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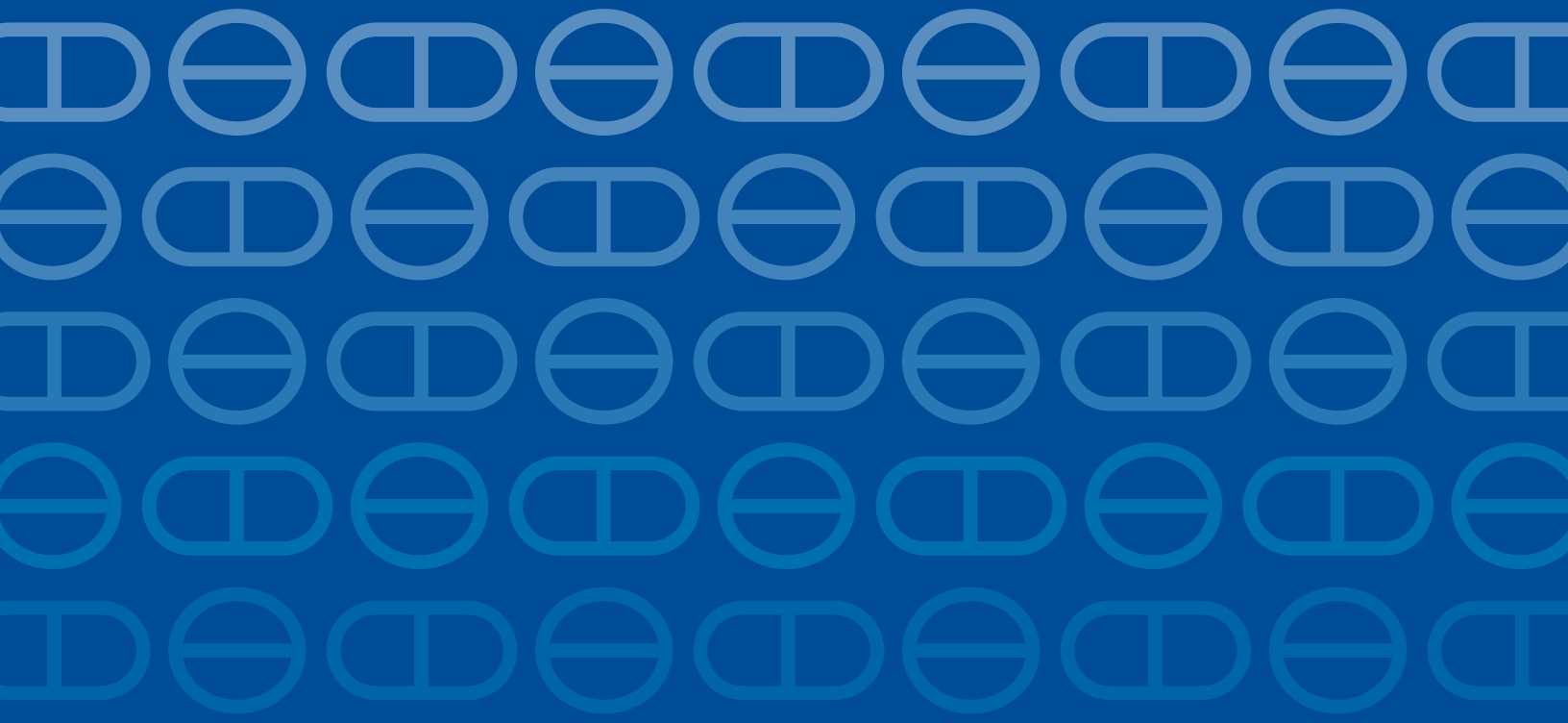
Managing lipids to prevent cardiovascular events:

A practical review of current data on lipid-lowering therapy



Managing lipids to prevent cardiovascular events

A practical review of current data on lipid-lowering therapy

Principal Consultant: Jing Luo, M.D., M.P.H.

Series Editors: Niteesh K. Choudhry, M.D., Ph.D. (principal editor), Jerry Avorn, M.D., Michael Fischer, M.D., M.S., Dae Kim, M.D., Sc.D., Ellen Dancel, PharmD, M.P.H.

Medical Writer: Stephen Braun

Consultant: Jennifer Lewey, M.D.

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Activity Overview:

The goal of this activity is to educate prescribers about the most recent guidelines, including understanding risk groups, the new pooled cohort risk calculator, and statin regimen intensity; provide management strategies for patients with statin intolerance; and the role of ezetimibe and PCSK9 inhibitors. In addition to providing this evidence report, the education program uses an innovative approach: academic detailing, which involves one-on-one educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials for family members are also provided.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Identify patients who are candidates for LDL lowering therapy based on current guidelines
- Summarize the differences between the Framingham and ASCVD risk calculators
- Develop treatment plans with lifestyle modifications and statins
- Identify statin intolerance and how to manage patients with statin associated muscle symptoms
- Describe the efficacy and safety profiles for the PCSK9 inhibitors

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Faculty and Planners:

Jing Luo, M.D., MPH, is an Instructor of Medicine in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital. Dr. Luo has no relevant financial relationships to disclose.

Niteesh K. Choudhry, M.D., Ph.D. is an Associate Professor of Medicine at Harvard Medical School and a hospitalist at Brigham and Women's Hospital. His research focuses on the use of medications to treat common chronic conditions. Dr. Choudhry has no relevant financial relationships to disclose.

Jerry Avorn, M.D. is a Professor of Medicine at Harvard Medical School and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 30 years. Dr. Avorn has no relevant financial relationships to disclose.

Michael Fischer, M.D., M.S. is an Associate Professor of Medicine at Harvard Medical School and a primary care internist who studies cost–effective drug use in outpatient practices. Dr. Fischer has no relevant financial relationships to disclose.

Jennifer Lewey, M.D. is a Cardiology Fellow at Columbia University Medical Center and a Research Fellow at Brigham and Women’s Hospital. Dr. Lewey has no relevant financial relationships to disclose.

Dae Kim, M.D., Sc.D., is an Assistant Professor of Medicine, Harvard Medical School and a geriatrician and epidemiologist at Brigham and Women's Hospital. Dr. Kim has no relevant financial relationships to disclose.

Ellen Dancel, PharmD, M.P.H., is the Director of Clinical Materials Development at Alosa Health. Dr. Dancel has no relevant financial relationships to disclose.

Stephen Braun, B.A. is a medical writer based in Amherst, MA. Mr. Braun has no relevant financial relationships to disclose.

Reviewers:

Thomas Gaziano, M.D., M.Sc., is an Assistant Professor of Medicine at Harvard Medical School and a cardiologist at Brigham and Women's Hospital. Dr. Gaziano has no relevant financial relationships to disclose.

Jillian West is the Manager of Educational Development and Accreditation for Harvard Medical School Department of Continuing Education. Her role is to review CME proposals for compliance with regulatory requirements. Ms. West has no relevant financial relationships to disclose.

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Email: cme@alosahealth.org

Mailing address:

Alosa Health

419 Boylston Street, 6th Floor

Boston, MA 02116

Fax: 857-350-9155

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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Introduction

Primary care physicians are on the front lines of advancing care for patients at risk of atherosclerotic cardiovascular disease (ASCVD). Managing high cholesterol levels is a key element in that effort. In recent years, clinical studies and professional guidelines have reconsidered the approach to cholesterol-lowering medications and have changed the paradigm for assessing and treating patients with high cholesterol.[1-3] In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released new guidelines for managing hyperlipidemia that relied only on randomized controlled trial data (or meta-analyses) that evaluated "hard" ASCVD outcomes (i.e. death from cardiovascular causes, nonfatal myocardial infarction [MI], or fatal and nonfatal stroke).[3] The guideline authors wanted to acknowledge the so-called "prevention paradox" where the majority of ASCVD events happen among low-risk individuals who may not be currently receiving lifestyle modification or medication treatment.[4]

Despite the evidence-based focus of the 2013 guidelines, some of the recommendations have been controversial:

- Statin initiation for primary prevention among those at low-to-moderate risk (~48.6% of US adults).
- Starting treatment regardless of low-density lipoprotein (LDL) levels.
- Once treatment has started, not titrating doses to a particular LDL target or goal.

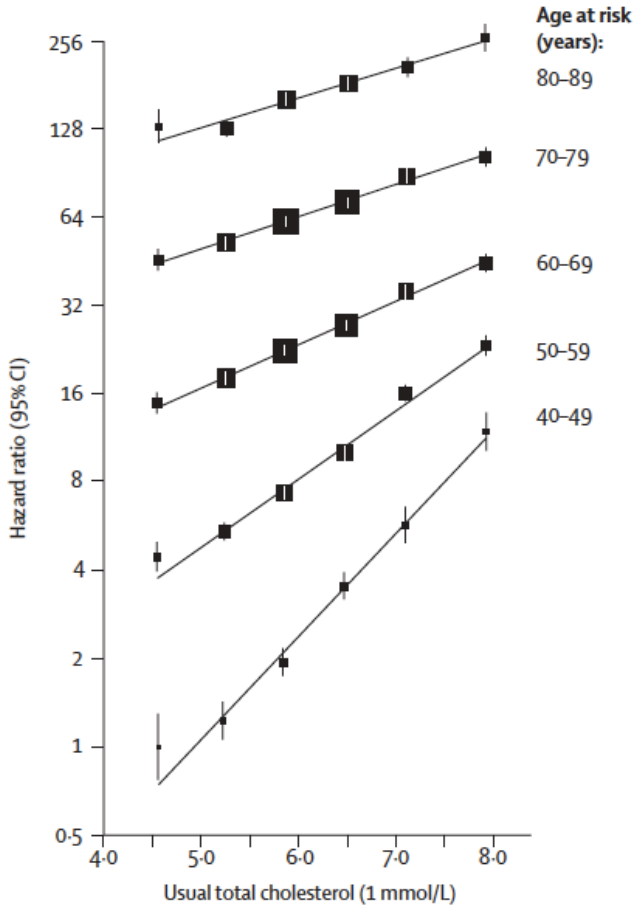
This document reviews the new guidelines and summarizes the evidence on which those guidelines are based. The treatment section focuses on statins because the evidence supporting their use to reduce ASCVD risk is particularly strong, although non-statin treatments, particularly ezetimibe and the PCSK-9 inhibitors, are also discussed.

Key Terms	
CVD	Cardiovascular disease. All diseases of the circulatory system including hypertension, ischemic heart disease, pulmonary heart disease, cerebrovascular disease.
ASCVD	Atherosclerotic cardiovascular disease. Pathology in any artery (e.g., coronary, carotid, peripheral) caused by plaque buildup.
CHD	Coronary heart disease. Pathology of the coronary arteries typically caused by plaque buildup. Also known as ischemic heart disease.

Epidemiology

Across age groups, a graded and continuous relationship exists between serum cholesterol levels and ischemic heart disease mortality (Figure 1).[5]

Figure 1: Association between death from ischemic heart disease and total cholesterol levels[6]



Reassuringly, both the prevalence of hyperlipidemia and the overall death rate from cardiovascular disease have declined over the past 20 years (Figures 2 & 3, next page).

