

Dyslipidemia

Revised: January 16, 2015

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Key points

- Dyslipidemia is a heterogeneous disorder of abnormal serum lipid and lipoprotein levels. It is a major, modifiable risk factor for atherosclerosis and cardiovascular disease
- Lipids (cholesterol and triglycerides) are carried in the circulation by lipoprotein particles, and persons with dyslipidemia usually have elevated levels of lipoprotein particles
- Dyslipidemia is usually asymptomatic until serum cholesterol levels, serum triglyceride levels, or both are severely elevated and well beyond the range at which cardiovascular morbidity and mortality are increased
- Identification of patients who would benefit from lipid-modifying therapy depends on screening of adults and certain children for abnormal serum lipid levels, as well as obtaining a careful history to detect risk factors that suggest the patient would benefit from lipid-modifying therapy, even if serum lipid levels are within the reference ranges
- Atherogenic lipoproteins include all of the classes of apolipoprotein B (apoB)–containing lipoproteins: chylomicron remnants, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and lipoprotein (a). The presence of the lipoproteins in the subendothelial space of arteries acts as the trigger for the atherosclerotic process, initiating the inflammatory reaction with subendothelial macrophages
- Effective and well-tolerated therapy for lowering LDL cholesterol (LDL-C) and atherogenic lipoprotein levels depends on risk stratification of the patient to identify appropriate lipid level ‘targets’

- Lifestyle modifications, such as weight loss, exercise, and dietary changes, are key in long-term management. Medications to lower lipids, such as statins, should be considered for persons in whom lifestyle modifications alone do not achieve lipid goals
- Statins should also be considered as secondary prevention after an acute coronary syndrome or as primary prevention in patients at increased risk for heart disease and for the pretreatment of LDL-C levels >100 mg/dL
 - Epidemiologic studies predict that for each 1% reduction in the level of LDL-C, there is a 1% to 1.5% reduction in the risk of major cardiovascular events
 - It has been shown that risk of recurrent cardiovascular events is significantly lowered with intensive statin therapy in patients at high risk. Intensive statin therapy should be considered as part of initial therapy in any patient admitted with an acute coronary syndrome or myocardial infarction
- Directed pharmacotherapy for high triglyceride levels should be primarily for persons at risk for pancreatitis due to hyperchylomicronemia (which is most likely to occur when the triglyceride level is >2,000 mg/dL) but should be considered in persons with lower levels to decrease their cardiovascular risk
- A high level of high-density lipoprotein cholesterol (HDL-C) is not pathologic by itself. However, a low level of HDL-C is associated with higher cardiovascular risk. The clinical trial evidence to date does not support targeting HDL-C levels with pharmacotherapy, but persons with low levels should be treated with therapies known to reduce cardiovascular risk

Treatment

Summary approach

- The goal of treatment for dyslipidemia is to reduce the risk of atherosclerosis and cardiovascular disease, as well as the risk of pancreatitis if levels of triglycerides (transported in chylomicrons) are markedly elevated
- The specific dyslipidemia should always be considered and the proper diagnosis pursued, because treatments can vary even in the face of apparently obvious lipid abnormalities. Primarily, it is important to rule out reversible secondary causes. The underlying inherited lipid abnormality mostly has relevance for clarifying the diagnosis for the patient, dispelling myths for the patient, and reducing anxiety associated with vilification of particular activities commonly associated with abnormal lipid levels
- Familial inheritance patterns must also be considered, because this has ramifications for family counseling
- Dietary therapy specific for the type of dyslipidemia is the first step in therapy and is fundamental to any treatment program. The response to diet modification should be quantified and goals assessed before drug therapy is considered in the primary prevention of coronary artery disease, even in people with clear genetic predisposition to their condition
- Excess body weight or, more precisely, abdominal adiposity may be an important factor and should always be addressed. Patients who have excess abdominal adiposity or have any of the clear risk factors for dyslipidemia should be counseled and prescribed dietary therapy immediately
- Physical exercise is an important ancillary therapy
- Contributory diseases such as hypothyroidism or diabetes should be evaluated and adequately treated

- Medications should be considered after reasonable attempts have been made to obtain satisfactory results with nonpharmaceutical methods (generally 3-6 months)

Treatment approach based on NCEP-ATPIII

The Framingham score is an integral part of cardiovascular risk assessment according to NCEP-ATPIII:

- If a person does not have clinical heart disease or risk equivalent for disease, and has 2 or more cardiovascular risk factors other than LDL-C, then the Framingham score should be calculated
- Points are assigned based on gender, age group, total cholesterol, smoking status, HDL-C level, systolic blood pressure, and blood pressure treatment status
- The National Heart, Lung, and Blood Institute website offers a 10-year risk calculator as well as simple tables for quickly assessing 10-year risk
- This calculation is to be done before instituting pharmacotherapy for dyslipidemia and has unknown relevance after pharmacotherapy has already been started
- People with primary severe dyslipidemia have high lifetime risk for clinical heart disease, and different treatment goals apply. The Framingham risk score does not adequately estimate their true risk. For example, those identified as having familial hypercholesterolemia should be treated once their condition has been diagnosed. The National Lipid Association recommends a 50% LDL-C reduction as the primary treatment goal in these patients, as opposed to relying on the NCEP guidelines for setting LDL-C or non-HDL-C goals

Score one point for any of the following major risk factors:

- Hypertension (blood pressure >140/90 mm Hg, or treatment for hypertension)
- Cigarette smoking (any within the past month)

- HDL-C level <40 mg/dL
- Male gender and age >45 years
- Female gender and age >55 years
- Family history of premature coronary heart disease (clinical disease or sudden death in first-degree male relative before age 55, or first-degree female relative before age 65)
- If HDL-C level is 60 mg/dL or more, subtract one point from the total

Patients with low risk:

- Fewer than 2 major risk factors and 10-year risk <10%
- Treatment goal is LDL-C <160 mg/dL

Patients with moderate risk:

- Two or more major risk factors and 10-year risk of <10%
- Treatment goal is LDL-C <130 mg/dL

Patients with moderately high risk:

- Two or more risk factors and 10-year risk of 10% to 20%
- Treatment goal is LDL-C <130 mg/dL, and optional goal of <100 mg/dL, according to updated recommendations from ATP III

Patients with high risk:

- Clinical coronary heart disease or equivalents, (symptomatic carotid artery disease, abdominal aortic aneurysm, peripheral vascular disease, or diabetes) and 10-year risk >20%

- Treatment goal is LDL-C <100 mg/dL. Medication is recommended for LDL-C >100 mg/dL. Optional treatment goal is LDL-C <70 mg/dL according to updated recommendations from ATP III

Patients with very high risk:

- Severe, poorly controlled risk factors, including continued smoking
- Multiple other major risk factors for coronary heart disease, such as diabetes
- Multiple risk factors for metabolic syndrome (especially triglycerides >200 mg/dL, non-HDL-C >30 mg/dL, and HDL-C <40 mg/dL)
- Patients with acute coronary syndromes
- Treatment goal is LDL-C <100 mg/dL. Optional goal is <70 mg/dL according to updated recommendations from ATP III

