females must be at least 1 year postmenarche) if, despite an adequate diet and other nonpharmacologic measures, the following are present: LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL and the patient has a family history of premature cardiovascular disease or 2 or more cardiovascular disease risk factors."

B. <u>Lipid-lowering medications in Heart Failure patients</u>

Not recommended: Statins as adjunctive therapy when used solely for the diagnosis of heart failure in the absence of other indications (eg, hyperlipidemia) for their use (Yancy 2013).[47]

"Treatment of Dyslipidemia and Vascular Risk: Patients with known atherosclerotic disease are likely to develop HF. Clinicians should seek to control vascular risk factors in such patients according to guidelines."[75]=> Referring to the 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.[65] "Aggressive treatment of hyperlipidemia with statins reduces the likelihood of HF in at-risk patients."[76,77]

C. <u>Lipid-lowering medications in patients with Chronic Kidney Disease (CKD)</u>

Please refer to appendix 3.

Clinical Efficacy

The product labels for both alirocumab and evolocumab state that the effect on cardiovascular morbidity and mortality has not been determined.[1]

Systematic Reviews & Meta-analyses

No Cochrane or other reviews (reviews that met the inclusion criteria for the Database of Abstracts of Reviews of Effects/DARE) were identified in the Cochrane library (searched 9/14/2015).

The Institute for Clinical and Economic Review (ICER) reported that they identified high quality meta-analyses that found that the LDL-C lowering effects of the two PCSK9 inhibitors were similar and there are no head to head trials that compare alirocumab to evolocumab.[34,78] Please refer to appendix 2 for copies of the abstracts of these reviews.

The systematic review by Navarese et al. included phase 2 or 3 RCTs (24 RCTs comprising 10 159 patients).[78] The authors of this review concluded that PCSK9 antibodies seem to be effective for adults with dyslipidemia.[78] Results showed that treatment with PCSK9 antibodies (vs no antibodies) is effective in reducing "LDL-C levels (mean difference, −47.49% [95% CI, −69.64% to −25.35%]; P < 0.001] and other atherogenic lipid fractions, and it reduced all-cause mortality (odds ratio [OR], 0.45 [CI, 0.23 to 0.86]; P = 0.015; heterogeneity P = 0.63; I2 = 0%) and cardiovascular mortality (OR, 0.50 [CI, 0.23 to 1.10]; P = 0.084; heterogeneity P = 0.78; I2 = 0%). The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR, 0.49 [CI, 0.26 to 0.93]; P = 0.030; heterogeneity P = 0.45; I2 = 0%), and increases in the serum creatine kinase level were reduced (OR, 0.72 [CI, 0.54 to 0.96]; P = 0.026; heterogeneity P = 0.65; I2 = 0%)."[34,78] The ICER report states that the effect on all-cause mortality is described as "an important preliminary signal of survival benefit compared to no anti PCSK9 treatment."[34,78] The authors (Navarese et al.) note limitations of the review; "results were derived from study-level data rather than patient-level data, and clinical outcome data are rare."[34,78]

The authors of another recently published systematic review (Zhang et al. 2015) of 25 RCTs (12,200 patients) concluded that both evolocumab and alirocumab "substantially reduced the LDL-C level by over 50 %, increased the HDL-C level, and resulted in favorable changes in other lipids."

The ICER draft report (PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks), identified 41 references (8 phase II, 16 phase III, and one long-term follow-up study.[34] According to the CEPAC analysis, use of PCSSK9 inhibitors may reduce non-fatal MIs, non-fatal strokes, and cardiovascular deaths over 20 years.[34]

Safety

Hypersensitivity reactions, including some severe reactions requiring hospitalization (eg, hypersensitivity vasculitis), have been reported with the use of alirocumab. It is therefore important to monitor the patient and it is recommended to discontinue treatment and initiate supportive treatment in patients who develop serious allergic reactions.[47] In general these medications appear to be well tolerated, but long-term safety information is not available yet. It has been reported that 5-year outcomes studies (Alirocomab ODYSSEY OUTCOMES: NCT01663402; Evolocumab FOURIER: NCT01764633) are underway and results are due in 2-3 years (Dec 2017; Feb 2018).[7,34]

Please refer to appendix 1 & 2 for additional information.

A recent systematic review (Navarese et al. 2015) reported that serious adverse events did not increase with administration of PCSK9 antibodies, and concluded that PCSK9 antibodies seem to be safe and effective for adults with dyslipidemia.[78]

Zhang et al. (2015) reported no significant difference in the rates of common adverse effects between anti-PCSK9 antibodies and placebo (or ezetimibe). Also, "no significant difference in safety outcomes was detected between monthly 420 mg and biweekly 140 mg evolocumab treatments."Increased injection site reactions were reported with alirocomab compared to placebo (RR: 1.48, 95 % CI: 1.05 to 2.09, P = 0.02). The authors concluded that "evolocumab and alirocumab were safe and well-tolerated."[79]

Place in therapy and potential criteria to be reviewed

Factors and limitations to consider:

- **Not an initial therapy option:** Patients should be on appropriate diet and maximally tolerated statin or intolerant to statins if used for HeFH or clinical ASCVD (Repatha & Praluent); and on appropriate diet and other LDL-lowering therapies (e.g. statins, ezetimibe, and LDL apheresis) and still require additional lowering of LDL-C if used for HoFH (Repatha). Limitations of the PCSK-9 inibitors include lack of evidence of effect on cardiovascular outcomes (such as stroke and myocardial infarction), lack of long-term safety information, and cost.
  Milani et al. reported that in a recent study of mipomersen in patients without a genetic disorder of lipid metabolism (Thomas et al), only 40% were taking the maximum statin dose and only 57% were taking a second lipid-lowering agent.[19,80] Milani et al suggest that we should refocus our delivery system to better manage and control health measures.[19]
- **Adherence**: It is important to ensure adherence to statins and other LDL-lowering therapies before considering alternative treatment options. According to the New England Comparative Effectiveness Public Advisory Council (CEPAC) report adherence to the PCSK9 inhibitors may also be lower than observed in clinical trials as these medications have to be self-injected and may have higher co-pays.
- **Administration regimen**: Evolocumab=> Max dose 140 mg Q2 week (W) or 420 mg Q month (M); Alirocumab=>starting dose 75 mg Q2W and up-titration to 150 mg Q2W if adequate response not achieved within 4-8 weeks.[1,2,7]
- **Muscle-related statin intolerance:** It has been reported that muscle-related symptoms from other causes are common (especially in older individuals) and it is therefore difficult to pinpoint statin intolerance.[34] There is a lack of standardized nomenclature or standardized assessment of statin intolerance.[81] Medical terms could include myalgia, myopathy, myositis, or rhabdomyolysis, but it has been reported that these are often used interchangeably and incorrectly.[81] Researchers analyzed patient records and found that chart information for statin-treated patients may contain the ICD-9 code for rhabdomyolysis, but no validation by elevated creatine kinase levels and muscle symptoms, or cases of probable rhabdomyolysis were identified for which the ICD-9 code was not used.[82]
- **Specific LDL targets:** The 2013 ACC/AHA guidelines do not recommend specific LDL-C or non-HDL-C targets, but the NLA guidelines recommend target LDL-C and HDL-C goal levels.
- **Special Populations:** Refer to guideline section for information for children and adolescents, patients with heart failure, and those with chronic kidney disease.
- **Pregnancy:** <u>Alirocumab:</u> **"**Adverse events were not observed in animal reproduction studies. Information specific to alirocumab in pregnancy is not available. However, IgG molecules are known to cross the placenta, with increasing amounts during the second and third trimesters of pregnancy."[47] <u>Evolocumab:</u> There are no adequate studies which determined safety or efficacy in human pregnancy (fetal risk cannot

be ruled out). It is recommended to weigh the potential benefits of drug treatment against potential risks before prescribing this drug during pregnancy.[83]