Figure 2: Total cholesterol levels by racial/ethic group across 3 time periods[7]

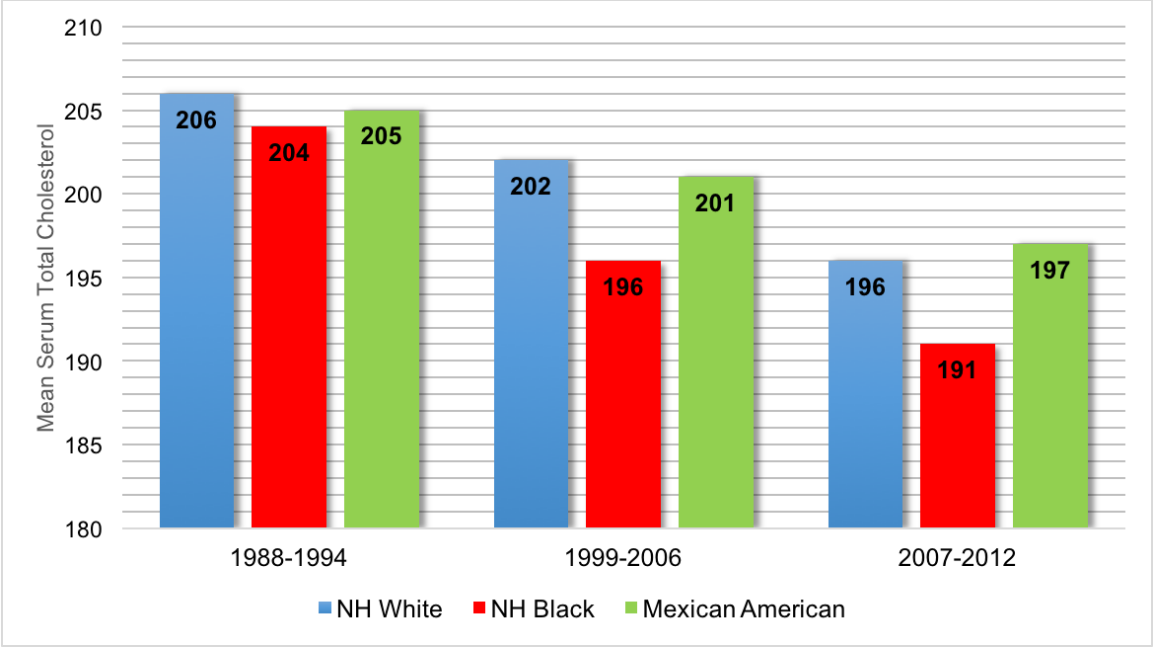
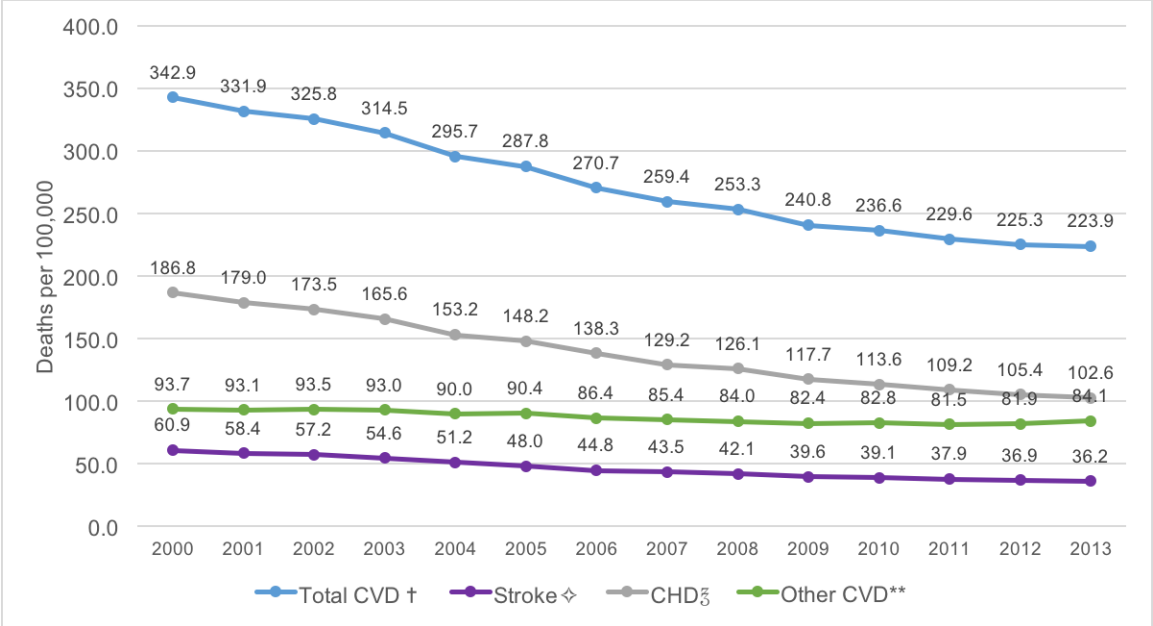


Figure 3: Cardiovascular disease mortality 2000-2013[7]



Some of the reduction in both hypercholesterolemia and total cardiovascular disease (CVD) mortality may be related to the increasing use of cholesterol-lowering drugs, primarily statins. Between 2003 and 2012 the percentage adults age 40 and older who used a cholesterol-lowering medication rose from 20% to 28%.[8]

Nonetheless, CVD still accounts for a large proportion of mortality, morbidity, and health care costs. In 2013, CVD was the underlying cause for 31% of all deaths in the United States, and an

estimated 2200 Americans die each day from CVD (1 every 40 seconds).[7] CVD claims more lives each year than cancer and lower respiratory disease combined, and if all major CVD were eliminated, average life expectancy would rise by almost 7 years.[7] The direct and indirect costs of CVD are estimated at $316.6 billion per year.[7]

Clearly, more efforts can be made to reduce CVD. Although, in 2014, 263 million prescriptions were written for lipid-lowering drugs,[9] less than half of those medically eligible for treatment of high cholesterol currently receive medication. This is true even among high-risk patients, for whom the evidence of benefit from these treatments is extremely strong.[10,11] In addition, adherence with statin therapy is low and decreases further with time (Table 1).[12]

Table 1: Adherence with statin therapy over time[12]

Duration of treatment (months)	Proportion of patients adherent
3	60%
6	43%
60	26%
120	32%

Overview of 2013 ACC/AHA Guidelines

The 2013 ACC/AHA guidelines shifted the paradigm of cholesterol management. Instead of targeting LDL levels, the current guidelines identify risk groups of patients who have benefited from statin therapy in trials. While both guidelines are based on clinical trial data, the old guidelines centered on a surrogate marker, LDL levels, while the new guidelines focus on achieving “hard” trial outcomes, such as reducing cardiovascular events.

The 2013 ACC/AHA cholesterol guidelines recommend statin treatment in 4 clinical scenarios where the benefits of LDL-lowering therapy are believed to outweigh risks:[3]

Patients with clinical ASCVD

Clinical ASCVD includes a history of prior myocardial infarction, acute coronary syndrome, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.

Patients with LDL levels ≥190 mg/dL

Patients with primary severe elevations of LDL (≥190 mg/dL) have a high lifetime risk of ASCVD and have increased risk of genetic hyperlipidemia. Patients in whom a secondary cause of hyperlipidemia is suspected should be first assessed and treated for reversible causes before pursuing genetic testing. These causes include obesity, medications, hypothyroidism, and nephrotic syndrome.

Diabetic patients age 40-75 years

Statins for primary prevention in diabetics are recommended for those with LDL levels 70-189 md/dL. Patients with levels ≥190 mg/dL should receive statin therapy based on level alone, whereas using statins for primary prevention with low LDL levels (<70 md/dL) has not been

studied. Individuals younger than 40 years or older than 75 years may also benefit from statin therapy, although this population has not been traditionally included in randomized controlled trials. In these patients, the consideration of additional risk factors and risks of therapy is warranted.

Patients age 40-75 years at high-risk of ASCVD, defined as a 10-year risk >7.5%

Patients without clinical ASCVD with LDL levels <190 mg/dL who are 40-75 years old with an elevated 10-year risk of ASCVD may benefit from statins. Assessing risk in this primary prevention population will be discussed in detail below. Individuals younger than 40 years or older than 75 years may also benefit from statin therapy if ASCVD risk is high, although this population has not been traditionally included in randomized controlled trials. In these patients, the consideration of additional risk factors and risks of therapy is warranted.

The 7.5% or greater 10-year risk of ASCVD threshold is lower than that used in prior guidelines but is thought to represent a more meaningful balance of statin risk versus benefit.

The 2013 Pooled Cohort ASCVD Risk Equations (ASCVD calculator), released as part of the 2013 ACC/AHA cholesterol guidelines, was developed to approximate ASCVD risk in a racially diverse patient population using data pooled from the Framingham cohort as well as the ARIC, CHS, and CARDIA cohort studies. The Framingham risk score used variables such as age, gender, cholesterol levels, smoking status, and hypertension to predict the risk of fatal or non-fatal MI and was well-validated in European and American populations.[13] The new calculator adds race (i.e., White, African American, or "Other") and presence of diabetes to these variables and predicts 10-year risk of "hard" cardiovascular end-points, including coronary heart disease death, non-fatal MI, and fatal and non-fatal stroke. Similar to prior risk scores, the ASCVD calculator overestimates cardiovascular risk in Hispanic and Asian-Americans.[2] Even among white and black populations, several studies have suggested that the ASCVD calculator generally overestimates the risk more than the Framingham-based calculators.[14] In fact, some physicians have suggested a higher 10-year ASCVD risk threshold, such as 10% or 12.5%, for statin initiation.[15] On the other hand, Pandya et al., conducted a cost-effectiveness study of the 10-year ASCVD risk thresholds and found that even if the calculator over-estimates risk, the cost-effectiveness of the lower threshold persists.[16]

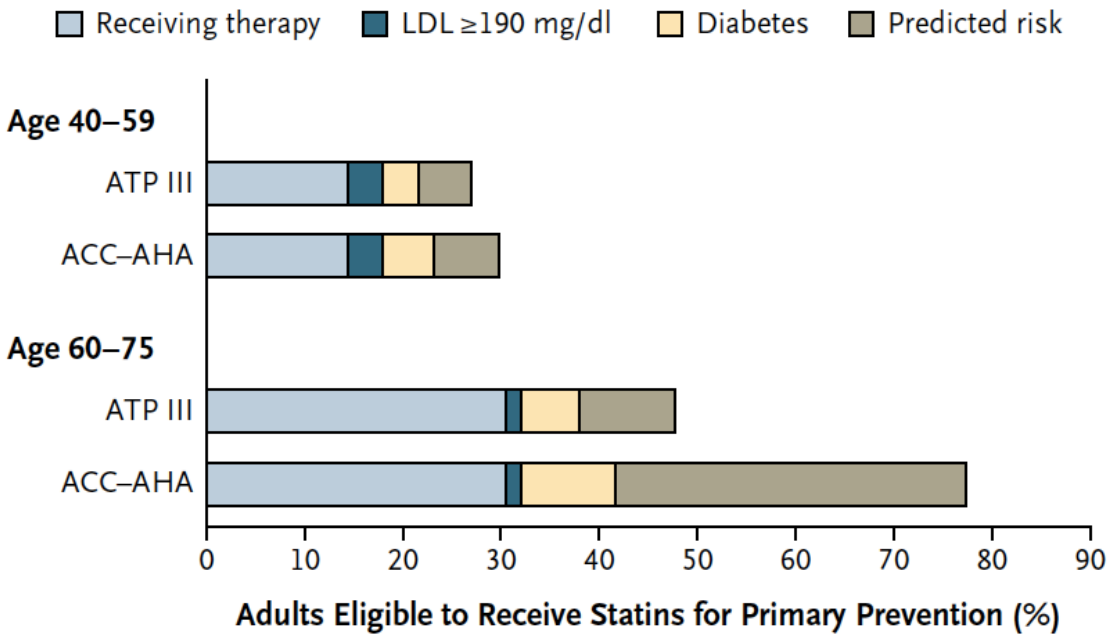
As noted above, the 2013 guidelines differ from the 2003 National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines that recommended specific LDL goals and for treating patients with statins who had certain high-risk comorbidities (such as CHD or risk equivalents) or who were at high-risk of developing CHD over 10 years, as assessed by the Framingham Risk Score.[13] The key differences between the old and the new guidelines are summarized below.