Pediatric patients:

- Treatment is recommended to maintain LDL-C <130 mg/dL in patients younger than 20 years

Treatment approach based on ACC/AHA guidelines

- There are four treatment groups that warrant pharmacotherapy, on the basis of evidence from RCTs that focus on efforts to reduce ASCVD events in secondary and primary prevention: (1) patients with clinical ASCVD, (2) those with LDL-C >190 mg/dL, (3) those with diabetes mellitus (types 1 or 2) who are aged 40 to 75 years, and (4) those with estimated 10-year ASCVD risk $\geq 7.5\%$ and who are aged 40 to 75 years. Other than the second group, treatment is directed at the underlying atherosclerotic disease and not particularly focused on treating dyslipidemia. In fact, the writing group for the ACC/AHA acknowledges that primary dyslipidemia syndromes represent unique high cardiovascular risk and potential need for referral to lipid specialists

- Statin therapy is recommended for persons with ASCVD risk, and the guidelines identify doses of specific statins as high-, moderate-, or low-intensity therapy. The choice of statin intensity should be based on a person's risk category in the guidelines
- The level of evidence for the use of nonstatin therapy was felt to be inadequate to meet the standards of the task force, but treatment with nonstatin pharmacotherapy is left to the discretion of the clinician when it is felt to be necessary
- LDL-C and non-HDL-C goals are not part of the ACC/AHA guidelines. The Expert Panel, after reviewed 19 RCTs, addressed the issue of treatment to specific LDL-C (and non-HDL-C) goals for secondary prevention. 'Although supported conceptually by an extrapolation of observational studies and observational data from RCTs, no data were identified regarding treatment or titration to a specific LDL-C goal in adults with clinical ASCVD. Most studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed-dose statin therapy to lower LDL-C levels.'

Hypercholesterolemia

- Treatment of hypercholesterolemia is based on the risk for coronary artery disease events. Pharmacologic and nonpharmacologic therapy should take into account coronary risk factors, including age, gender, smoking, hypertension, cardiovascular events, diabetes, and positive family history of premature coronary artery disease
- Recommendations from the NCEP Adult Treatment Panel III (ATPIII) define target levels for treatment based on cardiovascular risk and include optional, more aggressive, lower target LDL-C goals for patients at higher risk
 - According to the ATPIII guidelines, people with documented cardiovascular disease should be treated aggressively to achieve specified LDL-C/non-HDL-C goals

- Those without cardiovascular disease should be treated to less intensive LDL-C/non-HDL-C goals defined by level of cardiovascular risk
- Risk is considered low in persons with fewer than 2 major cardiovascular risk factors, but in those with 2 or more risk factors, assessment involves calculating the Framingham score for 10-year risk of developing hard coronary heart disease, including myocardial infarction and death, plus determining the number of major risk factors for coronary heart disease
- In November 2013, the ACC/AHA task force released its 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults . This was meant to replace the previous guidelines issued by the ACC/AHA and to take the place of the next iteration of the aforementioned NCEP-ATPIII guidelines previously created by the National Heart, Lung, and Blood Institute of the National Institutes of Health
- The new guidelines are meant to be a summary review of available clinical trials and emphasize those studies and conclusions that have the highest level of evidence for reducing ASCVD risk; they rely heavily on randomized controlled trials (RCTs). The authors acknowledge the process was not meant to be a comprehensive approach to all lipid disorders. They add that ‘for the many questions regarding complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management.’

General pharmacologic approach for hypercholesterolemia:

- Primary hypercholesterolemia with normal triglyceride levels can be from high LDL-C level, high HDL-C level, or both; the former is a target for therapy, whereas the latter is considered to be cardioprotective/desirable

- Of the available lipid-lowering medicine, statin drugs, cholesterol absorption inhibitors (*eg*, ezetimibe), nicotinic acid, and bile acid sequestrants lower LDL-C consistently and are used for that purpose
- The NCEP recommends using pharmacotherapy that lowers LDL-C by >30% in those patients who require medication. To date, statin drugs are the only therapy that consistently meets the NCEP standard
- Statins are more effective than other medications in reducing LDL-C. They are less effective than fibrates, however, for reducing triglycerides and less effective than niacin and fibrates for raising HDL-C
- Statins are the medication of choice in patients with a high risk of coronary artery disease, coronary artery bypass surgery, or angioplasty because of the LDL-C lowering potency and wealth of data supporting the benefit of their use. They are also indicated for patients with other manifestations of arteriosclerotic vascular disease (such as nonhemorrhagic cerebrovascular accident, transient ischemic attacks, or peripheral vascular disease), and the treatment of heterozygous familial hypercholesterolemia, combined hypercholesterolemia, and common hypercholesterolemia
- Statins are specifically recommended in the ACC/AHA guidelines (2013) as primary therapy for the aforementioned four treatment groups. The writing group suggests that physicians can consider nonstatin drugs as add-on to statin therapy in patients with high ASCVD risk (*eg*, those with ASCVD present, with LDL-C >190 mg/dL [baseline], or with diabetes) when the condition does not respond as expected to high-intensity statin therapy or when the patients cannot take statin drugs
- Fibrates may be combined with statins to reduce a mixed dyslipidemia. There are no prospective clinical trials with this combination to support its use, but monotherapy studies and extrapolated goals from clinical epidemiology and other lipid lowering medication trials have led to common usage. There are specific statin/fibrate

combinations that have high risk for serious medication adverse effects and muscle complications in particular (as discussed in the statin and fibrate sections)

- Nicotinic acid is a second line medication recommended by the NCEP in treatment of elevated LDL-C levels. It can be used as treatment for lowering LDL-C, triglyceride, and lipoprotein (a) levels and raising HDL-C levels in adults as an add-on to statin therapy to achieve these lipid responses
- Ezetimibe is indicated for the treatment of elevated total cholesterol or LDL-C, but not isolated hypertriglyceridemia. Best use will probably be as a second line therapy in patients not ideally controlled by statins or in patients intolerant to statins
- Bile acid-binding resins are indicated for elevated total cholesterol and LDL-C. This class can have the unintended consequence of raising triglyceride levels in susceptible people
- Therapy to enhance serum HDL-C, which exerts potentially antiatherogenic effects, is an interesting potential treatment strategy. Several classes of agents are being researched. Although none of the following strategies are yet in standard use for treatment of hypercholesterolemia, they hold promise as potential future treatments. It may be insufficient to conceive of therapy that raises HDL-C unless it also improves HDL function; investigation into this concept is underway
 - CETP is involved in cholesterol metabolism and transport. Two CETP inhibitors, evacetrapib and anacetrapib, are under investigation. Two other agents from that class, torcetrapib and dalcetrapib, were both considered failed therapy (because of harm and inadequate response, respectively)
 - Another therapeutic strategy under investigation is the development of synthetic HDL, such as a complex of recombinant apoA-I (Milano) with phospholipid, reconstituted HDL, and apoA-I mimetics