- **Breastfeeding:** Alirocumab: "Information specific to alirocumab is not available, however, IgG molecules are known to be present in breast milk. Serum concentrations to a nursing infant are not expected to be substantial. According to the manufacturer, the decision to breastfeed during therapy should take into account the risk of exposure to the nursing to the infant, and the benefits of treatment to the mother."[47] Evolocumab: It is not known if evolocumab is excreted in human breast milk and it is recommended to weigh the benefits and risks (available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding): "Decide whether to discontinue breast feeding or to discontinue therapy based on benefits to the mother versus risk to the child."[83]
- **Adverse effects:** Refer to safety section, appendix 1, and appendix 3: Advantages and disadvantages of lipid-lowering therapy.
- **Duplication of therapy/Concomitant use:**
  - Praluent (alirocumab) and Repatha (evolocumab) should not be used concurrently
  - Praluent (alirocumab) and Repatha (evolocumab) should not be used concurrently with Juxtapid (lomitapide) or Kynamro (mipomersen)
  - The 2013 ACC/AHA Blood Cholesterol Guidelines state that "The Expert Panel could find no data supporting the routine use of non-statin drugs combined with statin therapy to further reduce ASCVD events. In addition, no RCTs that assessed ASCVD outcomes in statin-intolerant patients were found."[21]
  - The 2013 ACC/AHA Blood Cholesterol Guidelines state that the addition of a non-statin cholesterol-lowering therapy may be considered in high risk patients (those with ASCVD, those with LDL-C ≥190 mg/dL, and those with diabetes 40–75 years of age):
    1) who have a less-than-anticipated response to statins,
    2) who are unable to tolerate a less-than-recommended intensity of a statin, or
    3) who are completely statin intolerant.

    It is recommended to prescribe drugs "that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences."[21]
  - Both evolocumab and alirocumab were studied with and without background statin therapy (reported to consistently lower LDL-C ≥50%). The PCSK9 effect is additive to statins.[7]
  - Can it be used in patients receiving lipid apheresis? Studies are ongoing.[7]
- **Monitoring:** Refer to appendix 1. The 2013 ACC/AHA Blood Cholesterol Guideline state that adherence to lifestyle changes and statin therapy should be considered and reemphasized before the addition of any non-statin drug is considered.[21]
- **Efficacy/Patients who may benefit:** Refer to labelled indications, clinical efficacy section and clinical guideline recommendations.
- **Lack of evidence/research needed:** Large scale long-term trials and "clinical trials that compare treating to a specific cholesterol target with PCSK-9 inhibitors vs more traditional statins."[3] Studies evaluating the effects of more prolonged, high-dose statin treatment on muscle tissue function and performance.[58]
- **Cost-effectiveness:** According to the CEPAC analysis use of PCSSK9 inhibitors may reduce non-fatal MIs, non-fatal strokes, and cardiovascular deaths over 20 years, but it is reported that their "value-based price benchmark for each PCSK9 inhibitor is $2,177 annually, which represents an 85% reduction from the list price of $14,600."[34] Several limitations are discussed in the full report.

Utah Medicaid Utilization Data

The data provided below is for 2012-2015 (to date and 2015 therefore do not represent a full year).

No utilization is documented for alirocumab and evolocumab in the Utah Medicaid population. However these agents only recently became available, Praluent™ (alirocumab) was approved by the FDA in July 2015 and Repatha (evolocumab) in August 2015. It is important to review utilization data in the Utah Medicaid population (including the broader scope of treatment of other lipid disorders) to identify utilization (including potential off-label use) and trends.

(A) Utilization data for antihyperlipidemic drugs (using the AHFS classification system) have been included in Appendix 4.

(B) We attempted to identify the diagnosis code for FH. ICD-9 272.0 (pure hypercholesterolemia) is listed as FH, but it appears people are using different codes. According to Joshua Knowles, MD, PhD, the Chief Medical Officer for the FHF, there is no distinct ICD-9 code for FH and very little population-based data from the US.[14] The table below shows the number of patients that filled prescriptions for antihyperlipidemic medications in whom diagnosis codes were submitted for any disorder of lipoid metabolism (as specified below).

DIAGNOSIS*	**ICD**	**2012**		**2013**		**2014**		**2015**	
All Disorders of Lipoid Metabolism	**2720-2729**	**4,204**	**55%**	**3,997**	**52%**	**4,385**	**55%**	**2,565**	**40%**
Pure Hypercholesterolemia	2720	1,015	13%	930	12%	982	12%	535	8%
Pure Hyperglyceridemia	2721	192	2%	168	2%	200	2%	101	2%
Mixed Hyperlipidemia	2722	686	9%	675	9%	770	10%	409	6%
Hyperchylomicronemia	2723	4	0%	1	0%	0	0%	4	0%
Other and Unspecified Hyperlipidemia	2724	3,040	40%	2,937	38%	3,234	40%	1,827	29%
Lipoprotein Deficiencies	2725	27	0%	19	0%	22	0%	16	0%
Lipodystrophy	2726	1	0%	1	0%	1	0%	0	0%
Lipidoses	2727	38	0%	22	0%	22	0%	7	0%
Other Disorders of Lipoid Metabolism	2728	8	0%	5	0%	6	0%	5	0%
Unspecified Disorder of Lipoid Metabolism	2729	25	0%	29	0%	41	1%	17	0%
TOTAL PATIENTS USING ANTIHYPERLIPIDEMICS		**7681**		**7703**		**8042**		**6388**	