Table 2: A comparison of the older ATP III guidelines and the more recent ACC/AHA guidelines

	ATP-III (2004)	ACC/AHA Guidelines (2013)
Whom to treat	Use coronary heart disease (CHD) risk factors and baseline LDL level	One of four ASCVD risk groups
What to treat with	Statins and/or other cholesterol lowering drugs	Statins only
How to choose statin dose	Based on LDL level	Based on risk group and age
Role of LDL in follow-up	To set treatment goal and guide medical titration	To assess adherence

The 2013 guidelines recommend treatment for substantially more older adults than previous or alternative guidelines (Figure 4). A 2015 longitudinal community-based cohort study of 2435 statin-naïve participants found that the ACC/AHA guidelines for determining statin eligibility, compared with the ATP III, were associated with greater accuracy and efficiency in identifying increased risk of incident CVD and subclinical coronary artery disease, particularly in intermediate-risk participants.[17]

Figure 4: Comparison of ATP-III and ACC-AHA guideline treatment recommendations[4]



Treatment goals

Based on treatment strategies studied in RCTs, the 2013 Cholesterol Guidelines do not recommend titrating statin dose to a specific LDL level. Instead, the guidelines suggest measuring a baseline LDL level and then monitoring LDL for the percentage LDL reduction from that baseline expected with the statin as a way to assess patient adherence to the statin.[3]

BOTTOM LINE: ASCVD is a leading cause of morbidity and mortality. A large body of evidence supports the use of statins to reduce ASCVD risk, but they are underused. The ACC/AHA updated guidelines include major differences from ATP-III including a treatment focus on 4 clinical populations. The new guidelines do not recommend titrating statin dose to a specific LDL level; instead, they suggest measuring a baseline LDL level and then monitoring LDL for the percentage reduction from that baseline expected with the statin used.

Lifestyle modifications to treat high cholesterol

All guidelines for the treatment of hypercholesterolemia stress the importance of encouraging and supporting healthy eating habits, increasing physical activity, and achieving and maintaining a normal BMI. Interventions to meet these goals have been shown to produce modest, yet potentially significant, results. In overweight patients, a dose-response relationship exists between the amount of weight lost and lipid profile improvements.[18] For example, a 3 kg weight loss is associated with a mean reduction in triglycerides of at least 15 mg/dL.[18] A 5-8 kg weight loss is associated with LDL reductions of about 5 mg/dL, and HDL increases of 2-3 mg/dL.[18] Adopting a diet high in cholesterol-lowering foods, such as plant sterols, viscous fibers, and soy protein can reduce LDL by up to 13%.[19]

For motivated patients with a 10-year risk of ASCVD >7.5%, 3-6 months of therapeutic lifestyle changes can be attempted before initiating a lipid-lowering medication for primary prevention. The 2013 ACC/AHA guidelines recommend the following dietary practices for patients who would benefit from lower LDL:[20]

- diet high in vegetables, fruits, and whole grains
- low-fat dairy products
- protein primarily from fish, legumes, and poultry
- healthy fats (vegetable oils and nuts)
- limit sugar-sweetened beverages and red meats
- only 5-6% of calories from saturated fat
- reduce percentage of calories from trans fat

The OMNIHeart study randomized 164 adults to 3 types of healthy diets, each with reduced saturated fat, cholesterol, and sodium, and rich in fruits, vegetables, fiber, potassium, and other minerals. The results showed significant reductions in CHD risks, with diets rich in proteins (approximately half from plant sources) and monounsaturated fats showing the largest reduction in CHD risk (Table 3, next page).[21]

Table 3: Results from the OMNIHeart study[21]

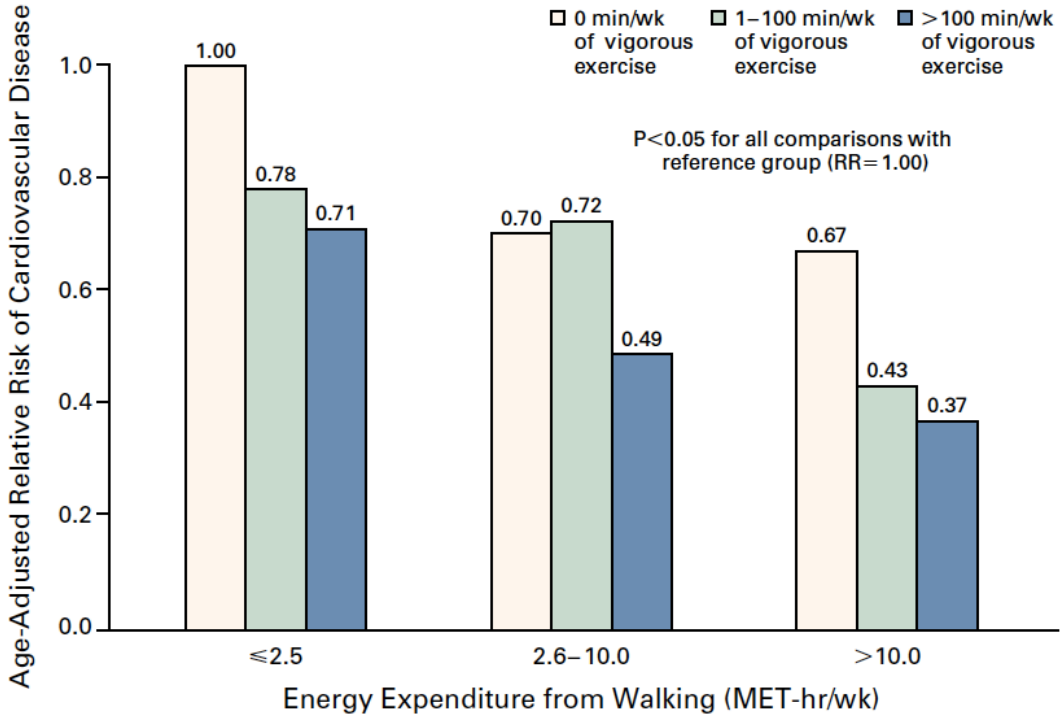
	Baseline	Carbohydrate Diet	Protein Diet	Unsaturated fat Diet
All Estimated 10-year CHD risk	5.1	4.3	4.0	4.1
Change from baseline		-16.1%	-21.0%	-19.6%
Change from carbohydrate			-5.8%	-4.2%

Even relatively modest dietary changes can lower CVD risk. For example, a meta-analysis of 10 cohort studies found that the consumption of 7 grams of fiber daily reduced the risk of CVD events by 9%.[22] Another study of 2033 men who survived an MI found a 29% relative reduction in the risk of CVD or death among those randomized to receive advice to eat two servings weekly of fatty fish (e.g., mackerel, salmon, trout).[23]

Evidence is mixed, however, for a benefit from dietary supplementation with omega-3 fatty acids in reducing ASCVD events. A 2013 trial of 12,503 patients randomized to receive 1 gram fatty acids or placebo found no difference in the risk of death or hospitalization from cardiovascular causes (HR 0.97; 95%CI: 0.88 – 1.08).[24]

Higher levels of physical activity (in the form of walking) are associated with lower CVD risk, as demonstrated in a study of 73,743 postmenopausal women (Figure 5). An additional reduction in risk was achieved with participating in the vigorous exercise.

Figure 5: Relative risk of CVD with both amount of vigorous exercise and energy expenditure from walking.[25]



The recommended exercise regimen for patients wanting to lower LDL:[3]

- Moderate to vigorous intensity aerobic exercise 3-4 times per week lasting on average 40 minutes per session.

Moderate intensity exercise is defined as: 3-6 metabolic equivalent of tasks (METS): e.g., walking briskly (3-5 miles per hour), bicycling slower than 10 miles per hour, yoga, gardening. Vigorous intensity is defined as ≥6 METS: e.g., race walking (>5 miles per hour), jogging, swimming laps, bicycling faster than 10 miles per hour.

As valuable as lifestyle changes can be, however, they can be difficult for patients to sustain long-term. When lifestyle changes alone fail to lower CVD risk to normal levels, abundant evidence supports treating hypercholesterolemia with medications (primarily statins) to reduce cardiovascular mortality in patients with or without known coronary artery disease.[26,27,28]

BOTTOM LINE: All patients should receive counseling on lifestyle modification consisting of diet (a pattern that emphasizes vegetables, fruits, whole grains) and exercise. For patients with a 10-year risk of ASCVD >7.5%, attempt therapeutic lifestyle changes for 3-6 months before considering lipid-lowering therapy. This approach should be used for patients who are highly motivated and have an ASCVD risk that could be reasonably reduced to <7.5% with optimal risk factor control.

An Overview of LDL-lowering medications

While statins are by far the most widely-used LDL-lowering class of medications, other classes can be used as alternatives or in addition to statins. The classes of lipid-lowering medications and their mechanisms of action are listed below, and their clinical characteristics are listed in Table 4.[29]

Drugs that have been shown to improve hard ASCVD outcomes in randomized trials

Statins inhibit HMG-CoA reductase, an enzyme involved in cholesterol synthesis in the liver. They decrease serum LDL concentrations by reducing levels of cholesterol in the hepatocyte, causing it to up-regulate expression of LDL receptors. Statins reduce LDL by 18-55%, and are first-line therapy in patients without contraindications.