- Pioglitazone treatment in patients with type 2 diabetes has been shown to be associated with increases in serum HDL-C and improvement in carotid intima-media thickness (IMT), suggesting that it may be a useful therapeutic agent
- Two relatively large clinical trials with niacin added to statin therapy in people with high risk for cardiovascular disease events and well-controlled LDL-C levels found no benefit of therapy compared with placebo, despite an increase in HDL-C

Hypertriglyceridemia

General pharmacologic approach for hypertriglyceridemia:

- The three major medications used to treat hypertriglyceridemia are fibrates, omega-3 fatty acids, and nicotinic acid
- Fibrates are the medication of choice for treating elevated triglyceride levels, especially when >500 mg/dL. They also raise HDL-C and have been shown to lower inflammatory markers such as C-reactive protein and to improve vascular function. Fibrates have variable effect on LDL-C but will lower non-HDL-C and apoB levels
- Omega-3 fatty acids reduce triglycerides. Prescription-dose omega-3 fatty acids are approved by the Food and Drug Administration (FDA) for the treatment of severe hypertriglyceridemia (when levels >500 mg/dL). As with fibrates, the effect on LDL-C is not as predictable, but the regimen can lower non-HDL-C and apoB levels when triglycerides are elevated
- Nicotinic acid is also indicated as adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them

Refractory/severe dyslipidemia

- Patients with homozygous familial hypercholesterolemia (HoFH) have extremely high rate of very premature cardiovascular disease, so treatment should be initiated

as early as possible. Myocardial infarction is expected in these patients when they are as young as 10 to 15 years. Patients with this condition may be offered early lipoprotein apheresis. Two new pharmacologic agents, lomitapide and mipomersen , were recently approved by the FDA for adults with HoFH (pediatric studies are underway)

- Other treatments include combined pharmacotherapy using high-dose/high-potency statin therapy, portacaval anastomosis surgery, or liver transplant
- Plasmapheresis/plasma exchange can be used in the urgent or emergent setting to lower severely high triglyceride levels
- Plasma transfusion can be used in the urgent or emergent setting to lower severely high triglyceride or chylomicron levels in persons with known or suspected apoC-II deficiency
- Encourage beneficial lifestyle changes, even though the effect on LDL-C levels may be negligible. Therapeutic lifestyle changes have more activity in treatment of hypertriglyceridemia

Medication combinations

- Combinations of medication classes can be useful, especially for patients with severe hypercholesterolemia and combined dyslipidemia
- Combining a statin with a bile acid-binding resin is an attractive option for lowering LDL-C because of the synergistic effects of their different mechanisms of action
- Combining a statin and ezetimibe is an attractive option for lowering LDL-C because of the synergistic effects of their different mechanisms of action. Studies show that the same level of LDL-C reduction can be attained by adding ezetimibe to a lower dose of a statin as with a high dose of the same statin

- Combining nicotinic acid and colestipol may result in a decrease in LDL-C and an increase in HDL-C. This combination has been shown to be associated with a reduction in the progression of coronary atherosclerosis
- In early studies, combining a statin and nicotinic acid in slow- or extended-release form in patients with low levels of HDL-C was shown to slow the progression of atherosclerosis and provide measurable clinical and angiographic benefits in patients with coronary artery disease. However, more recently, studies of combining niacin with statins (\pm ezetimibe) in persons who achieve low LDL-C levels have found no benefit in cardiovascular outcomes
- There are fixed-dose combinations of a statin with ezetimibe and a statin with niacin SR (sustained release), including: lovastatin-niacin SR, simvastatin-niacin SR, simvastatin-ezetimibe, atorvastatin-ezetimibe
- There is no evidence that combination pharmacotherapy using a statin plus another agent reduces major cardiovascular events. However, it is difficult to test reduction in risk directly. There is strong supporting evidence that reductions in LDL-C, non-HDL-C, and (by extension) apoB and LDL particle levels correlate well with risk reduction. Therefore, combination therapy remains the primary strategy for achieving lipid level goals in appropriately selected patients.
- Individual physicians must weigh the pros and cons of combination therapy with their patients in deciding whether the additional pharmacotherapy is warranted to achieve goals suggested in national guidelines

Alternative therapies

- Phytosterols, garlic , dietary fiber , and soy protein may help in lowering cholesterol
- Red yeast rice extracts typically contain low levels of pharmacologic-grade statin therapy, but they are not regulated by the FDA. Use of this supplement can effectively lower LDL-C, but its safety and consistency are difficult to assess

- Plant-derived stanol esters , which are available as tablets or added to margarine and other food products, may also help in modest lowering of cholesterol

Medications

Statins

Indication

- First line medical therapy for dyslipidemia, hypercholesterolemia, high cardiovascular risk

Dose information

Standard dosing

Atorvastatin :

- Oral (adult): 10 to 80 mg/d
- Oral (children older than 10 years): 10 to 20 mg once a day
- Usual starting dose in adults: 10 mg/d

Fluvastatin :

- Oral: 20 to 80 mg/d, given in 1 to 2 divided doses
- Usual starting dose: 20 to 40 mg/d
- Extended-release version available as 80-mg single daily dose

Lovastatin :

- Oral: 10 to 80 mg/d, given in 1 to 2 divided doses
- Usual starting dose: 20 mg/d

Pitavastatin :

- Oral: 1 to 4 mg/d
- Usual starting dose: 2 mg/d
- Starting and maximum dose: 1 mg/d and 2 mg/d for patients with moderate renal impairment (glomerular filtration rate, 30 to <60 mL/min/1.73 m²) and end-stage renal disease on hemodialysis

Pravastatin :

- Oral (adult): 10 to 80 mg/d
- Oral (children 8 to 13 years): 20 mg once a day
- Oral (children 14 to 18 years): 40 mg once a day
- Usual starting dose in adults: 40 mg/d

Rosuvastatin :

- Oral: 5 to 40 mg/d
- Usual starting dose: 10 mg/d
- Patients who do not require aggressive cholesterol reductions, or who have predisposing factors for myopathy (Asian ethnicity, severe renal impairment, concomitant therapy with cyclosporine) should be started on a 5-mg dose

Simvastatin :

- Oral: 5 to 40 mg/d
- Oral (children): 5 to 40 mg once a day
- Usual starting dose: 20 mg/d

- Dose should be reduced in patients coadministered medicines metabolized by the cytochrome P450-3A4

Alternate dosing per 2013 ACC/AHA guidelines

High intensity:

- Rosuvastatin 20 or 40 mg daily
- Atorvastatin 40 or 80 mg daily

Moderate intensity:

- Rosuvastatin 5 or 10 mg daily
- Atorvastatin 10 or 20 mg daily
- Simvastatin 20 or 40 mg daily
- Pravastatin 40 or 80 mg daily
- Fluvastatin 40 mg twice daily or Fluvastatin XL (extended release) 80 mg daily
- Lovastatin 40 mg daily
- Pitavastatin 2 or 4 mg daily

Low intensity:

- Simvastatin 10 mg daily
- Pravastatin 10 or 20 mg daily
- Fluvastatin 20 or 40 mg daily
- Lovastatin 20 mg daily
- Pitavastatin 1 mg daily

Major contraindications

- Rosuvastatin
 - Breastfeeding
 - Hepatic disease
 - Pregnancy

- Atorvastatin
 - Breastfeeding
 - Cholestasis
 - Hepatic disease
 - Hepatic encephalopathy
 - Hepatitis
 - Jaundice
 - Pregnancy

- Simvastatin
 - Breastfeeding
 - Cholestasis
 - Hepatic disease
 - Hepatic encephalopathy
 - Hepatitis
 - Jaundice

- Pregnancy
- Pravastatin
- Breastfeeding
- Hepatic disease
- Hepatic encephalopathy
- Jaundice
- Pregnancy
- Fluvastatin
- Breastfeeding
- Cholestasis
- Hepatic disease
- Hepatic encephalopathy
- Hepatitis
- Jaundice
- Pregnancy
- Lovastatin
- Breastfeeding
- Hepatic disease
- Pregnancy
- Pitavastatin

- Breastfeeding
- Cholestasis
- Hepatic disease
- Hepatic encephalopathy
- Hepatitis
- Jaundice
- Pregnancy

Comments

- Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 2 to 4 weeks
- Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during long-term therapy
- Statins are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors
- The efficacy of statins has not been evaluated in patients with combined elevated total cholesterol and hypertriglyceridemia (>500 mg/dL) or in patients with elevated IDLs as their primary lipid abnormality
- Statins may occasionally cause skeletal muscle pain (in approximately 5% of patients) and gastrointestinal disturbances, which may raise noncompliance issues. There is anecdotal evidence that patients who experience muscle aching with one

statin without creatine phosphokinase [CPK] elevation may tolerate an alternative statin better

- A variety of strategies to reduce the occurrence of statin-associated myalgia (SAM) have been proposed, and expert panels and commentary have addressed this concern. It is not appropriate for physicians to instruct patients to ignore or live with constant pain due to SAM. However, intermittent low-level discomfort can be considered tolerable by both the clinician and the patient in the appropriate circumstance
- Elevations of CPK may indicate more significant myopathy, but because CPK levels can vary widely within an individual, especially after exercise, it is not necessary to discontinue the statin when CPK is less than 10 times the reference upper limit in a resting patient more than 48 hours after exercise
- Strategies for dealing with SAM are difficult to validate in clinical trials. Several expert commentaries and reviews have been published and suggest the following:
 - Avoid/minimize dehydration
 - Avoid/minimize drug combinations that predispose to myalgias
 - Retry same statin after a longer-than-2-week trial off statin; consider using lower-dose statin
 - Retry different statin after a longer-than-2-week trial off statin
 - Evaluate and treat very low vitamin D levels and all potential nonstatin causes of myalgia, then re-treat with statin therapy
 - Pretreat with coenzyme Q₁₀(ubiquinol) at ≥ 200 mg daily dose
 - Combine low-intensity or interrupted-dose statin/high-potency therapy (*eg*, rosuvastatin 2.5 or 5 mg 2 to 3 times per week or atorvastatin 5 or 10 mg 2 to 3 times

per week) with nonstatin therapy (*eg*, bile acid sequestrant, ezetimibe, omega-3 fatty acids, fibrate, or niacin)

- Statin use may rarely cause severe myopathy (rhabdomyolysis) with CPK elevations greater than 10 times the reference upper limit. This may occur with or without acute renal failure secondary to myoglobinuria. Rhabdomyolysis has been reported most commonly with high-dose simvastatin and with statin use combined with use of other drugs that increase statin blood level
- There are reports of increases in serum transaminase levels, but this does not exceed rates associated with placebo in RCTs. Discontinue statin if liver function test results are three or more times the reference upper limit, and monitor until they return to the reference range
- Investigation into other causes of transaminase levels is indicated when levels are persistently elevated, because statin use is an unusual cause for this problem
- Confirm that transaminase elevations occur only while the patient is taking statin drugs, because common fatty liver can cause fluctuating transaminase levels independent of statin use
- Statins interact with several medications, and the list of the patient's current medications should be reviewed to ensure that such interactions are absent

Statin effects on serum lipid profile

- The primary target of statin therapy is LDL-C. All of the statins are efficacious in lowering LDL-C, and the degree of change in LDL-C levels is related to statin dose and choice of drug
- At maximum dose, the following reductions in LDL-C have been seen:
 - Atorvastatin (80 mg), 55%
 - Simvastatin (40 mg), 39%

- Lovastatin (80 mg), 41%
- Pravastatin (40 mg), 34%
- Fluvastatin (80 mg), 34%
- Rosuvastatin (40 mg), 65%
- Pitavastatin (4 mg), 43%
- A secondary target of therapy is increase in the proportion of HDL-C levels. Regardless of the dosing or statin used, HDL-C levels have increased between 4% and 8%, although atorvastatin 80 mg/dL can result in lowering HDL-C levels
- Finally, triglyceride levels decrease with statin therapy, with the degree of change related to both dose and choice of statin and to triglyceride level before treatment
- At maximum doses, the following reductions in triglyceride levels have been seen:
 - Atorvastatin (80 mg), 25% to 35%
 - Simvastatin (40 mg) 15%
 - Lovastatin (80 mg), 15% to 25%
 - Pravastatin (40 mg), 10% to 20%
 - Fluvastatin (80 mg), 10% to 20%
 - Pitavastatin (4 mg), 18%
 - Rosuvastatin (40 mg), 26%

Statin effects on risk reduction of coronary heart disease

- At LDL-C levels as low as 70 mg/dL, statins have been shown to lower the risk of cardiovascular disease. A marked lowering of LDL-C is usually seen within 2 weeks of initiation, with maximum therapeutic response occurring within 4 to 6 weeks
- In patients with hypercholesterolemia without clinically evident coronary heart disease, including prior myocardial infarctions, statins have been found to reduce the risk of myocardial infarction; reduce the risk of undergoing myocardial revascularization procedures; and reduce the risk of cardiovascular mortality, stroke, or transient ischemic attack with no increase in death from noncardiovascular causes
- Independent of therapy, there is a log-linear relationship between absolute LDL-C levels and relative risk of coronary heart disease, with data consistently suggesting that for every 30-mg/dL decrease in serum LDL-C, there is a 30% proportional reduction in relative risk of coronary heart disease (with a relative risk of 1.0 set for LDL-C = 40 mg/dL)
- When statin therapy is used to lower serum LDL-C levels, there is also a clear, significant reduction in risk of coronary heart disease, even if LDL-C levels are only modestly elevated at baseline. Further, aggressive targets of LDL-C levels below 100 mg/dL have been associated with further reductions in risk over previously 'acceptable' levels
- Pravastatin therapy that reduced LDL-C levels by an average of 34% was associated with a 19% reduction in major coronary events (nonfatal myocardial infarction and cardiovascular death), a 24% reduction in coronary heart disease mortality, and a 25% reduction in transient ischemic attacks
- Atorvastatin therapy that reduced LDL-C levels (from a baseline average of 132 mg/dL) by an average of 29% was associated with a 27% reduction in fatal and nonfatal stroke, a 21% reduction in cardiovascular events, and a 29% reduction in total coronary events at 3.3 years