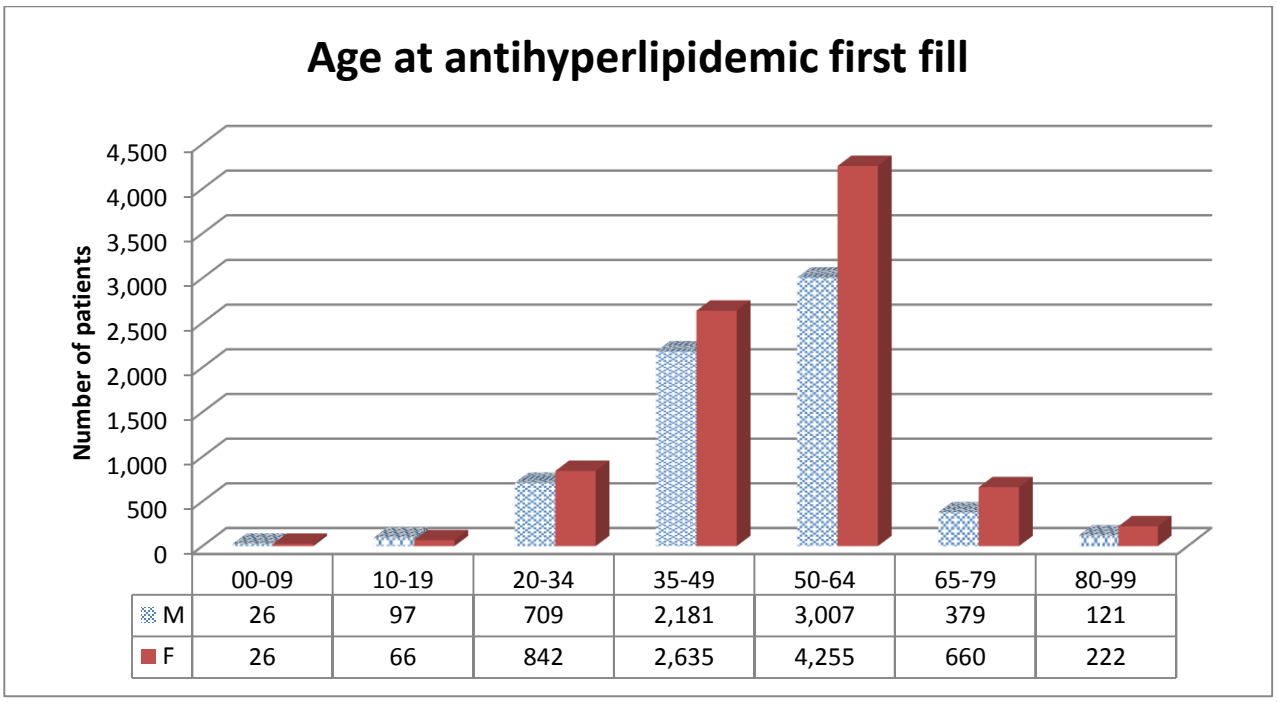
* Diagnosis date within 30 days of an antihyperlipidemic prescription fill.

(C) We attempted to identify patients for whom diagnosis or procedural codes were submitted for apheresis (see below), but did not find any of those diagnosis codes in the data (reviewed the ICD Master data at DOH and the CPT data) and the CPT code 36516 was found, but there were no claims for that procedure. According to a recent review, an estimated 400 patients receive apheresis in the US (only 40 centers provide care) even though the number of patients who qualify and may benefit from this treatment is thought to be significantly higher.[10,84]

DIAGNOSIS*	**ICD**
Therapeutic Plasmapheresis	99.71
Extracorporeal Plasmapheresis	99.76
Other Therapeutic Apheresis	99.79
PROCEDURE*	**CPT**
Therapeutic Apheresis with Extracorporeal Selective Adsorption or Selective Filtration and Plasma Reinfusion	36516

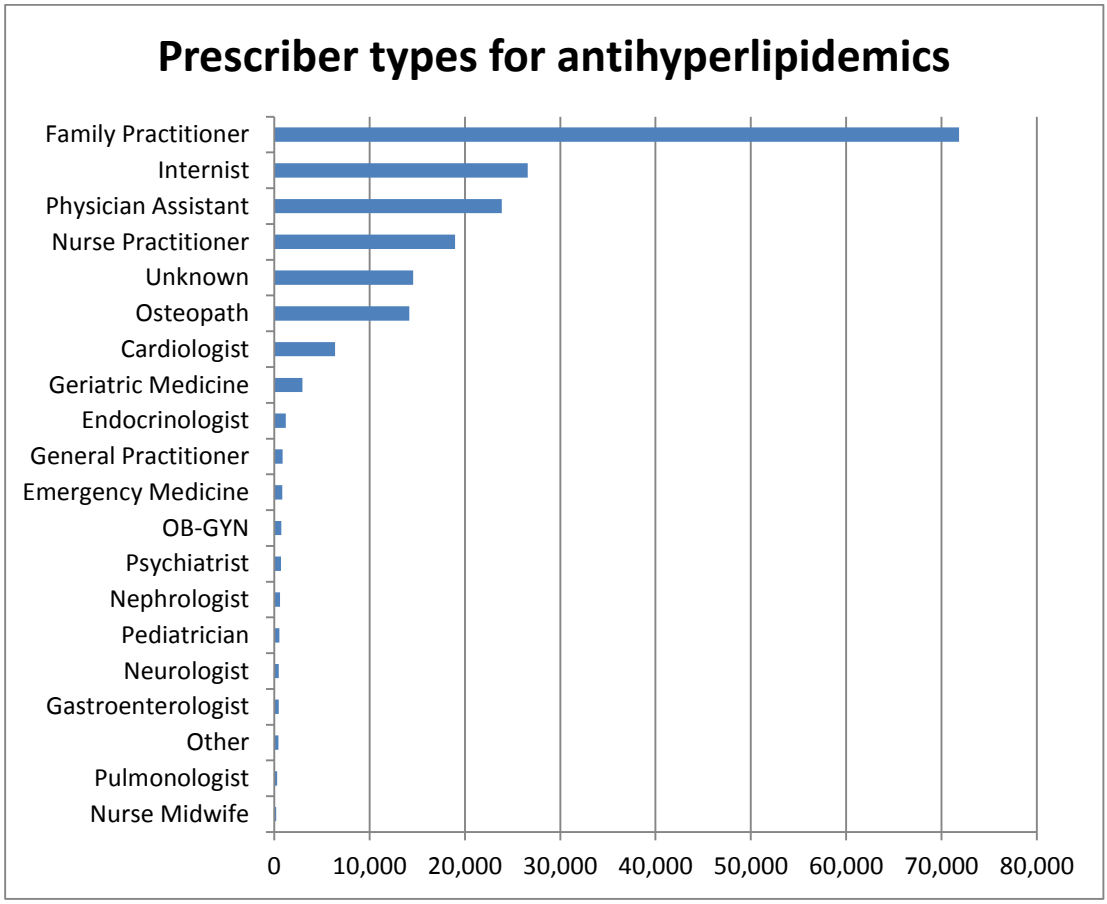
* Procedure date within 30 days of an antihyperlipidemic prescription fill.

(D) Ages of patients that filled prescriptions for antihyperlipidemic drugs in the Utah Medicaid population (2012-2015). This applies to any fill for an antihyperlipidemic which would include any disorder of lipoid metabolism included in (B) as well as patients for whom no diagnosis code was submitted for any of those diagnosis codes listed in (B).