Ezetimibe inhibits cholesterol absorption in the small intestine, reducing dietary intake of cholesterol and promoting its excretion in the bile. Ezetimibe has been shown to reduce LDL by an average of 18% and can be used concurrently with statins with similar additive effects.[30]

PCSK-9 inhibitors. Proprotein convertase subtilisin kexin 9 (PCSK9) is a protease produced predominately in the liver that facilitates the breakdown of hepatocyte LDL receptors and causes decreased clearance of LDL cholesterol. PCSK9 inhibitors are monoclonal antibodies that are injected subcutaneously to inhibit PCSK9 and significantly lower serum LDL levels.

Drugs that have *not* been shown to improve ASCVD outcomes in randomized trials

Bile acid sequestrants (e.g., cholestyramine) bind bile salts in the intestine, leading to conversion of cholesterol to bile acids, up-regulation of LDL receptors, and, therefore, to less circulating LDL. Bile acid sequestrants are moderately effective in reducing LDL (15-30% reduction), and are thought to be safer for use in pregnancy.[13]

Fibrates (e.g., gemfibrozil) alter gene expression in target cells, and activate a gene that increases HDL levels and decreases triglyceride levels. Fibrates can reduce LDL cholesterol by 5-20%.[13]

Nicotinic acid (niacin or vitamin B3) binds to a receptor on adipocytes, inhibiting lipolysis and release of fatty acids. It also decreases very low-density lipoprotein (VLDL) synthesis and secretion, and raises HDL levels. Niacin can reduce LDL cholesterol by 5-25% and triglycerides by 20-35%.[13] It is the most effective medication for increasing HDL (15-35%).[13]

Table 4. Efficacy and clinical characteristics of lipid-lowering drugs[30,13]

	LDL reduction	HDL increase	Cardiovascular risk reduction	Major side effects
Statins	18-55%	5-15%	About 20% reduction in risk of ASCVD for every 39 mg/dL reduction in LDL levels.[31]	Myopathy, diabetes mellitus (rare), cognitive impairment, liver toxicity (very rare)
Ezetimibe	10-20%	Minimal	6% relative reduction in combined CV events after acute coronary syndrome[32]	Myopathy, upper respiratory infection, fatigue, sinusitis, elevated transaminases when used with statin.
PCSK9 Inhibitors	60%	6%	More than 50% relative reduction in all-cause mortality and MI in early studies[33]	Myalgia, neurocognitive effects, injection site reactions (uncommon)
Bile acid sequestrants	15-30%	Minimal	No significant reduction	Nausea, bloating, cramping; impairs absorption of other drugs
Fibrates	5-20%	5-20%	13% relative reduction in coronary events; no significant reduction in mortality[34]	Increased creatinine, myopathy. Should not be co-administered with statin.
Nicotinic acid	10-25%	15-35%	No significant reduction	Flushing, pruritus, nausea, myopathy, hepatotoxicity. Should not be co-administered with statin.[35]

The authors of the 2013 AHA/ACC guidelines found no data supporting the routine use of non-statin drugs combined with statin therapy to further reduce ASCVD events,[3] but those guidelines were written prior to the publication of results from the IMPROVE-IT trial and many of the PCSK9

inhibitor trials. In 2016 the results of an ACC Expert Consensus panel were published, which recommended adding ezetimibe or PCSK9 inhibitors in selected patient populations who fail to respond to statins, despite good adherence, or who are unable to tolerate several statins (Table 5).[36]

Table 5. Recent guidance on PCSK9 inhibitors and ezetimibe.[36]

	PCSK9 inhibitors	ezetimibe
When to use	*Strongest evidence* • In high-risk patients with ASCVD	• In patients with ACS
	Expert opinion • In patients unable to tolerate several statins	• In high-risk patients with ASCVD • In patients with diabetes for primary prevention • In patients unable to tolerate several statins

BOTTOM LINE: Of all lipid-lowering therapies, statins are supported by the most robust evidence that they reduce CV risk. Emerging evidence supports the use of PCSK-9 inhibitors and ezetimibe in selected patients. No evidence supports the use of other non-statin lipid-lowering agents.

Statins

Statins have been shown to improve mortality in primary and secondary prevention of CAD, and their benefits also apply to elderly patients without life-threatening co-morbid conditions (see evidence summaries in subsequent sections).[27,37] Seven statin products are available, most as generics, with the products varying in their ability to lower LDL (but all with a dose-dependent LDL-lowering ability).

Table 6: Statin products

Generic name	Brand name
atorvastatin	Lipitor
fluvastatin	Lescol, Lescol XL
lovastatin	Altoprev*, Mevacor
pitavastatin**	Livalo
pravastatin	Pravachol
rosuvastatin	Crestor
simvastatin	Zocor

* Altoprev does not have a generic equivalent FDA approved.
** Generic options are not available.

The 2013 AHA/ACC Guidelines classified statins according to the degree by which they reduce LDL levels (Table 7). On average, high intensity statins reduce LDL levels by ≥50% whereas moderate intensity statins reduce LDL levels by 30% to 50%.

Table 7. Classification of statins by degree to which they reduce LDL

High-intensity statins	Moderate-intensity statins	Low-intensity statins
Lowers LDL by ≥50%	**Lowers LDL by 30-50%**	**Lowers LDL by <30%**
Atorvastatin 40-80 mg* Rosuvastatin 20-40 mg**	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg** Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 40 mg BID Fluvastatin XL 80 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin XL 20-40 mg

* Atorvastatin 80 mg daily is preferred but 40 mg daily can be used if higher dose not tolerated

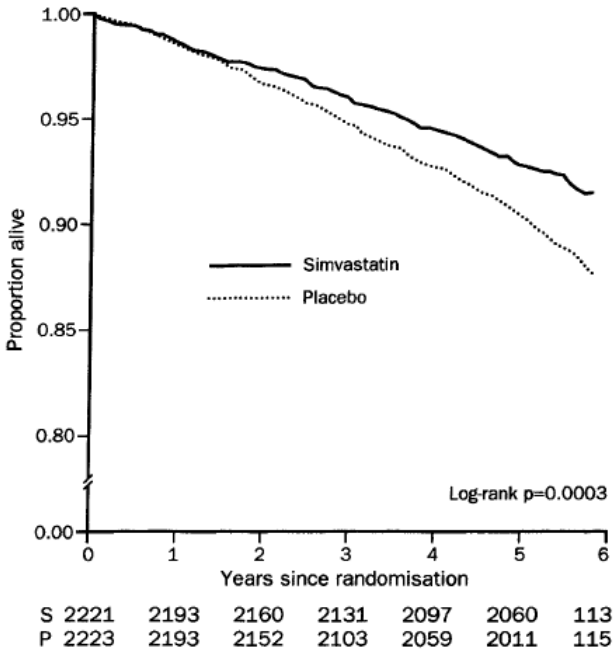
BOTTOM LINE: Because equipotent doses of statins appear equally effective and equally safe, which statin to prescribe should be based primarily on the intensity of LDL lowering recommended for a given ASCVD risk, and on generic availability.

Statins for secondary prevention

A meta-analysis of data from >90,000 patients with known CVD risk found that statin therapy can reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 20% per 39 mg/dL reduction in LDL levels.[31] The absolute benefit relates mainly to the patient's absolute risk level and to the absolute reduction in LDL cholesterol achieved.[31]

Statin treatment among those with previous ASCVD is associated with lower risk of death, as illustrated by the data from the Scandinavian Simvastatin Survival Study (4S). The 4S study randomized 4444 patients with angina pectoris or previous MI to simvastatin or placebo and found a 30% lower risk of death among treated subjects after 6 years on therapy (RR of death 0.70; 95% CI: 0.58–0.85).[38]

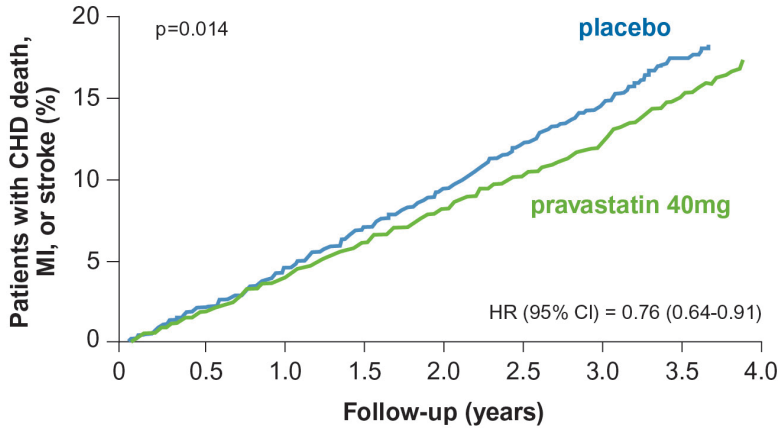
Figure 6: Results from the 4S study[38]



High-intensity statins are more effective than moderate-intensity statins for reducing ASCVD risk among adults younger than 75. A pooled analysis of 8,658 post-ACS patients from the A to Z (Aggrastat to Zocor) and PROVE IT-TIMI 22 trials found that by 8 months, LDL levels were significantly lower in the intensive statin therapy group (median 64 mg/dL) than in the moderate therapy group (median 87 mg/dL; $p<0.001$).[39] All-cause mortality was significantly reduced in the intensive therapy group compared with the moderate therapy group (3.6% vs. 4.9%; HR, 0.77; 95% CI: 0.63-0.95; p=0.015).[39] This reduction in all-cause mortality with intensive statin therapy was consistent across key subgroups. One death was prevented for every 95 patients treated with high-dose statin therapy for 2 years.[39]

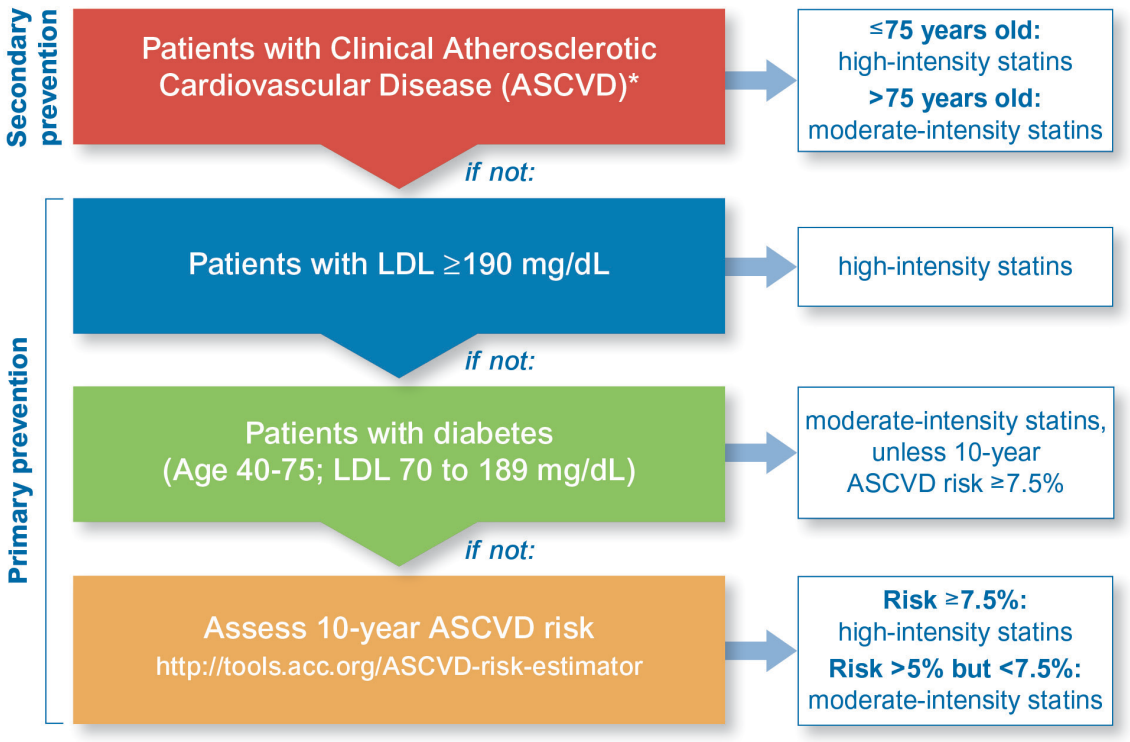
An important caveat to the results showing benefit for higher-intensity LDL lowering is that patients older than 65 or who had baseline LDL levels below 125 may be less likely to benefit from more intensive treatment.[40] The benefit of moderate-intensity statins in older adults was demonstrated in the PROSPER study, which randomized 5804 subjects with pre-existing vascular disease ages 70-82 to pravastatin 40 mg or placebo and found a 15% reduction in risk of experiencing CV death, non-fatal MI, or fatal or nonfatal stroke (HR 0.85; 95%CI 0.74 – 0.97).[41]