- In a trial comparing pravastatin with atorvastatin, high-risk patients who achieved the lowest LDL-C levels (62 mg/dL in the atorvastatin group) trended to even further reduced risk compared with patients whose levels were reduced to 95 mg/dL (pravastatin group), suggesting that even lower target levels are beneficial in high-risk patient populations
- A trial comparing daily doses of 80 mg of atorvastatin with 10 mg of atorvastatin in stable coronary heart disease patients showed that intensive lipid-lowering therapy with 80 mg of atorvastatin provided significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin
- Only one-third of patients with coronary heart disease are at or below even the more liberal therapeutic LDL-C goal of <100 mg/dL
- Studies have not yet identified a 'floor' effect of statin therapy; LDL-C may warrant therapy regardless of absolute serum levels if atherosclerotic disease develops

Evidence

Statin drugs effect on lipid profile and safety:

- The STELLAR trial (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) is a multicenter, open-label randomized trial comparing the efficacy and safety of rosuvastatin with those of atorvastatin, pravastatin, and simvastatin. Rosuvastatin reduced LDL cholesterol significantly more than simvastatin and pravastatin in all 14 pairwise comparisons analyzed. The best LDL cholesterol reduction (55%) was achieved in the rosuvastatin 40-mg group and was not significantly different ($P=.006$) from the next highest LDL cholesterol reduction (51%) observed in the atorvastatin 80-mg group. Drug tolerability was similar across treatments. [9] *Level of evidence: 2*
- A systematic review of 8 randomized placebo-controlled trials (897 participants; period, 1996-2005) evaluated the LDL-C lowering efficacy and safety of statin drugs (lovastatin, pravastatin, simvastatin, or atorvastatin) in a pediatric population with

heterozygous familial hypercholesterolemia. After an average of 6 months, as compared with placebo group, the pooled estimate of the difference in mean relative reductions of LDL-C in the statin group was -32.15% (95% CI, -34.90% to -29.40%), and there was no significant elevation of transaminase levels or CPK levels in the statin group. [10] *Level of evidence:1*

- A randomized, placebo-controlled clinical trial of pravastatin 20 or 40 mg daily vs placebo in Dutch children with diagnoses of familial hypercholesterolemia found that pravastatin use resulted in a change in carotid IMT when used for 2 years. Compared with placebo, the mean change in IMT was 0.014 [SD= $.046$] mm ($P=.02$), and the mean reduction in LDL-C levels was $+0.03\%$ and -24.1% , respectively ($P<.001$). [11] *Level of evidence:2*
- A meta-analysis of 49 clinical trials evaluated 14,236 patients for the safety of atorvastatin 10 mg or 80 mg, used for between 2 weeks and 54 months. Compared with placebo, there was no difference in incidence of treatment-associated adverse events in the two treatment groups. [12] *Level of evidence:2*

Statin drugs reduce overall mortality, cardiovascular mortality, and nonfatal cardiovascular events in patients with coronary heart disease who are at high risk for ischemic coronary events.

- A systematic review of 18 studies ($n=14,303$) was undertaken to assess safety and effect of statins in patients with acute coronary syndrome. Compared with patients on no statins, at 4 months there was a significant reduction in the number of unstable angina episodes (RR, 0.76 ; 95% CI, $0.59-0.96$). Myopathy, defined as creatinine kinase levels more than 10 times the reference upper limit, was found in nine (0.13%) statin-treated patients, compared with one (0.015%) in the control groups. Serious muscle toxicity was primarily found with higher-dose (80-mg) simvastatin. [13] *Level of evidence:1*

- A randomized double-blinded controlled trial evaluated the efficacy of simvastatin versus placebo in 4,444 patients with angina or previous myocardial infarction and elevated serum cholesterol. All patients were instructed on a low-fat diet. After about 5 years, simvastatin produced mean changes in total cholesterol of -25%, LDL-C of -35%, and HDL-C of +8% compared with the control group, with few adverse effects. The relative risk of death in the simvastatin group was 0.70 (95% CI, 0.58-0.85; $P=.0003$). In the placebo-versus-simvastatin group, there were 189 versus 111 coronary deaths (RR, 0.58; 95% CI, 0.46-0.73) and 622 versus 431 with one or more major coronary events (RR, 0.66; 95% CI, 0.59-0.75; $P<.00001$). [14] *Level of evidence:1*
- The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study is an RCT involving 1,600 people with coronary heart disease that compared atorvastatin with 'usual care' (management without statins). During this study, 196 (24.5%) of the usual care patients had a CHD recurrent event or died, compared with 96 (12%) of the patients on atorvastatin (RR, 0.49; 95% CI, 0.27-0.73; $P<.0001$), with a significant decrease in total mortality, coronary mortality, and stroke. [15] *Level of evidence:1*
- The West of Scotland Coronary Prevention Study (WOSCOPS) is an RCT that evaluated the efficacy of pravastatin 40 mg in 6,595 middle aged men with elevated cholesterol (mean level, about 270 g/dL). After an average of about 5 years, compared with placebo, in the treatment group there was a decrease in definite coronary events (RR, 31%; 95% CI, 17-43%; $P<.001$). nonfatal definite myocardial infarctions (RR, 31%; $P<.001$), death from coronary heart disease (definite cases alone: RR, 28%; $P=.13$; definite plus suspected cases: RR, 33%, $P=.042$); and death from all cardiovascular causes (RR, 32%; $P=.033$). [16] *Level of evidence:1*
- A subsequent RCT, the Heart Protection Study Collaborative Group (MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin) compared simvastatin with placebo in 20,536 high-risk people with and without coronary heart disease. All-cause mortality was significantly lower in the simvastatin group,

primarily owing to 18% proportional reduction in the coronary death rate. There were also significant reductions in the first event rate for nonfatal myocardial infarction or coronary death (8.7%vs11.8%; $P<.0001$), for nonfatal or fatal stroke (4.3%vs5.7%; $P<.0001$), and for coronary or noncoronary revascularization (9.1%vs11.7%; $P<.0001$). [17] *Level of evidence:1*

Elderly patients at high risk of cardiovascular disease appear to benefit from cholesterol-lowering therapy.