	00-09	10-19	20-34	35-49	50-64	65-79	80-99
M	26	97	709	2,181	3,007	379	121
F	26	66	842	2,635	4,255	660	222

(E) Prescribers of antihyperlipidemic drugs (2012-2015)



PRESCRIBER TYPE	TOTAL CLAIMS 2012-15	
Nurse Midwife	185	0.10%
Pulmonologist	309	0.17%
Other	448	0.24%
Gastroenterologist	452	0.24%
Neurologist	474	0.25%
Pediatrician	545	0.29%
Nephrologist	612	0.33%
Psychiatrist	702	0.38%
OB-GYN	747	0.40%
Emergency Medicine	833	0.45%
General Practitioner	861	0.46%
Endocrinologist	1,208	0.65%
Geriatric Medicine	2,949	1.58%
Cardiologist	6,365	3.41%
Osteopath	14,153	7.58%
Unknown	14,565	7.80%
Nurse Practitioner	18,965	10.16%
Physician Assistant	23,872	12.79%
Internist	26,602	14.25%
Family Practitioner	71,857	38.49%
	186,704	

Conclusions

Cardiovascular events have huge implications for both the patient and healthcare system therefore it is important to optimally treat patients in considering all the available treatment options and evaluating the associated safety and cost-effectiveness of those options. "The 2013 ACC/AHA Blood Cholesterol Guideline state that adherence to lifestyle changes and statin therapy should be considered and reemphasized before the addition of a non-statin drug is considered.[21] However, Tompkins et al. report that statin use is expected to increase because the new guidelines include a broader range of patients for which statins are indicated and use of other lipid-lowering drugs are less supported.[26]

Praluent™ (alirocumab) and Repatha (evolocumab) offer new costly treatment options for lowering LDL-C levels in patients with HeFH or clinical ASCVD on appropriate diet and maximally tolerated statin treatment (or intolerant to statins) who still require additional lowering of LDL-C.[1] Repatha (evolocumab) is another new agent for patients with HoFH on appropriate diet and other lipid-lowering therapies (e.g. statins, ezetimibe, and LDL apheresis) who require additional lowering of LDL-C. The effect of these therapies on cardiovascular morbidity and mortality has not been determined.[1]

Tomkins et al. also report that increased statin prescribing, or use of more moderate to high doses (as recommended by the 2013 ACC/AHA Blood Cholesterol Guideline instead of targeting LDL levels), may lead to more statin-related adverse effects or intolerance.[26] This could lead to broader use of the new PCSK-9 inhibitors instead of using lower doses of the same statin or an alternative statin.[21]

The Utah Medicaid Utilization Data documented no utilization of the new agents Praluent™ (alirocumab) and Repatha (evolocumab). The potential pool of patients for usage of these agents including off-label use for other lipid disorders and patients appropriate based on the FDA indication(s) depends on how it is interpreted. To optimize and control usage, a prior authorization assessment is warranted.

This statement in response to the IMPROVE-IT trial generally: "As always, the NLA urges clinicians to customize clinical decisions to individual patient clinical needs and circumstances, and to use the best available evidence."[36] The purpose of the prior authorization is to encourage appropriate prescribing so that newer treatment options are considered only in those patients where medically necessary and appropriate.

Potential clinical criteria

You may wish to consider the following criteria (limited to FDA-approved indications):
Patient has a diagnoses of any of the following:

A. Heterozygous Familial Hypercholesterolemia (HeFH) and >18 years old and prescribed by (or in consultation with) cardiologist, endocrinologist, or lipid specialist.

AND
(any of the following)
Confirmation or evidence that patient is on **appropriate diet** and **maximally tolerated statin*** and require additional lowering of LDL (if it is not possible to attain desirable levels of atherogenic cholesterol, a reduction of at least 50% is recommended)

OR
Statin is contraindicated♦

OR
Intolerant to statins†

B. Clinical Atherosclerotic Cardiovascular Disease (CVD) and >18 years old and prescribed by (or in consultation with) cardiologist, endocrinologist, or lipid specialist.

AND
Confirmation or evidence that patient is on **appropriate diet** and **maximally tolerated statin***

AND
LDL-C >70 mg/dL or non-HDL-C > 100 mg/dL
(Recommended NLA treatment goal/consider drug therapy)

OR
Statin is contraindicated♦

OR
Intolerant to statins†

Specific to Repatha (evolocumab):
C. Homozygous Familial Hypercholesterolemia (HoFH) and prescribed by (or in consultation with) cardiologist, endocrinologist, or lipid specialist.

AND
Confirmation or evidence that patient is on **appropriate diet** and **other LDL-lowering therapies** (e.g. statins, ezetimibe, and LDL apheresis) and **still require additional lowering of LDL-C** if used for HoFH (if it is not possible to attain desirable levels of atherogenic cholesterol, a reduction of at least 50% is recommended)

*Evidence of maximally tolerated statin:

- A trial of at least 2 different statins including a high-potency statin at the maximally tolerated dose
- Regimen was tried for at least 4-12 weeks
- Confirmation of compliance (e.g. filled regularly for at least 3 months and confirmation that patient was asked simply and directly about adherence to medication and appropriate diet and exercise).
  Educational:
  An adherence toolkit is available at: https://www.lipid.org/practicetools/tools/adherence
  "The Patient Adherence subcommittee of the NLA developed a patient toolkit to address the importance of patient adherence to medications and lifestyle modifications. The purpose of the patient adherence toolkit is to be a resource to the clinician on how to counsel their patients. The toolkit will challenge the clinician to view adherence like a disease, which requires an understanding of what adherence is, how to "diagnose" it in patients, and what interventions have been successful at improving patient adherence."

†Evidence of statin intolerance:

- A serious adverse event to a statin

OR

- Confirmation that at least 2 statins were not tolerated (at least one should be at the lowest starting daily dose)
- Dose reduction and/or change in dosing regimen with continued symptoms
- Other potential causes of muscle-related adverse effects have been eliminated (e.g. hypothyroidism, advanced age, reduced renal function, vitamin D deficiency, abnormalities in serum electrolytes, underlying muscle disease, significant changes in physical activity, drug interactions or reduced hepatic function (causing reduced metabolism of the statins that result in accumulation and toxicity).[34,60]
- Confirmation of temporal relationship (e.g. resolution of symptoms upon discontinuation; return of symptoms when restarting therapy where appropriate)

♦ Contraindications to statins from Lexicomp:

- "Hypersensitivity to simvastatin or any component of the formulation;
- active liver disease;
- unexplained persistent elevations of serum transaminases;
- concomitant use of strong CYP3A4 inhibitors (eg, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, posaconazole, voriconazole, protease inhibitors [including boceprevir and telaprevir], telithromycin, cobicistat-containing products), cyclosporine, danazol, and gemfibrozil;
- pregnancy;
- breast-feeding"[47]

Initial authorization: Valid for 6 months
Re-authorization: Required every 12-24 months with documentation the initial requirements remain met PLUS evidence of sufficient additional LDC-reduction. **at what additional percentage do you call if a failure and discontinue the med? Some improvement is improvement, right? You likely want to say – if 50% reduction or achieving goal is not met after 12 months – d/c med. That may be a tough sell. Consider…..