Figure 7: Results from the PROSPER trial of moderate-intensity statin use in higher-risk older adults[41]



The algorithm in Figure 8 summarizes recommendations in the 2013 ACC/AHA guidelines for secondary prevention of CVD.

Figure 8: Algorithm for secondary and primary prevention of CVD[3]



*Clinical ASCVD: acute coronary syndrome (ACS), myocardial infarction (MI), angina, revascularization, stroke, TIA, or peripheral arterial disease.

BOTTOM LINE: Among those with previous ASCVD, some statins are better than no statins and higher-intensity statins are better than lower-intensity statins. For those over age of 75, the evidence is strongest for moderate intensity statins (e.g., pravastatin 40 mg).

Lipid lowering for primary prevention

Statins for primary prevention are effective over a wide range of LDL-C levels and 10-year ASCVD risk and provide a similar relative risk reduction as that observed in secondary prevention trials. The 2013 ACC/AHA cholesterol guidelines recommend statin treatment for primary prevention in three classes of patients: those with LDL levels ≥190 mg/dL; those with diabetes ages 40-75; and those age 40-75 years at high-risk of ASCVD, defined as a 10-year risk >7.5% (see Figure 8 on previous page).[3]

The 2013 ACC/AHA guidelines recommend cholesterol screening beginning at age 40 and continuing every 5 years until age 79 for individuals without clinical ASCVD. The guidelines recommend a fasting lipid profile in order to calculate the LDL cholesterol level (LDL cholesterol = total cholesterol − HDL cholesterol − [triglycerides ÷ 5]). In non-fasting states, LDL and triglyceride levels can vary by as much as 20%. However, some patients do not undergo lipid testing due to the inconvenience of fasting or early morning blood draws. Given the possible benefits of increased patient adherence to screening and the ease of testing, it is reasonable to offer non-fasting lipid testing for lower-risk individuals on a routine clinic visit and to use fasting lipid profile testing for higher-risk patients.

Patients with LDL levels ≥190 mg/dL

Patients with LDL levels ≥190 mg/dL have a high lifetime risk of ASCVD and have increased risk of genetic hyperlipidemia. The value of statins for primary prevention in this group was demonstrated in the 1995 West of Scotland Coronary Prevention Study (WOSCOPS) of 6595 middle-aged men randomized to either pravastatin 40 mg, or placebo and followed for about 5 years. The results showed a 33% relative reduction of coronary mortality (1.9% versus 1.3%; P=0.04) in the pravastatin group compared to placebo.[28] Major coronary events (nonfatal MI or death from CHD) were 31% lower in the pravastatin participants compared to the placebo group.[28]

Patients with diabetes age 40-75 years

The Collaborative Atorvastatin Diabetes Study (CARDS) assessed the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in patients with type 2 diabetes who did not have high LDL levels.[42] 2838 patients aged 40-75 years in the UK and Ireland were randomized to placebo (n=1410) or atorvastatin 10 mg daily (n=1428). The median duration of follow-up was 3.9 years. 127 patients allocated placebo (2.46 per 100 person-years at risk) and 83 allocated atorvastatin (1.54 per 100 person-years at risk) had at least one major cardiovascular event (rate reduction 37% [95% CI -52 to -17]; p=0.001).[42]

Assessed separately, acute coronary heart disease events were reduced by 36% (-55 to -9), coronary revascularizations by 31% (-59 to 16), and rate of stroke by 48% (-69 to -11).

Atorvastatin reduced the death rate by 27% (-48 to 1; p=0.059). No excess of adverse events was noted in the atorvastatin group.[42]

Patients age 40-75 years at high-risk of ASCVD, defined as a 10-year risk >7.5%

For patients without diabetes and LDL-C levels between 70 and 189, the 2013 ACC/AHA guidelines recommend obtaining an estimate of 10-year ASCVD risk and using that estimate to guide discussions with the patient about starting statin therapy. Among individuals with low risk (i.e., between 5% - 7.5%) the potential benefits of statin therapy must be weighed against the risk of adverse events.

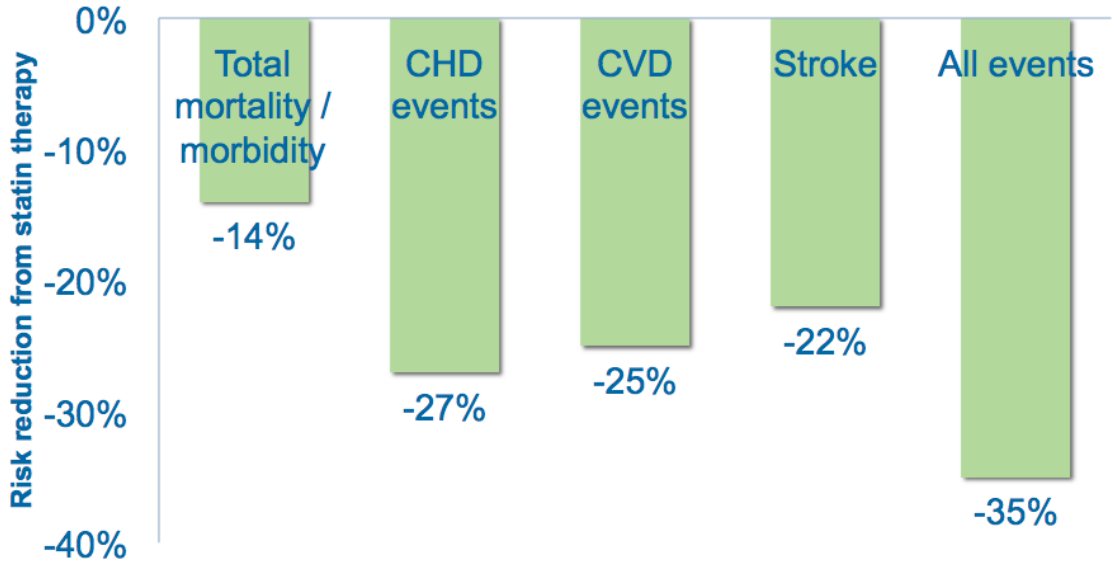
The rationale for initiating statin therapy for primary prevention at a 10-year ASCVD risk of ≥7.5% is based on a significant body of evidence from large, well-controlled trials, as well as a meta-analysis of 22 statin trials (including 6 primary prevention trials) showing that LDL-C reduction reduced major vascular events, regardless of baseline risk.[43]

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPs) of approximately 6600 men and women with no history of CAD randomized participants to lovastatin (20-40 mg) or placebo with both arms receiving low saturated fat and low cholesterol diet intervention.[44] After an average follow-up of 5.2 years, lovastatin reduced LDL levels by about 25% and reduced the incience of first major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) by 37% (RR 0.63; 95% CI: 0.50-0.79). There were too few events to perform a survival analysis on coronary mortality.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) of 10,300 patients was stopped after 3 years due to a 36% relative reduction of nonfatal myocardial infarction or CHD mortality and a 21% relative reduction in total cardiovascular events in the atorvastatin treated participants, whose baseline LDL level was reduced from 131 mg/dL to 88 mg/dL.[45]

More recently, a 2013 Cochrane meta-analysis of 18 studies of statin use for primary prevention found that statins reduced all-cause mortality by 14% (OR 0.86; 95% CI 0.79-0.94), combined fatal and non-fatal CVD events were reduced 25% (RR 0.75; 95% CI 0.70-0.81), combined fatal and non-fatal CHD events were reduced 27% (RR 0.73; 95% CI 0.67-0.80) and combined fatal and non-fatal stroke was reduced 22% (RR 0.78; 95% CI 0.68-0.89).[46]

Figure 9: Risk reduction from statin therapy for primary prevention[46]



ASCVD risk assessment

ASCVD risk assessment tools have evolved to include increasing numbers of risk factors as well as alternate end-points.

Table 8: Common cardiovascular risk calculators

Risk Score	Outcome	Characteristics
ASCVD Risk Calculator (aka Pooled Cohort Equations Risk Estimator)	CHD death, non-fatal MI, and fatal and non-fatal stroke	Derived from NHLBI-funded cohort studies. Outcomes are "hard" CV endpoints that patients care about
Framingham Risk Score (ATP-III calculator)	Fatal and non-fatal MI	Statin initiation threshold previously recommended at 20%. Using a lower threshold is reasonable.
Framingham Risk Score (Global CVD)	Coronary events, cerebrovascular events, PAD, heart failure	May be helpful to provide global CV risk to patients
Reynolds Risk Score	MI, ischemic stroke, coronary revascularization, or CV death	Includes family history, diabetes status, and hs-CRP levels in risk calculation

MI: myocardial infarction. PAD: peripheral arterial disease. CV: cardiovascular
Coronary events: MI, coronary death, acute coronary syndrome, angina; Cerebrovascular events: ischemic or hemorrhagic stroke, transient ischemic attack; PAD: intermittent claudication.