- The PROSPER study (Prospective Study of Pravastatin in the Elderly at Risk) was an RCT designed to evaluate the efficacy of pravastatin 40 mg on cholesterol serum levels and mortality in 5,804 patients aged 70 to 82 years with a history of, or risk factors for, vascular disease. Compared with placebo, LDL-C was decreased by 34% in the treated group, and the number of primary–end point events was 473 versus 408, respectively (HR, 0.85; 95% CI, 0.74-0.97; $P=.014$). Coronary death and nonfatal myocardial infarction risk was also reduced (HR, 0.81; 95% CI, 0.69-0.94; $P=.006$), as was the hazard ratio for transient ischemic attack (HR, 0.75; 95% CI, 0.55-1.00; $P=.051$), but the risk for stroke was unaffected. [18] *Level of evidence:1*

Aggressive cholesterol lowering in high-risk patients appears to be beneficial, and evidence suggests that target LDL-C should be lower than that suggested by current national guidelines.

- The Treating to New Targets (TNT) study evaluated the effect in 10,001 participants randomly assigned to treatment with atorvastatin 80 mg versus 10 mg in the period after the occurrence of a first cardiovascular event. This is a post hoc time-to-next-event analysis that concluded that treatment with atorvastatin 80 mg continued to significantly decrease the risk of any cardiovascular event over time compared with atorvastatin 10 mg in patients who had survived previous events; follow-up lasted 4.9 years on average. [19] *Level of evidence:1*

- The IDEAL trial (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) was an RCT comparing the secondary prevention provided by high-dose versus standard-dose statin therapy. Intensive lowering of LDL-C level with atorvastatin 80 mg daily (mean LDL-C level, 81 mg/dL) or simvastatin 20 mg daily (mean LDL-C level, 104 mg/dL) did not result in a significant difference in reduction of major coronary events, cardiovascular mortality, or all-cause mortality but did reduce the risk of nonfatal acute myocardial infarction and several composite secondary end points. [20] *Level of evidence:1*
- A post hoc analysis of the IDEAL trial assessed the efficacy of high-dose atorvastatin versus usual-dose simvastatin for secondary prevention. Compared with simvastatin, the atorvastatin group had a relative risk reduction of first through fifth cardiovascular event by 17% ($P<.0001$), 24% ($P<.0001$), 19% ($P=.035$), 24% ($P=.058$), and 28% ($P=.117$), respectively. [21] *Level of evidence:2*
- A meta-analysis considered 26 large, long-running (<2 years) RCTs comparing varying degrees of statin regimens against placebo (21 trials) or each other (5 trials) in 169,138 patients. With each 1-mmol/L reduction in LDL-C level, the annual rate of myocardial infarction, revascularization, or ischemic stroke was reduced by just over a fifth. There was no evidence of threshold, which suggested that reduction of LDL-C by 2 to 3 mmol/L would reduce risk by about 40% to 50%. [22] *Level of evidence:1*
- The Post Coronary Artery Bypass Graft Trial was designed to compare the effects of 2 lipid-lowering regimens and low-dose anticoagulation versus placebo on progression of atherosclerosis in saphenous vein grafts after coronary artery bypass graft surgery. A total of 1,351 patients were randomized to receive either aggressive reduction of cholesterol levels with lovastatin (plus cholestyramine if required) to goal LDL-C <100 mg/dL or more moderate reduction with the same drugs (achieving a mean LDL-C of 132-136 mg/dL) after coronary artery bypass graft. At 4 years, aggressive treatment significantly reduced the need for repeat revascularization. At 7.5 years of follow-up, there was a 30% reduction in

revascularization procedures and a 24% reduction in patients assigned to the aggressive strategy compared with patients assigned to the moderate strategy ($P=.0006$ and 0.001 , respectively). [23] *Level of evidence:1*

- The PROVE IT-TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators) compared standard therapy of 40 mg of pravastatin daily versus intensive therapy with 80 mg of atorvastatin daily in 4,162 patients whose study treatment started within 10 days of an acute coronary syndrome. The median LDL-C level achieved during treatment was 95 mg/dL in the standard-dose pravastatin group and 62 mg/dL in the high-dose atorvastatin group ($P<.001$). The event rate in high-intensity treatment was 22.4%, compared with 26.3% in the standard treatment arm, representing a 16% reduction in the hazard rate for the primary end point, a composite of death from any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, and stroke. [24] *Level of evidence:1*
- In a follow-up of the PROVE IT-TIMI 22 study, the authors conducted an analysis of high-intensity versus standard-dose statin therapy for the prevention of recurrent events. In results similar to those of the prevention-of-events analysis previously published, they concluded that additional events were also reduced by 19% with atorvastatin 80 mg ($n=275$ vs $n=340$, respectively; $P=.009$). [25] *Level of evidence:1*
- The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial is a multinational double-blind RCT comparing a moderate lipid-lowering regimen consisting of 40 mg of pravastatin versus an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin in 654 patients for changes in atheroma burden as measured by intravascular ultrasonography. Comparing the moderate-dose versus intensive-dose groups after 18 months, there was a significant decrease in serum LDL-C levels (110 mg/dL vs 79 mg/dL; $P<.001$) and percentage drop in C-reactive protein levels (5.2% vs 36.4%; $P<.001$). There was a significantly lower end point and progression rate in atheroma volume in the atorvastatin (intensive) group. Compared with baseline, progression of coronary atherosclerosis occurred in the

pravastatin group (2.7%; 95% CI, 0.2%-4.7%; $P=.001$) but not in the atorvastatin group (-0.4%; 95% CI, -2.4% to 1.5%; $P=.98$). [26] *Level of evidence:2*

Statins are effective in reducing cardiovascular outcomes in patients with diabetes at higher risk of macrovascular complications. Although patients with diabetes are at higher cardiovascular risk whether or not they have other risk factors, trial data on statins in patients with diabetes with a low 10-year cardiovascular risk are lacking.