Not allowed:
Duplication of therapy/Concomitant use:

- Praluent (alirocumab) and Repatha (evolocumab) should not be used concurrently
- Praluent (alirocumab) and Repatha (evolocumab) should not be used concurrently with Juxtapid (lomitapide) or Kynamro (mipomersen)

Monthly Quantity limitation via FDA-approved dosage(s):

Drug	**Quantity Limit**
Praluent (alirocumab)	
75 mg/mL prefilled syringe	2 syringes/28 days
75 mg/mL pen-injector	2 pens/28 days
150 mg/mL prefilled syringe	2 syringes/28 days
150 mg/mL pen-injector	2 pens/28 days
Repatha (evolocumab)	
140 mg	2 syringes/28 days
420 mg	2 syringes/28 days

Appendix 1 – Drug information

Table 1: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibodies
(Source: Product Labels[1,2], Lexicomp[47] and Micromedex[83])

Drug & Dosage Form	Dosing	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/ Precautions/ Drug-Interactions
PRALUENT™ (alirocumab) • Subcutaneous • Single-use pen-injector (solution) • Single-use prefilled syringe (solution) • 75 mg/mL (1 mL) • 150 mg/mL (1 mL):	SubQ: 75 mg once every 2 weeks If an adequate response is not achieved within 4-8 weeks: may be increased to 150 mg once every 2 weeks (max dose).	**Hyperlipidemia:** Adjunct to diet and maximally tolerated statin therapy for adults who require additional lowering of LDL-cholesterol (LDL-C) for: D. Heterozygous familial hypercholesterolemia (HeFH) E. Atherosclerotic cardiovascular disease (CVD) Limitation of use: Effect on cardiovascular morbidity and mortality has not been determined.	No known off-label use	Gastrointestinal: Diarrhea (5%) Hepatic: Liver enzyme disorder (3%), increased serum transaminases (>3X ULN; 2%) Hypersensitivity reaction Infection: Influenza (6%) Injection site reaction (7%) Neuromuscular & skeletal: Myalgia (4%), muscle spasm (3%) Respiratory: Cough (3%) <1%, postmarketing, and/or case reports: Confusion, memory impairment	• Serious hypersensitivity to alirocumab • Monitor LDL cholesterol (LDL-C) within 4 to 8 weeks of initiation or dose titrations. • *Avoid combination* with belimumab (Monoclonal Antibodies may enhance the adverse/toxic effect of belimumab).
REPATHA (evolocumab) • Subcutaneous • Single-use prefilled syringe (solution) • Single-use pre-filled SureClic®autoinjector (solution) • 140 MG/ML	Primary HeFH or hypercholesterolemia, CVD, in combination with a statin: 140 mg subQ every 2 weeks OR 420 mg subQ once monthly	**Hyperlipidemia:** Adjunct to diet and maximally tolerated statin therapy for adults who require additional lowering of LDL-cholesterol (LDL-C) for: F. Heterozygous familial hypercholesterolemia (HeFH)	No known off-label use	Cardiovascular Effects: Hypertension (3.2%) Dermatologic Effects: Contusion (1%), Injection site reaction, rash (1%), urticaria (0.4%) Gastrointestinal Effects: Diarrhea (3%), gastroenteritis (3%-6.1%), nausea (1.8%) Immunologic Effects: Antibody development (0.1%), influenza (7.5% to 9.1%)	• Serious hypersensitivity to evolocumab • Measure LDL-C in patients with homozygous familial hypercholesterolemia 4 to 8 weeks after therapy initiation

Amgen has filed an application to the FDA (licence variation) to allow the 420 mg monthly dose to be administered as a single SC injection.[85] *Repatha was approved by the FDA in August 2015; anticipated availability is September 2015*	HoFH, In combination with other lipid-lowering therapies: 420 mg subQ once monthly	G. Atherosclerotic cardiovascular disease (CVD) **Homozygous familial hypercholesterolemia:** Adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) for adults and pediatric patients 13 years and older who require additional lowering of LDL-C for: ➢ Homozygous familial hypercholesterolemia (HoFH)	Musculoskeletal Effects: Backache (3.2%-6.2%), musculoskeletal pain (3.3%), myalgia (4%) Neurologic Effects: Dizziness (3.7%), headache (4%) Renal Effects: Urinary tract infectious disease (4.5%) Respiratory Effects: Cough (1.2% to 4.5%), nasopharyngitis (6.1%-10.5%), sinusitis (4.2%), upper respiratory infection (9.1%-9.3%) Other: Fatigue (1.6%)

Appendix 2 – Systematic review(s) and other reviews

Table 3: Systematic Reviews

Zhang XL, et al. (2015) Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials[79]
"Background Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has been intensively studied to lower low-density lipoprotein cholesterol (LDL-C) levels. The purpose of this meta-analysis was to evaluate the safety and efficacy of anti-PCSK9 antibodies in randomized, controlled trials (RCTs). Methods PubMed, EMBASE, CENTRAL databases, and recent conferences were searched. Safety outcomes were rates of common adverse events. Efficacy outcomes included percentages of LDL-C lowering and other lipid changes compared with placebo and ezetimibe, respectively. Results Twenty-five RCTs encompassing 12,200 patients were included. The rates of common adverse events were firstly reported in our study by pooling together all evidence in RCTs, showing largely no significant difference between anti-PCSK9 antibodies and placebo (or ezetimibe), except that alirocumab was associated with reduced rates of death (relative risk (RR): 0.43, 95 % confidence interval (CI): 0.19 to 0.96, P = 0.04) and an increased rate of injection-site reactions (RR: 1.48, 95 % CI: 1.05 to 2.09, P = 0.02); evolocumab reduced the rate of abnormal liver function (RR: 0.43, 95 % CI: 0.20 to 0.93, P = 0.03), both compared with placebo. No significant difference in safety outcomes was detected between monthly 420 mg and biweekly 140 mg evolocumab treatments. Monthly 420 mg evolocumab treatment significantly reduced LDL-C by −54.6 % (95 % CI: −58.7 to −50.5 %) and by absolute −78.9 mg/dl (95 % CI: −88.9 to −68.9 mg/dl) versus placebo, and by −36.3 % (95 % CI: −38.8 to −33.9 %) versus ezetimibe, and increased high-density lipoprotein cholesterol (HDL-C) by 7.6 % (95 % CI: 5.7 to 9.5 %) versus placebo and 6.4 % (95 % CI: 4.3 to 8.4 %) versus ezetimibe. An equal or even greater change was observed following biweekly 140 mg administration. Significant and favorable changes were also detected in other lipids following evolocumab treatment. Biweekly 50 to 150 mg alirocumab lowered LDL-C by −52.6 % (95 % CI: −58.2 to −47.0 %) versus placebo, by −29.9 % (95 % CI: −32.9 to −26.9 %) versus ezetimibe, and increased HDL-C by 8.0 % (95 % CI: 4.2 to 11.7 %) versus placebo. Conclusions Evolocumab and alirocumab were safe and well-tolerated from our most-powered analyses. Both antibodies substantially reduced the LDL-C level by over 50 %, increased the HDL-C level, and resulted in favorable changes in other lipids."[79]

Navarese EP, et al. (2015) Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis[78]
"Background: Guidelines recommend statins as first-line therapy for dyslipidemia. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new lipid-lowering approach. Purpose: To assess the efficacy and safety of PCSK9 antibodies in adults with hypercholesterolemia. Data Sources: MEDLINE, PubMed Central, and Google Scholar; conference proceedings; and the ClinicalTrials.gov registry through 4 April 2015. Study Selection: Phase 2 or 3 randomized, controlled trials (RCTs) comparing treatment using PCSK9 antibodies with no anti-PCSK9 therapy in adults with hypercholesterolemia.