For example, the Framingham risk score predicts global CVD events, including coronary events, stroke, claudication, and incident heart failure.[47] Most of these risk scores were derived in predominately white populations and later validated in cohorts with white and black patients. Using these tools, cardiovascular risk tends to be overestimated in certain ethnic groups,

including Hispanic and Japanese-American men, Native-American women, and Chinese men and women.[48] The ASCVD Risk Calculator recommended in the 2013 ACC/AHA Guidelines was derived from major NHLBI funded cohort studies and predicts 10-year risk of hard ASCVD endpoints such as death from cardiovascular causes, nonfatal MI, and fatal or nonfatal stroke. Nonetheless, a 2014 study using a European cohort found that both the new ACC/AHA pooled cohort calculator and the ATPIII calculator overestimated risk and that, because age is a major driver of risk, the ACC/AHA calculator ends up recommending statins for nearly all men age 55 and older and two-thirds of women.[49]

The use of a clinical decision aid may be helpful in discussing the risks and benefits of statin therapy. The Mayo Clinic Decision aid facilitates the use of the ASCVD, ATP-III, and Reynolds risk calculators. For a link to the Mayo Clinic Decision aid and Risk calculators, see AlosaHealth.org/modules/lipids.

BOTTOM LINE: A large body of evidence supports the claim that statins reduce CV events, even among those with low or intermediate risk. The ACC/AHA-recommended calculator may slightly overestimate risk, but it is the best tool currently available. For patients with 10-year risk of ASCVD ≥7.5%, attempt lifestyle changes for 3-6 months and discuss risks and benefits of treatment before initiating statin therapy.

Statin adverse effects

Adverse effects associated with statin use tend to be dose-related. Although monitoring for hepatotoxicity was previously recommended for patients taking a statin, the actual incidence of new liver disease was so low that this approach is no longer recommended. Patients should, however, be screened for normal liver function before starting a statin. It should be noted that cancer is *not* a risk from statins, as evidenced by results from several meta-analyses and a 20-year follow-up study.[50,51,52]

Muscle related symptoms

Myalgia is one of the most common patient complaints from statin therapy and can contribute to lack of adherence. Myalgia can occur with and without an elevation in biomarkers such as creatine kinase (CK).

Table 9. Prevalence of more serious statin-associated muscle symptoms[53]

Symptom	Prevalence
Myalgia	3-5%
Myopathy	0.1-0.2%
Rhabdomyolysis	0.01%

In clinical registries, between 7% and 29% of patients report muscle symptoms.[54] Preclinical studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, providing a potential causal link between statins and muscle symptoms.[54]

Approximately 90% of muscle symptoms appear in the first 6 months of statin therapy or after a dose up-titration, and of these, 75% occur in the first 10-12 weeks.[53] Physically active patients appear to experience muscle symptoms more often than inactive patients.[54] Higher doses of a statin increase the risk of muscle symptoms, although the absolute risk seen in clinical trials (as opposed to observational or registry data) is low. In the SEARCH trial, among participants taking 80 mg simvastatin, 53 out of 6031 (0.9%) reported muscle symptoms compared to only 2 out of 6033 (0.0%) taking 20 mg simvastatin.[55]

Rhabdomyolysis is a rare, but potentially fatal, complication of statin use. The highest risk of statin-induced rhabdomyolysis was associated with cerivastatin, which was taken off the market in 2001.[56] The general prevalence of rhabdomyolysis with current statins is approximately 0.01%.[53] Rhabdomyolysis might be triggered by prescription of high doses of statins or by statin accumulation due to interactions with concomitant medications that compete with the cytochrome p450 system. If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria.[3]

Table 10: Risk factors for statin-associated muscle symptoms

Endogenous factors	Exogenous factors
• Age >80 years • Female • Asian ethnicity • Low BMI, frail • History of existing muscle pain or elevated creatine kinase • Family history of myopathy or myopathy with statin therapy • Neuromuscular diseases • Severe renal disease • Acute/decompensated liver disease • Hypothyroidism (untreated) • Diabetes • Genetic polymorphisms	• Alcohol abuse • Illicit drug use • Drug interactions – e.g., fibrates, amiodarone, verapamil, warfarin, macrolides, and more • Surgery with severe metabolic demands • Heavy and/or unaccustomed exercise

Among patients with statin-associated muscle symptoms who discontinue therapy, over 90% are ultimately able to tolerate the same statin or a different statin with careful reintroduction and monitoring.[57] Use of non-statin drugs may also be an option in highly selected cases. In the 2016 GAUSS-3 randomized trial of 511 adult patients with a history of stain intolerance, the active study drug was stopped for muscle symptoms in only 5 of 73 ezetimibe-treated patients (6.8%), and 1 of 145 evolocumab-treated patients (0.7%).[58]

Statins have been shown to reduce coenzyme Q10, a key component of the mitochondrial respiratory chain. Mitochondrial dysfunction may be associated with statin-related muscle symptoms (SAMS) or myalgia. It has been theorized that supplementation with coenzyme Q10 may reduce muscle symptoms. One small, 32 subject, double-blind, randomized trial compared coenzyme Q10 to vitamin E for patients reporting statin associated muscle symptoms. After 30 days, the group randomized to coenzyme Q10 had a 40% relative reduction in the severity of pain and a 38% reduction in limitation of daily activities due to pain compared to patients randomized to vitamin E.[59]

Another small study of 44 patients found that coenzyme Q10 improved the ability to tolerate a statin, although the results were not statistically significant.[60] After a two week wash-out, patients who self-reported muscle symptoms were randomly assigned to coenzyme Q10 or placebo with baseline therapy with simvastatin 40mg per day. At 12 weeks, 73% (16 of 22) of patients were able to tolerate simvastatin compared to 59% (13 of 22) of patients receiving placebo.[60] Since coenzyme Q10 poses relatively mild side effects (e.g., nausea, upset stomach) and in light of the conflicting data, a trial of coenzyme Q10 in patients with statin-associated muscle symptoms may be an option for select patients.

Diabetes

Statin treatment appears to increase the incidence of diabetes by a small amount. This increased risk is generally out-weighed by the benefit derived from statin use among high risk patients. In a subgroup analysis of the Cholesterol Treatment Trialists (CTT) meta-analysis of 14 statin trials including 71,370 non-diabetic participants, there was one extra case of diabetes over 4 years for every 255 people treated with statin.[61] In the same studies, statin treatment resulted in a reduction of 5.4 major coronary events (coronary mortality and non-fatal myocardial infarction) per 255 patients treated for the same period of time.[61]

The slight increase in risk for type 2 diabetes is based on two trials (JUPITER and AFCAPS/TexCAPS) where 342 of 12,205 subjects (2.8%) on statins developed diabetes compared to 290 (2.4%) on placebo.[46] In an analysis of the JUPITER trial a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed.[62] When compared to 6095 participants without risk factors for diabetes, there was a 52% reduction in primary endpoints (HR 0.48; 95% CI: 0.33–0.68) but no new cases of diabetes.[62]

Although the absolute risk of causing new-onset diabetes with statins is low, the risk of incident diabetes needs to be considered whenever statins are prescribed. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines.[3] Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy diet, exercise, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.[3]

Cognitive impairment

Concerns have been raised about the association between statin use and memory loss or cognitive impairment. Meta-analyses of RCTs have not confirmed that statins negatively impact memory; however such changes could have been underreported.[63] Although the literature is inconclusive, the FDA has acknowledged that statins may be associated with cognitive impairment in rare cases, though causality is not certain.[64] The expert panel of the 2013 ACC/AHA cholesterol guidelines found no evidence that statins had an adverse effect on either cognition or risk of dementia.[3] In the PROSPER trial, during 42 months of follow-up, pravastatin use was not associated with a decline in long term cognitive function.[65] A 2015 retrospective study showed that both statins and other lipid-lowering drugs were associated with an increased risk of acute memory loss, which the authors suggest could be attributed to detection bias.[66]

BOTTOM LINE: Muscle symptoms are the most commonly-reported adverse effect associated with statins. Prevalence rates of myalgia vary from 3–5% of patients in controlled trials to between 7% and 29% of patients in registries. Rates reported for myopathy are 0.1–0.2% and for rhabdomyolysis 0.01%. Symptoms typically occur early in treatment and are more likely in physically active patients. Most patients are able to tolerate the same statin or a different statin with careful reintroduction and monitoring.

Statins are associated with a low risk of new-onset type 2 diabetes and patients should be assessed for diabetes risk prior to treatment initiation. Evidence that statins increase the risk of cognitive impairment is inconclusive.

Guidelines for minimizing statin adverse effects

The 2013 AHA/ACC guidelines recommend the following steps to improve the safety of statin use:[3]

- Measure baseline alanine/aspartate transaminase (ALT) levels before initiating a statin.
- Recheck hepatic function if symptoms of hepatotoxicity develop (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, yellowing of skin or sclera).
- Consider decreasing statin dose when 2 consecutive values of LDL levels are <40 mg/dL.
- Avoid initiating simvastatin at 80 mg daily or increasing simvastatin dose to 80 mg daily.
- Use caution prescribing statins in patients 75 years or older.
- Use caution prescribing statins in patients taking concomitant medications that alter drug metabolism or who are taking multiple/complex medications.
- Evaluate patients presenting with confusion or memory impairment while on statin therapy for non-statin causes, such as exposure to other drugs and systemic neuropsychiatric causes, in addition to considering the possibility of adverse effects associated with statin therapy.
- Have patients avoid grapefruit juice since this may increase risk of side effects.

Statin initiation and follow-up

Recommended baseline and follow-up labs for patients being considered for a statin are presented in Table 11.

Table 11: Recommended baseline and follow-up labs[3]

Recommended lab testing	
Prior to statin initiation	Fasting lipid panel and ALT level
4-12 weeks after statin initiation	Fasting lipid panel
Up to every 12 months thereafter	Fasting lipid panel
As needed lab testing	
Creatine Kinase (CK)	Check at baseline in patients at high risk of myopathy (personal or family history of muscle disease, statin intolerance, or medications that increase risk). Check during follow-up if muscle symptoms or generalized fatigue
ALT	Check during follow-up if evidence of hepatoxicity

On follow-up, evaluate for anticipated therapeutic response: LDL decrease by >50% for high intensity statin or 30-50% for moderate intensity statin. If a patient has a smaller response and therapy is tolerated, assess adherence to lifestyle changes and medication regimen. In some cases, screening for secondary causes of hyperlipidemia will be necessary. If improvement in adherence does not improve LDL response, some patients may benefit from non-statin therapy to lower cholesterol (see section on non-statin therapies below).

Dealing with statin intolerance

Statin intolerance is defined as either biomarker abnormalities (i.e., elevated creatine kinase or liver function tests) or uncomfortable or intolerable symptoms (most often muscle related). If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria.