- A meta-analysis of 5 RCTs ($n=32,752$) evaluated the association of intensive-dose versus moderate-dose statin therapy with new-onset diabetes. The incidence of diabetes after about 5 years was 1,449 in intensive-dose therapy and 1,300 in moderate-dose therapy. After about 5 years, cardiovascular events were 3,134 and 3,550, respectively, representing 6.5 fewer cases in the intensive-dose group per 1,000 patient-years. Odds ratios were 1.12 (95% CI, 1.04-1.22; $I^2=0\%$) for new-onset diabetes and 0.84 (95% CI, 0.75-0.94; $I^2=74\%$) for cardiovascular events for participants receiving intensive therapy compared with moderate-dose therapy, respectively. [27] *Level of evidence:1*
- A meta-analysis involving 13 statin trials with 91,140 participants evaluated the relationship between statin use and development of diabetes. After an average of 4 years, statin therapy was associated with a 9% increased risk for incident diabetes (OR, 1.09; 95% CI, 1.02-1.17), with little heterogeneity ($I^2=11\%$) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants. [28] *Level of evidence:1*
- A systematic review of statin benefit for composite cardiovascular outcomes (cardiovascular mortality, myocardial infarction, stroke, revascularization, and unstable angina) in patients with treated diabetes was undertaken. Risks were significantly reduced with statins versus placebo in people with diabetes in both primary prevention (6 studies) and secondary prevention (8 studies), with similar relative risk reduction (0.78 and 0.76, respectively). [29] *Level of evidence:1*

- A large RCT compared simvastatin 40 mg with placebo, and subgroup analysis was performed for 5,963 participants with diabetes. At 4.8 years, major cardiovascular events were significantly reduced in patients receiving statin therapy, including participants without established cardiovascular disease or a raised LDL-C level. [30] *Level of evidence:1*
- Subgroup analysis considered the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, which measured the effects of pravastatin therapy, 40 mg/d over 6 years, on the risk of CHD death or nonfatal myocardial infarction and other cardiovascular outcomes in 1,077 patients with diabetes and 940 patients with impaired fasting glucose. Compared with placebo, the treatment group had a reduction of a major CHD event from 15.9% to 12.3% (relative risk reduction [RRR], 24%; $P<.001$) and 23.4% to 19.6% in the diabetic group (RRR, 19%; $P=.11$). Treatment in patients with diabetes or impaired fasting glucose also reduced the risk of a cardiovascular event, from 52.7 to 45.2% (21%; $P<.008$) and from 45.7 to 37.1% (26%; $P=.003$), respectively, and the risk of stroke from 9.9 to 6.3% (RRR, 39%; 95% CI, 7%-61%; $P=.02$) and from 5.4 to 3.4% (RRR, 42%; 95% CI, -9% to 69%; $P=.09$), respectively. [31] *Level of evidence:1*
- An RCT (the Collaborative Atorvastatin Diabetes Study [CARDS]) compared primary prevention of atorvastatin 10 mg in 2,838 participants with type 2 diabetes but without cardiovascular disease. Compared with controls after about 4 years, the treated group had a significantly reduced number of cardiovascular events (rate reduction, 37%; 95% CI, -52 to -17%; $P=.001$). [32] *Level of evidence:1*

There is evidence that statins reduce the rates of stroke, compared with placebo.

- A meta-analysis of 27 studies evaluated statin therapy versus placebo in 113,148 participants for ischemic stroke outcome. Compared with placebo, at stroke onset, statin treatment resulted in good functional outcome at 90 days (pooled OR, 1.41; 95% CI, 1.29-1.56; $P<.001$) but not 1 year (OR, 1.12; 95% CI, 0.9-1.4; $P=.31$). Reduction in fatality was significant at both 90 days (pooled OR, 0.71; 95% CI, 0.62-

0.82; $P < .001$) and 1 year (OR, 0.80; 95% CI, 0.67-0.95; $P = .01$). In one RCT reporting 90-day functional outcome, statin treatment was associated with good outcome (OR, 1.5; 95% CI, 1.0-2.24; $P = .05$), but no reduction in fatality was found in the 3 RCTs reporting such data ($P = .9$). In patients treated with fibrinolysis, there was no association between statin use and increased fatality at 90 days once data in the largest study were adjusted for age and stroke severity (adjusted OR, 1.14; 95% CI, 0.90-1.44; 4,012 patients). [33] *Level of evidence:2*

- A 2004 systematic review compared the effect of statins versus placebo on stroke and found that after a mean of 4.3 years, statin therapy significantly reduced the rate of stroke versus placebo or no treatment in >90,000 patients pooled in statin studies. The authors reported a 21% (OR, 0.79 [0.73 to 0.85]) relative risk reduction for stroke and no increase in hemorrhagic strokes (OR, 0.90 [0.65 to 1.22]). Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7-23.6) and carotid IMT by 0.73% per year (95% CI, 0.27-1.19). [34] *Level of evidence:2*
- A systematic review of eight studies on pharmacologic agents to lower cholesterol in about 10,000 people with a history of stroke showed that, of the cholesterol-lowering agents tested, only statins reduce subsequent risk for recurrent stroke (OR, 0.88; 95% CI, 0.77-1.00), but there was no effect (OR, 1.00; 95% CI, 0.83-1.20) on hemorrhagic stroke, mortality, or sudden death. Three statin trials showed a reduction in subsequent serious vascular events (OR, 0.74; 95% CI, 0.67-0.82). [35] *Level of evidence:2*

Patients with chronic kidney disease, dialysis, and kidney transplant who take statins have shown similar cholesterol reductions, but there is little or no effect on cardiovascular outcomes compared with the reduced outcomes found in the general population.

- A systematic review and meta-analysis investigated the effects of statins on major clinical outcomes. Thirty-one trials that include at least one mortality or major

morbidity event were identified, providing data for 48,429 patients with chronic kidney disease, including 6,690 major cardiovascular events and 6,653 deaths. Statin therapy produced a 23% (95% CI, 16%-30%) RR reduction for major cardiovascular events ($P<.001$), an 18% (95% CI, 8%-27%) RR reduction for coronary events, and a 9% (95% CI, 1%-16%) reduction in cardiovascular or all-cause deaths, but no significant effect on stroke (21%; 95% CI, -12% to 44%) nor clear effect on kidney failure events (5%; 95% CI, -1% to 10%). [36] *Level of evidence:1*

- A systematic review on the efficacy and safety of statins in patients with end-stage renal disease on dialysis. Statins had little or no effect on major cardiovascular events (4 studies; 7,084 participants; RR, 0.95; 95% CI, 0.88-1.03), all-cause mortality (13 studies; 4,705 participants; RR, 0.96; 95% CI, 0.90-1.02), cardiovascular mortality (13 studies; 4,627 participants; RR, 0.94; 95% CI, 0.84-1.06), and myocardial infarction (3 studies; 4,047 participants; RR, 0.87; 95% CI, 0.71-1.07). [37] *Level of evidence:1*
- A systematic review of 14 RCTs comparing statins with placebo in 2,086 patients receiving hemodialysis, continuous ambulatory peritoneal dialysis, or both found that after 12 weeks of treatment, statins decreased cholesterol levels in dialysis patients with efficacy similar to that seen in the general population. In patients on hemodialysis and taking statins, nonfatal cardiovascular events were reduced, but cardiovascular and overall mortality were not decreased. [38] *Level of evidence:1*
- A systematic review of 16 studies compared the effect of statin versus placebo (15 studies) or statin versus statin (1 study) in 3,229 patients with renal impairment. Point estimates trended toward decreased cardiovascular mortality (13 studies; RR, 0.68; 95% CI, 0.46-1.03) and nonfatal cardiovascular events (1 study; RR, 0.70; 95% CI, 0.48-1.01) in patients who used statins. [39] *Level of evidence:1*
- A systematic review of 26 studies with more than 25,000 patients with chronic kidney disease but not requiring dialysis showed that statins decreased both the risk of all-cause mortality (21 RCTs; 18,781 patients; RR, 0.81; 95% CI, 0.74-0.89) and

cardiovascular deaths (20 studies; 18,746 patients; RR, 0.80; 95% CI, 0.70-0.90). [40] *Level of evidence:1*