Data Extraction: Two investigators independently extracted data on study characteristics and lipid and clinical outcomes, and rated risk of bias of trials. Prespecified primary end points were all-cause and cardiovascular mortality.

Data Synthesis: Twenty-four RCTs comprising 10 159 patients were included. Compared with no antibody, treatment with PCSK9 antibodies led to marked reductions in low-density lipoprotein cholesterol levels (mean difference, −47.49% [95% CI, −69.64% to −25.35%]; P < 0.001] and other atherogenic lipid fractions, and it reduced all-cause mortality (odds ratio [OR], 0.45 [CI, 0.23 to 0.86]; P = 0.015; heterogeneity P = 0.63; I2 = 0%) and cardiovascular mortality (OR, 0.50 [CI, 0.23 to 1.10]; P = 0.084; heterogeneity P = 0.78; I2 = 0%). The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR, 0.49 [CI, 0.26 to 0.93]; P = 0.030; heterogeneity P = 0.45; I2 = 0%), and increases in the serum creatine kinase level were reduced (OR, 0.72 [CI, 0.54 to 0.96]; P = 0.026; heterogeneity P = 0.65; I2 = 0%). Serious adverse events did not increase with administration of PCSK9 antibodies.

Limitation: Results were derived from study-level data rather than patient-level data, and clinical outcome data are rare.

Conclusion: PCSK9 antibodies seem to be safe and effective for adults with dyslipidemia.

Primary Funding Source: CRC 1116 Masterswitches in Myocardial Ischemia, German Research Council DFG."[78]

Table 4: General Review of Lipid-lowering medications for children and adolescents

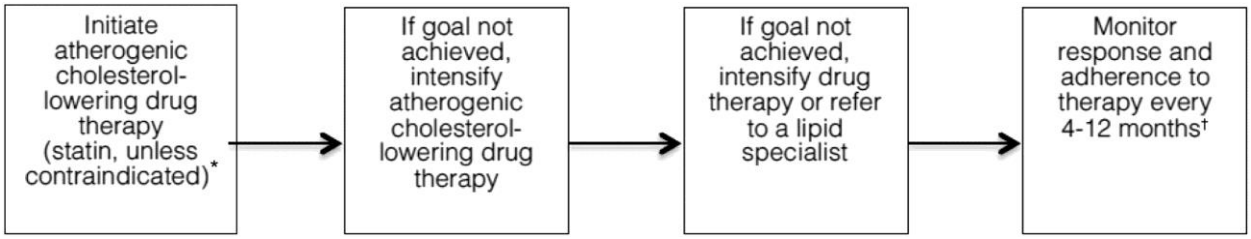
Miller ML et al. Lipid-lowering medications for children and adolescents. *J Clin Lipidol.* 2015 Sep-Oct;9(5 Suppl):S67-76.[86]
"As demonstrated by the 2011 publication of the National Heart, Lung, and Blood Institute Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, the information available regarding the treatment of pediatric lipid disorders has greatly expanded. HMG-CoA reductase inhibitor, or statin, therapy is now considered a first-line pharmacologic intervention for pediatric patients with severe dyslipidemias failing treatment with diet and exercise alone. Despite their ability to effectively reduce cholesterol levels, bile acid sequestrants continue to pose challenges for pediatric patients because of their unpalatability and are typically used as adjunctive therapy or for patients not able to tolerate statins. Fibric acid derivatives, as a class of medications, not only lack a Food and Drug Administration (FDA)-approved agent, but also continue to lack significant pediatric safety and efficacy data. Niacin, a potential adjunct therapy, lacks FDA approval for pediatric patients and is plagued by significant adverse effects making it an unlikely therapy option for pediatric patients. Ezetimibe provides clinicians with an alternative adjunct therapy option when synergistically paired with an HMG-CoA reductase inhibitor or it can be used as monotherapy for patients intolerant to statins and bile acid sequestrants. Finally, despite several marketed formulations, omega-3 fish oils currently lack FDA approval in pediatric patients and have failed to demonstrate statistically significant lipid lowering in pediatric and adolescent patients. Although recent years have witnessed a dramatic increase in data available for the use of lipid-lowering medications for pediatric patients, long-term study data are still generally lacking and continues to present an active focus of research."

Appendix 3 – Blood Cholesterol Management

Please refer to the guidelines for complete information.

NLA recommendations (part 1)

Direct excerpt from Jacobson et al.[53]



"Progression of atherogenic cholesterol-lowering drug therapy. *A moderate- or high-intensity statin should be first-line drug therapy for treatment of elevated levels of atherogenic cholesterol, unless contraindicated. In a patient with very high triglycerides (≥500 mg/dL), a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Other atherosclerotic cardiovascular disease risk factors should be managed appropriately in parallel. †In most cases, goal levels should be achieved in approximately 6 months."

Table 2 Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL

Risk Category	Treatment Goal		
	Non-HDL-C	**LDL-C**	**Apo B***
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

Apo, apolipoprotein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol.

*Apo B is a secondary, optional target of treatment.

Please refer to table 3 in the published guidelines for Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy.[53]

2013 ACC/AHA Blood Cholesterol Guidelines

2013 AHA/ACC statin classification

Direct excerpt from New Guidelines for cholesterol management: What has changed?[4]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL by approximately ≥50%	Daily dose lowers LDL by approximately 30% to <50%	Daily dose lowers LDL-C by <30%
Atorvastatin (40)–80 mg QD **Rosuvastatin 20** (40) **mg QD**	**Atorvastatin 10** (20) **mg QD** **Rosuvastatin** (5) **10 mg QD** **Simvastatin 20–40 mg QD** **Pravastatin 40** (80) **mg QD** **Lovastatin 40 mg QD** Fluvastatin XL 80 mg QD **Fluvastatin 40 mg BID** Pitavastatin 2–4 mg QD	Simvastatin 10 mg QD **Pravastatin 10 to 20 mg QD** **Lovastatin 20 mg** Fluvastatin 20 to 40 mg BID Pitavastatin 1 mg QD

Bold = evaluated in RCTs and demonstrated a reduction in major cardiovascular events. Italics = approved by the U.S. FDA but not tested in RCTs Individual responses to statins might vary in clinical practice. BID: Twice daily; QD: once daily

KDIGO Recommendations

Lipid-Lowering Therapy in patients with CKD

Direct excerpt from Lexicomp[47]