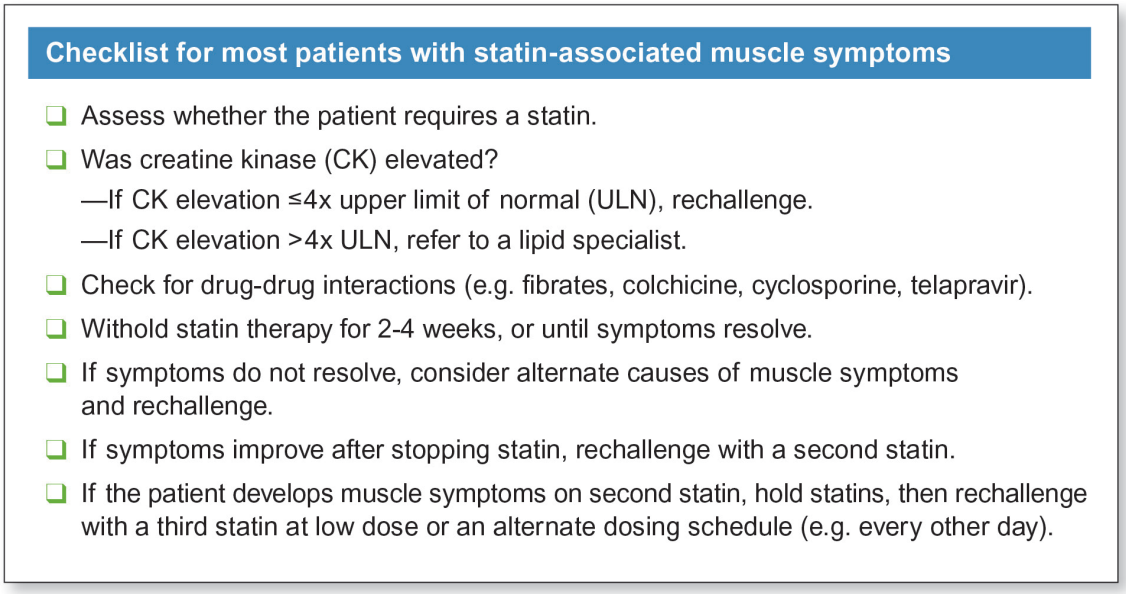
Figure 10 (next page) presents an algorithm for managing statin intolerance. Here are the key points:[3]

- Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
- Discontinue the statin for 2-4 weeks and assess symptoms.
  - If symptoms improve, try a second statin at the usual or starting dose. If the symptoms recur, try a low dose of a third statin or an alternative dosing pattern.
- If symptoms persist after the initial statin washout period, try a statin re-challenge at the original or a lower dose.

Patients who are intolerant to this strategy may need to be treated with non-statin therapies, depending on the clinical indication.

The 2013 AHA/ACC guidelines do not recommend routine CK testing for patients receiving statins, however such measurement is reasonable for those thought to be at risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.[3] Measuring CK levels is recommended in patients with muscle pain, tenderness, stiffness, cramping, weakness, or general fatigue.[3]

Figure 10: Checklist for managing statin intolerance[54]



BOTTOM LINE: Evaluate factors that may predispose patients to statin-associated myopathy. Review the indication for statin use and rechallenge patients if CK elevation <4x the upper limit of normal (ULN). Switch to an alternate statin, reduce daily dose, or use intermittent dosing options for patients at high risk of myopathy.

Are statins useful in heart failure?

Some studies have suggested that low cholesterol in patients with HF worsens prognosis, while other studies (post hoc and observational) and a systematic review have suggested that statins may be beneficial in HF.[67-69]

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial randomized 5,011 patients to treatment with rosuvastatin 10 mg daily or placebo, and followed them for a median of 33 months.[70,71] LDL levels declined from 137 mg/dL at baseline to 76 mg/dL at 3 months in the rosuvastatin group (a reduction of 44%), but did not change significantly in the

placebo group. There was no significant difference in the primary outcome (a composite of CV death, non-fatal MI and non-fatal stroke) between the rosuvastatin and placebo groups (HR 0.92; 95% CI: 0.83-1.02; p=0.12), nor in death from any cause (HR 0.95; 95% CI: 0.86-1.05; p=0.31).[70] The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca – Heart Failure) study randomized 4,574 patients to treatment with rosuvastatin 10 mg daily or placebo, and followed them for a median of 3.9 years.[72] There was no significant difference in death from any cause between the rosuvastatin and placebo groups (HR 1.00; 95% CI: 0.90-1.12; p=0.94).

Bottom line: Two large randomized controlled trials designed to assess the role of statins in HF failed to demonstrate a reduction in mortality or CV events. Statins cannot be recommended as routine therapy in the management of HF.

Do outcomes differ by sex?

Older studies comparing the benefits of statins in men as compared to women yielded conflicting results.[73] Two meta-analyses have examined sex differences in outcomes of statin therapy for both primary and secondary prevention. A 2012 meta-analysis focused on randomized, placebo-controlled trials of statin use for secondary cardiovascular prevention.[74] The study included 11 trials of 43,193 patients of whom only one-fifth were women. In secondary prevention of cardiovascular events, statins were equally effective in women and men (RR 0.81; 95% CI: 0.74-0.89 in women and RR 0.82; 95% CI: 0.78-0.85 in men).

Kostis et al. systemically reviewed randomized controlled trials of statin therapy with sex-specific data through 2010.[75] The review included 18 trials of primary (8) and secondary prevention (10) with 141,235 participants (29% women). A statistically significant reduction in the combined cardiovascular endpoint (including death, MI events, strokes, and revascularization) was observed in both women (OR 0.81; 95% CI: 0.75-0.89) and men (OR 0.77; 95% CI: 0.71-0.83) with no difference in risk reduction by sex (p= 0.1837).

BOTTOM LINE: Based on the existing data, statin use appears to reduce cardiac events and mortality to an equivalent degree in both women and men.

Non-statin therapies

Ezetimibe

Ezetimibe, FDA-approved in 2002, blocks cholesterol absorption in the gut and can reduce LDL level about 18% when used as monotherapy. Ezetimibe is also approved for, and can be used as, an adjunct to statins since it has a different mechanism of action from statins.

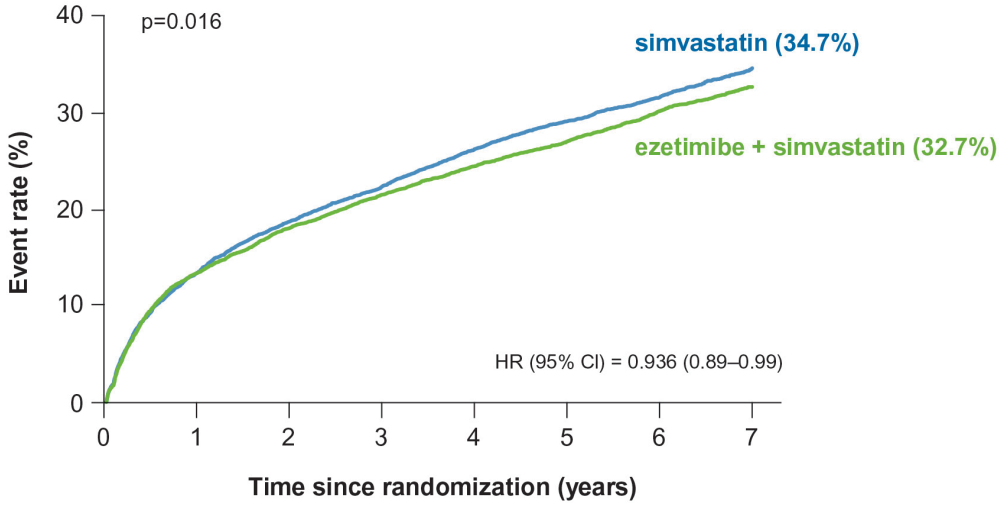
Efficacy

The 2008 ENHANCE study found that ezetimibe combined with simvastatin reduced LDL but had no additional effect on carotid wall thickness, which initially raised questions about the clinical importance of ezetimibe.[76]

The IMPROVE-IT trial, published in 2015, studied the incremental benefit of adding ezetimibe to simvastatin therapy in patients recently hospitalized for an acute coronary syndrome.[32] However, the 2016 ACC recommendations for non-stain therapies, as noted previously, includes ezetimibe as an option in selected patients.

The addition of ezetimibe to simvastatin lowered LDL-C by an additional 24% at one year, compared to simvastatin alone. The study also examined the impact of combination therapy on a combined endpoint of cardiovascular death, major coronary event, or non-fatal stroke. The rates of the primary end-point were 32.7% in the ezetimibe plus simvastatin group compared to 34.7% in the simvastatin group at 7 years, (absolute risk reduction of 2% (HR 0.94; 95% CI 0.89-0.99; p=0.016).[32]

Figure 11. Ezetimibe plus simvastatin versus simvastatin alone in reducing combined cardiac events[32]



A December 2015 FDA advisory committee voted against the expanded indication citing concerns such as a modest 2% absolute risk reduction and missing data (a 91% outcome ascertainment).[32] In a subgroup analysis, the effects of ezetimibe were seen mostly in those over age 75 and those with diabetes. Ezetimibe could be available as a generic starting as early as December 2016.

Safety

Detailed adverse event data were not reported in the ENHANCE trial comparing simvastatin monotherapy with simvastatin plus ezetimibe, although, in general, adverse events considered to be related to treatment were similar in the two groups (29.5% in the simvastatin-only group vs.

34.2% in the combined therapy group, p=0.18) and rates of discontinuation due to adverse events were similar in the two groups (9.4% vs. 8.1% respectively; p=0.56).[76]

In the IMPROVE-IT trial, no significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer.[32] Discontinuation due to an adverse event occurred in 10.1% of the patients in the simvastatin-monotherapy group and in 10.6% of those in the simvastatin–ezetimibe group.[32]

BOTTOM LINE: IMPROVE-IT showed that ezetimibe + simvastatin was modestly better than simvastatin alone in preventing CV events among high-risk patients with CAD. Ezetimibe may be considered as an add-on therapy to statins for patients recently hospitalized for acute coronary syndrome.

PCSK9 Inhibitors

Proprotein convertase subtilisin kexin 9 (PCSK9) is a protease produced predominately in the liver that facilitates the breakdown of hepatocyte LDL receptors and causes decreased clearance of LDL cholesterol. PCSK9 inhibitors are monoclonal antibodies that are injected subcutaneously to inhibit PCSK9 and significantly lower serum LDL levels.

Two PCSK9 inhibitors, evolocumab and alirocumab, have been tested in several phase 2 and phase 3 clinical trials. The majority of trials have tested the combination of PCSK9 inhibitor with statin compared to statin alone. Some trials have focused on the comparison with ezetimibe or the combination of ezetimibe plus statin. The GAUSS trials specifically have focused on statin intolerant patients.[77]

The FDA approved both alirocumab and evolocumab in July 2015 for patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical ASCVD who require additional lowering of LDL cholesterol. A year's supply of medication is estimated to cost over $14,000 in the United States. Given the high cost and the need by biweekly or monthly injections, it is likely that use of PCSK9 inhibitors will initially be limited to patients at highest ASCVD risk. Additionally, their use may be heavily restricted by third party payors (e.g. step-therapy requirements, prior authorizations, and prescriber limitations to cardiologists or lipid specialists).