Table 6. 2014 KDIGO Recommendations	
CKD Subgroup	**Treatment Recommendation**
≥50 years of age with eGFR <60 mL/min/1.73 m^2 (not treated with chronic dialysis or kidney transplantation) (GFR categories G3a to G5)	Statin or statin/ezetimibe combination
≥50 years of age with eGFR ≥60 mL/min/1.73 m^2 (GFR categories G1 to G2)	Statin
18 to 49 years of age with CKD (not treated with chronic dialysis or kidney transplantation) with one or more of the following: • Known coronary disease (myocardial infarction or coronary revascularization) • Diabetes mellitus • Prior ischemic stroke • Estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10%	Statin
Children <18 years with CKD (including those treated with chronic dialysis or kidney transplantation)	Do not initiate statins or statin/ezetimibe combination
Dialysis-dependent CKD	Do not initiate statins or statin/ezetimibe combination; continue statin or statin/ezetimibe combination if patient already on at the time of dialysis initiation
Kidney transplantation	Statin

Direct excerpt from Lexicomp[47]

Advantages and Disadvantages of Specific Lipid-Lowering Therapies

	Advantages	Disadvantages
HDL = high-density cholesterol, LDL = low-density lipoprotein, PCSK = proprotein convertase subtilisin kexin		
Bile acid sequestrants	Good choice for ↑ LDL, especially when combined with a statin (↓ LDL ≤50%); low potential for systemic side effects; good choice for younger patients	May increase triglycerides; higher incidence of adverse GI effects; moderately expensive; drug interactions; inconvenient dosing
Lomitapide	Homozygous Familial Hypercholesterolemia: ↓s LDL, especially when combined with a statin (↓ LDL ≤50%); ↓s triglycerides	High incidence of gastrointestinal adverse effects, especially if used with high-fat diet
Niacin	Good choice for almost any lipid abnormality; inexpensive; greatest increase in HDL	High incidence of adverse effects; may adversely affect type 2 diabetes mellitus (with high-dose >1.5 g/day) and gout; sustained release niacin may decrease the incidence of flushing and circumvent the need for multiple daily dosing; sustained release niacin may not increase HDL cholesterol or decrease triglycerides as well as immediate release niacin
HMG-CoA reductase inhibitors	Produces greatest ↓ in LDL; generally well-tolerated; convenient once-daily dosing; proven decrease in mortality	Expensive
Fibric acid derivatives	Good choice in patients with ↑ triglycerides when niacin is contraindicated or not well-tolerated	Variable effects on LDL
Ezetimibe	Additional cholesterol-lowering effects when combined with HMG-CoA reductase inhibitors	LDL-lowering effects similar to bile acid sequestrants
Omega-3 fatty acids (eg, Lovaza)	Good choice in patients with ↑ triglycerides	May ↑ LDL with high doses due to conversion of VLDL to LDL
PCSK9 Inhibitors	Administered every 2 weeks to monthly	Currently available agents require subcutaneous injection; expensive

Appendix 4 – Utilization data for antihyperlipidemic drugs in the Utah Medicaid Population

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Alirocumab	Praluent Injection 150MG/ML	0	0	0	0	0	0	0	0
Alirocumab	Praluent Injection 75MG/ML	0	0	0	0	0	0	0	0
Atorvastatin Calcium	Atorvastatin Tablet 10MG	674	279	2,337	452	2,506	493	1,987	428
Atorvastatin Calcium	Atorvastatin Tablet 20MG	909	403	3,596	712	4,500	954	3,646	861
Atorvastatin Calcium	Atorvastatin Tablet 40MG	1,101	473	3,886	768	5,482	1,131	4,849	1,146
Atorvastatin Calcium	Atorvastatin Tablet 80MG	388	161	1,717	308	2,105	414	1,652	400
Atorvastatin Calcium	Lipitor Tablet 10MG	1,164	277	4	4	0	0	0	0
Atorvastatin Calcium	Lipitor Tablet 20MG	1,602	416	0	0	0	0	0	0
Atorvastatin Calcium	Lipitor Tablet 40MG	1,758	422	1	1	0	0	0	0
Atorvastatin Calcium	Lipitor Tablet 80MG	678	159	3	3	0	0	0	0
Cholestyramine	Cholestyramine Powder 4GM	384	159	423	175	358	144	234	109
Cholestyramine Light	Cholestyramine Light Powder 4GM	96	45	96	46	83	44	43	25
Cholestyramine Light	Prevalite Powder 4GM	32	23	48	17	65	25	53	20
Choline Fenofibrate	Fenofibric Delayed Release Capsule 135MG	0	0	56	18	165	26	84	20
Choline Fenofibrate	Fenofibric Delayed Release Capsule 45MG	0	0	0	0	7	1	10	3
Choline Fenofibrate	Trilipix Delayed Release Capsule 135MG	1,441	220	771	157	475	67	187	35

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Choline Fenofibrate	Trilipix Delayed Release Capsule 45MG	87	15	60	10	45	5	25	5
Clofibrate	Atromid Capsule 500MG	0	0	0	0	0	0	0	0
Clofibrate	Clofibrate Capsule 500MG	0	0	0	0	0	0	0	0
Colesevelam HCl	Welchol Tablet 6-Pack 3750MG	20	12	8	7	10	6	0	0
Colesevelam HCl	Welchol Tablet Single 625MG	378	99	330	75	276	72	129	39
Colestipol HCl	Colestipol Tablet 5-Pack 5GM	2	2	0	0	0	0	1	1
Colestipol HCl	Colestipol Tablet Single 1GM	66	20	75	14	116	27	85	33
Evolocumab	Repatha Injection 140MG/ML	0	0	0	0	0	0	0	0
Ezetimibe	Zetia Tablet 10MG	1,662	243	1,306	204	1,059	165	535	105
Ezetimibe-Atorvastatin	Liptruzet Tablet 10MG	0	0	0	0	0	0	0	0
Ezetimibe-Atorvastatin	Liptruzet Tablet 20MG	0	0	0	0	0	0	0	0
Ezetimibe-Atorvastatin	Liptruzet Tablet 40MG	0	0	0	0	0	0	0	0
Ezetimibe-Atorvastatin	Liptruzet Tablet 80MG	0	0	0	0	0	0	0	0
Ezetimibe-Simvastatin	Vytorin Tablet 10-10MG	0	0	3	2	2	1	7	3
Ezetimibe-Simvastatin	Vytorin Tablet 10-20MG	7	2	49	14	34	10	25	8
Ezetimibe-Simvastatin	Vytorin Tablet 10-40MG	31	6	45	10	78	14	40	7
Ezetimibe-Simvastatin	Vytorin Tablet 10-80MG	20	2	0	0	10	1	0	0
Fenofibrate	Fenofibrate Capsule 50MG	0	0	0	0	0	0	1	1