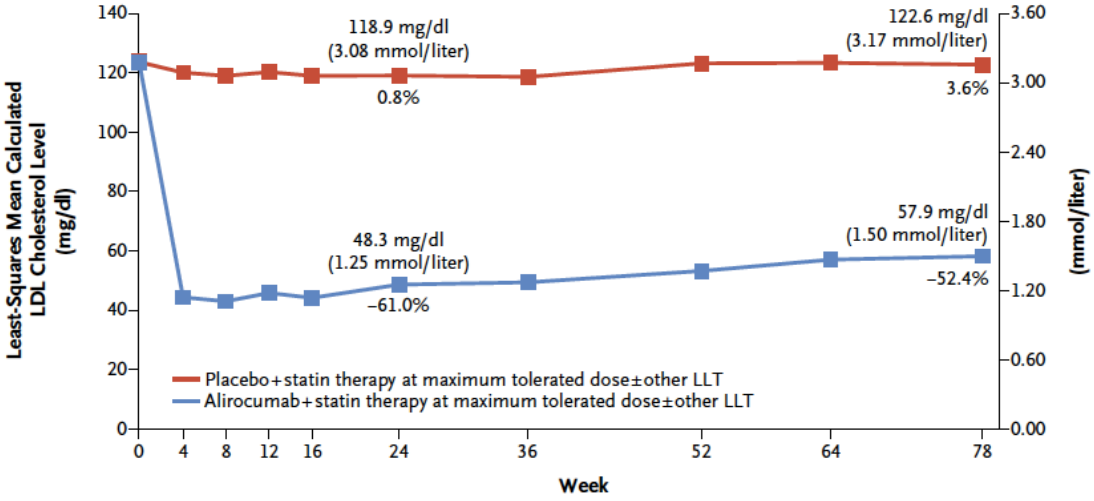
Efficacy

On average, the PCSK9 inhibitors reduce baseline LDL levels by nearly 60% compared to no PCSK9 inhibitor.[33] This degree of LDL reduction holds true even for patients on moderate- or high-intensity statins. When compared to ezetimibe, PCSK9 inhibitors reduce LDL by 36%.[33] Early evidence suggests that PCSK9 inhibitors significantly reduce the risk of CV events, even for patients on statin therapy, however the duration of follow-up has been limited.

The ODYSSEY LONG TERM trial followed 2341 patients at high risk for CV events treated with maximally tolerated dose of statin for 78 weeks. In addition to background statin therapy, patients were randomized to receive alirocumab (150 mg every 2 weeks) or placebo injection. Alirocumab

reduced LDL by 62% compared to placebo.[78] In a post-hoc analysis, the combined endpoint rate of CV events (death from coronary heart disease, non-fatal MI, fatal or non-fatal stroke, or unstable angina) in the alirocumab group compared to placebo was 1.7% versus 3.3% (HR 0.52; 95% CI 0.31-0.90; p=0.02).[78]

Figure 12. Alirocumab (Praluent) reduced LDL by about 60% when used in combination with other lipid lowering agents like statins.[78]



Similar results were found in the open-label OSLER trial, which compared evolocumab plus standard therapy compared to standard therapy alone.[79] Standard therapy was based on local guidelines for LDL treatment; 70% of patients were on concomitant statin therapy. After a median follow-up time of 11 months, the combined rate of CV events (death, MI, unstable angina, coronary revascularization, stroke, TIA, or heart failure) in the evolocumab group was 0.95% compared to 2.18% in the standard therapy alone group (HR 0.47; 95% CI 0.28-0.78; p=0.003).

Neither of these trials were powered to detect a significant difference in mortality. However, a recent meta-analysis of 24 PCSK9 phase 2 and phase 3 trials demonstrated a 55% relative decrease in all-cause mortality (OR 0.45; 95% CI 0.23-0.86; p=0.015).[33] Additional trials designed to confirm these preliminary findings are ongoing and results are expected in 2017.

Safety

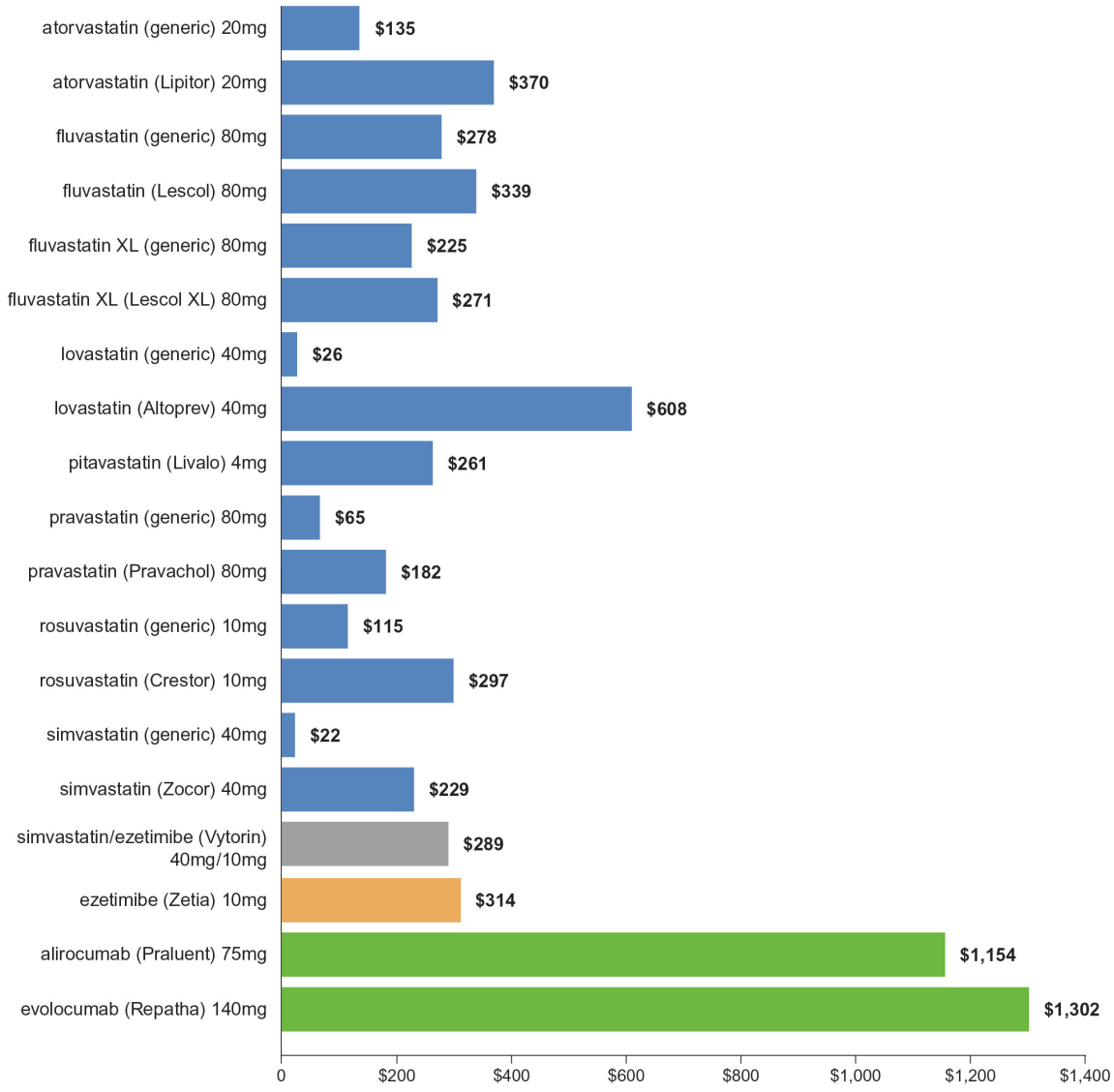
The ODYSSEY LONG TERM trial of alirocumab compared to placebo injection showed relatively low rates of adverse events, although rates were higher with alirocumab: injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%).[78]

In the OSLER trial of evolocumab, the most common adverse events were nasopharyngitis (12.2% with evolocumab vs. 9.8% with standard therapy), upper respiratory tract infection (7.7% vs. 7.6%), influenza (7.1% vs. 5.2%), arthralgia (6.9% vs. 4.3%) and back pain (6.5% vs. 5.4%).[79]

BOTTOM LINE: PCSK-9 inhibitors are a new class of medications approved as an adjunct to diet and maximal statin therapy in patients who have familial hypercholesterolemia or clinical ASCVD who require additional LDL lowering. PCSK-9 trials enrolled patients based on LDL inclusion criteria, despite the fact that the guidelines do not recommend treatment based on specific LDL targets. Common adverse events include nasopharyngitis, musculoskeletal complaints, neurocognitive events and injection site reactions. Cost and the need for biweekly or monthly injections may be disincentives to use.

Costs

Figure 13. Retail price for a 30-day supply of LDL lowering medications



Prices are from goodrx.com as of April 2016. Statin doses used are moderate-intensity. PCSK-9 inhibitor doses are the recommended starting doses.

Conclusions

Hyperlipidemia is a key risk factor for coronary artery disease and a contributor to CV mortality and morbidity. Statins remains the best-tested therapy to reduce CV outcomes in both primary and secondary prevention. Although there is evidence that statin use can be associated with myalgia and may slightly raise the risk of type 2 diabetes, these risks are generally out-weighed by the benefit derived from statin use. Of non-statin medications, PCSK-9 inhibitors and ezetimibe have the most robust evidence for efficacy on clinical outcomes, although both are associated with potentially significant side effects and PCSK-9 inhibitors are very expensive.

The following is a practical outline for screening and treating patients at risk for ASCVD:

- Screen all of those greater than 40 years old with a non-fasting lipid screening test at routine office visits unless the person has known CAD, then a fasting lipid screening test should be used.
- Statins are first-line treatment options for managing hyperlipidemia; when selecting a statin, consider the cost and potency of the statin guided by the patient's clinical scenario, 10-year estimated ASCVD risk or other individual factors.
- Evaluate factors that may predispose patients to statin-associated myopathy. Review the indication for statin use and rechallenge patients if CK elevation <4x the upper limit of normal (ULN).
- Switch to an alternate statin, reduce daily dose, or use intermittent dosing options for patients at high risk of myopathy.

Appendix 1. 2003 ATP III LDL Cholesterol Goals and Risk Categories[13]

Risk Category	LCL goal	LDL level at which to initiate therapeutic lifestyle changes (TLC)	LCL level at which to consider drug therapy
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20% ≥130 mg/dL
			10-year risk <10% ≥160 mg/dL
0-1 Risk factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyles changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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This material was produced by Jing Luo, M.D., M.P.H., Instructor in Medicine; Niteesh K. Choudhry, M.D., Ph.D., Associate Professor of Medicine (principal editor); Jerry Avorn, M.D., Professor of Medicine; Michael A. Fischer, M.D., M.S., Associate Professor of Medicine; Dae Kim, M.D., M.P.H., Sc.D., Assistant Professor of Medicine; all at Harvard Medical School; Jennifer Lewey, Research Fellow at Brigham and Women's Hospital, and Ellen Dancel, PharmD, MPH, Director of Clinical Material Development, Alosa Health. Drs. Avorn, Choudhry, Fischer, and Luo are physicians at the Brigham and Women's Hospital, and Dr. Kim practices at the Beth Israel Hospital, both in Boston. Dr. Lewey practices cardiology at the Columbia University Medical Center in New York. None of the authors accepts any personal compensation from any drug company.

Medical writer: Stephen Braun.

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