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Fenofibrate	Fenofibrate Tablet 145MG	57	56	1,834	329	1,179	194	624	136
Fenofibrate	Fenofibrate Tablet 160MG	82	20	1,422	277	1,516	250	872	198
Fenofibrate	Fenofibrate Tablet 48MG	3	3	219	38	150	28	90	23
Fenofibrate	Fenofibrate Tablet 54MG	17	3	154	33	175	34	101	25
Fenofibrate	Tricor Tablet 145MG	4,668	725	931	188	1,021	196	594	120
Fenofibrate	Tricor Tablet 48MG	529	95	135	38	181	35	118	25
Fenofibrate	Triglide Tablet 160MG	0	0	2	1	42	20	70	20
Fenofibrate Micronized	Antara Capsule 130MG	1	1	3	1	7	1	0	0
Fenofibrate Micronized	Antara Capsule 43MG	0	0	4	1	2	1	0	0
Fenofibrate Micronized	Fenofibrate Capsule 134MG	0	0	233	42	215	39	105	22
Fenofibrate Micronized	Fenofibrate Capsule 200MG	0	0	115	21	100	18	79	15
Fenofibrate Micronized	Fenofibrate Capsule 67MG	0	0	9	1	4	3	2	1
Fenofibric Acid	Fenofibric Tablet 35MG	0	0	0	0	0	0	0	0
Fenofibric Acid	Fenofibric Tablet 105MG	0	0	0	0	0	0	0	0
Fenofibric Acid	Fibricor Tablet 35MG	0	0	0	0	0	0	0	0
Fenofibric Acid	Fibricor Tablet 105MG	0	0	0	0	0	0	0	0
Fluvastatin Sodium	Fluvastatin Capsule 20MG	0	0	6	3	14	2	4	1
Fluvastatin Sodium	Fluvastatin Capsule 40MG	0	0	0	0	0	0	4	1

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Fluvastatin Sodium	Lescol 24-Hour Extended Release Tablet 80MG	0	0	1	1	2	1	1	1
Fluvastatin Sodium	Lescol Capsule 20MG	3	1	0	0	0	0	0	0
Gemfibrozil	Gemfibrozil Tablet 600MG	1,529	279	1,401	274	1,228	246	637	149
HMG CoA Reductase Inhibitor	Cholestin Capsule 600MG	0	0	0	0	0	0	0	0
Icosapent Ethyl	Vascepa Capsule 1GM	0	0	15	5	31	5	11	4
Lomitapide Mesylate	Juxtapid Capsule 5MG	0	0	0	0	2	1	0	0
Lomitapide Mesylate	Juxtapid Capsule 10MG	0	0	0	0	0	0	0	0
Lomitapide Mesylate	Juxtapid Capsule 20MG	0	0	0	0	0	0	0	0
Lovastatin	Altoprev 24-Hour Extended Release Tablet 20MG	7	2	0	0	0	0	0	0
Lovastatin	Altoprev 24-Hour Extended Release Tablet 40MG	3	3	1	1	0	0	0	0
Lovastatin	Lovastatin Tablet 10MG	167	33	218	39	176	36	105	29
Lovastatin	Lovastatin Tablet 20MG	796	176	747	143	663	142	350	92
Lovastatin	Lovastatin Tablet 40MG	686	113	700	115	595	100	392	89
Mipomersen Sodium	Kynamro Injectable Solution 200MG/ML	0	0	0	0	4	1	2	1
Niacin	Niacin Extended Release Tablet 1000MG	0	0	23	11	89	13	24	7
Niacin	Niacin Extended Release Tablet 500MG	0	0	28	12	84	16	10	4
Niacin	Niaspan Extended Release Tablet 1000MG	377	58	246	44	75	11	25	6
Niacin	Niaspan Extended Release Tablet 500MG	871	152	508	100	180	28	70	14

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Niacin	Niaspan Extended Release Tablet 750MG	31	5	25	3	4	1	0	0
Niacin-Lovastatin	Advicor 24-Hour Extended Release Tablet 500-20MG	0	0	0	0	0	0	0	0
Niacin-Lovastatin	Advicor 24-Hour Extended Release Tablet 750-20MG	0	0	0	0	0	0	0	0
Niacin-Lovastatin	Advicor 24-Hour Extended Release Tablet 1000-20MG	0	0	0	0	0	0	0	0
Niacin-Lovastatin	Advicor 24-Hour Extended Release Tablet 1000-40MG	0	0	0	0	0	0	0	0
Niacin-Simvastatin	Simcor 24-Hour Extended Release Tablet 500-20MG	0	0	0	0	0	0	0	0
Niacin-Simvastatin	Simcor 24-Hour Extended Release Tablet 500-40MG	0	0	0	0	0	0	0	0
Niacin-Simvastatin	Simcor 24-Hour Extended Release Tablet 750-20MG	0	0	0	0	0	0	0	0
Niacin-Simvastatin	Simcor 24-Hour Extended Release Tablet 1000-20MG	0	0	0	0	0	0	0	0
Niacin-Simvastatin	Simcor 24-Hour Extended Release Tablet 1000-40MG	0	0	0	0	0	0	0	0
Omega-3-acid Ethyl Esters	Lovaza Capsule 1GM	585	137	547	117	379	84	217	51
Pitavastatin Calcium	Livalo Tablet 1MG	0	0	0	0	1	1	0	0
Pitavastatin Calcium	Livalo Tablet 2MG	11	1	5	2	9	2	6	2
Pitavastatin Calcium	Livalo Tablet 4MG	2	1	5	1	12	1	9	1
Policosanol	Lipex Tablet 10MG	0	0	0	0	0	0	0	0
Policosanol	Policosanol Capsule 10MG	0	0	0	0	0	0	0	0
Policosanol	Zyncol Tablet 30MG	0	0	0	0	0	0	0	0
Pravastatin Sodium	Pravachol Tablet 40MG	6	1	1	1	0	0	0	0

GENERIC	DESCRIPTION	2012		2013		2014		2015	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Pravastatin Sodium	Pravastatin Tablet 10MG	331	83	443	104	327	86	186	53
Pravastatin Sodium	Pravastatin Tablet 20MG	1,848	434	1,788	401	1,935	420	1,147	279
Pravastatin Sodium	Pravastatin Tablet 40MG	2,764	585	2,995	606	3,089	607	1,877	423
Pravastatin Sodium	Pravastatin Tablet 80MG	636	111	617	135	589	119	384	81
Probucol	Lorelco Tablet 250MG	0	0	0	0	0	0	0	0
Probucol	Lorelco Tablet 500MG	0	0	0	0	0	0	0	0
Rosuvastatin Calcium	Crestor Tablet 10MG	1,050	188	340	104	320	58	211	51
Rosuvastatin Calcium	Crestor Tablet 20MG	1,244	212	423	126	397	82	306	68
Rosuvastatin Calcium	Crestor Tablet 40MG	933	144	519	102	471	79	315	61
Rosuvastatin Calcium	Crestor Tablet 5MG	199	37	55	17	52	15	35	10
Simvastatin	Simvastatin Tablet 10MG	1,831	371	2,002	397	1,860	372	1,325	276
Simvastatin	Simvastatin Tablet 20MG	9,352	1,797	9,095	1,730	8,314	1,576	4,709	1,056
Simvastatin	Simvastatin Tablet 40MG	9,007	1,621	8,168	1,485	7,210	1,345	4,067	885
Simvastatin	Simvastatin Tablet 5MG	27	6	62	14	129	25	77	18
Simvastatin	Simvastatin Tablet 80MG	366	104	170	33	130	28	62	18
Simvastatin	Zocor Tablet 10MG	1	1	0	0	0	0	0	0
	TOTALS	**52,520**	**7,681**	**51,029**	**7,703**	**50,339**	**8,042**	**32,816**	**6,388**

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