- The German Diabetes and Dialysis (4D) Study is an RCT comparing the effect from atorvastatin versus placebo in 1,255 patients with type 2 diabetes mellitus who were on maintenance hemodialysis. Atorvastatin treatment was not associated with a reduction in the relative risk of cardiovascular events or mortality irrespective of serum levels of C-reactive protein. [41] *Level of evidence:1*
- An RCT called AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects On Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events) evaluated the efficacy and safety of rosuvastatin 10 mg daily versus placebo in 2,776 patients, aged 50 to 80 years, who were undergoing maintenance hemodialysis. Rosuvastatin had no effect on individual components of the primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. There was also no significant effect on all-cause mortality (13.5vs14.0 events per 100 patient-years; hazard ratio, 0.96; 95% CI, 0.86-1.07;P=.51). [42] *Level of evidence:1*

References

Ezetimibe

Indication

- Ezetimibe is used as follows:
 - As monotherapy as an adjunct to diet therapy for primary hypercholesterolemia
 - As combination therapy with statins for primary (heterozygous familial and nonfamilial) hypercholesterolemia
 - As combination therapy with a statin for homozygous familial hypercholesterolemia
 - For homozygous sitosterolemia

- In combination with fibrates for the reduction of elevated total cholesterol and LDL-C levels in patients with mixed dyslipidemia, along with diet, when diet alone is not enough

Dose information

- 10 mg orally once a day

Major contraindications

- None

Comments

- Lowers total cholesterol by approximately 13% and LDL-C by approximately 18%
- No mortality or morbidity studies have yet been completed
- Avoid in patients with moderate to severe hepatic impairment

Evidence

- An RCT compared ezetimibe versus placebo in patients with hypercholesterolemia over a period of 12 weeks. Ezetimibe significantly reduced direct LDL-C (mean reduction, 16.9%, compared with an increase of 0.4% with placebo; $P < .01$) compared with placebo in 892 patients with primary hypercholesterolemia. Ezetimibe effects on LDL cholesterol occurred early (2 weeks) and persisted throughout the 12-week treatment period. Compared with placebo, ezetimibe 10 mg also significantly improved levels of apoB, total cholesterol, triglycerides, HDL-C, and HDL₃cholesterol ($P < .01$). [43] *Level of evidence: 2*
- A multicenter, 12-week, randomized, double-blind, parallel-group trial evaluated the efficacy and safety of various strengths of ezetimibe/simvastatin versus various strengths of atorvastatin in 1,289 patients with hypercholesterolemia aged 65 years or older with or without cardiovascular disease. Compared with atorvastatin, the

ezetimibe/simvastatin group trended toward a significantly greater percentage decrease in LDL-C (-54.2% for ezetimibe/simvastatin 10/20 mg vs -39.5% for atorvastatin 10 mg and -46.6% for atorvastatin 20 mg; -59.1% for 10/40 mg vs -50.8% for atorvastatin 40 mg; $P < .001$ for all comparisons). [44] *Level of evidence: 2*

- A multicenter, prospective, randomized, double-blind, placebo-controlled trial assessed the effect of ezetimibe versus placebo therapy on LDL-C levels in 108 patients with type 2 diabetes who had persistent albuminuria and elevated cholesterol levels despite long-term simvastatin use. After 2 months, adding ezetimibe to simvastatin therapy significantly decreased LDL-C levels and reduced total cholesterol and apoB levels; LDL-C levels were less than 70 mg/dL in only 17% of patients taking simvastatin plus placebo, compared with 72% of patients on simvastatin plus ezetimibe ($P < .0001$). [45] *Level of evidence: 2*
- A multicenter, randomized, double-blind, active-controlled clinical trial in 1,437 hypercholesterolemic, high-risk patients compared multiple medical regimens with an intervening washout period. In all groups, ezetimibe plus atorvastatin was more effective at reducing LDL-C than higher-dose atorvastatin or rosuvastatin ($P < .001$). [46] *Level of evidence: 2*
- An RCT in 769 patients with primary hypercholesterolemia who had not achieved adequate lipid reduction with dietary changes and statin monotherapy compared addition of ezetimibe with addition of placebo for 8 weeks. The group receiving ezetimibe had substantial reduction in LDL-C levels compared with the group receiving placebo. The combination of statin plus ezetimibe was well tolerated. [47] *Level of evidence: 2*
- A RCT assessed the efficacy and safety of ezetimibe administered with simvastatin in patients with hypercholesterolemia, who were randomized to receive ezetimibe alone, simvastatin alone, ezetimibe plus simvastatin, or placebo for 12 weeks. Ezetimibe plus simvastatin versus simvastatin alone significantly reduced LDL-C

levels and triglyceride levels and significantly increased HDL-C levels. The combination was well tolerated. [48] *Level of evidence:2*

- A double-blind RCT randomized participants with dyslipidemia to receive ezetimibe alone or with various dosages of atorvastatin compared with various doses of atorvastatin alone or placebo. After 12 weeks, ezetimibe plus atorvastatin significantly improved LDL-C, HDL-C, and triglyceride levels, total cholesterol/HDL-C ratio, and high-sensitivity C-reactive protein level compared with atorvastatin alone. [49] *Level of evidence:2*
- An RCT compared ezetimibe 10 mg plus response-based atorvastatin titration versus response-based atorvastatin titration alone. Participants at high risk for coronary heart disease were started on a 6- to 10-week dietary stabilization and atorvastatin 10 mg/d open-label run-in period, and those with LDL-C levels >130 mg/dL at the end of this period were then randomized to receive ezetimibe 10 mg/d versus an additional 10 mg/d of atorvastatin. The atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal. The proportion of participants reaching their target LDL-C level (<100 mg/dL) was significantly higher in the group receiving combination therapy versus atorvastatin monotherapy. The addition of ezetimibe to the starting dose of 10 mg/d of atorvastatin provided a more effective means for reducing LDL-C than continued doubling of atorvastatin. [50] *Level of evidence:2*
- A meta-analysis of the lipid-modifying effect of ezetimibe looked at 14 randomized, double-blind clinical trials that compared the effectiveness of adding ezetimibe to simvastatin versus the use of rosuvastatin as monotherapy. The analysis used pooled data for LDL-C, HDL-C, total cholesterol, triglyceride, non-HDL-C, apoA-I, and apoB levels in patients treated with ezetimibe/simvastatin compared with rosuvastatin at all available doses. At comparable doses in the range tested, the combination of ezetimibe and simvastatin achieved slightly better reductions than rosuvastatin as monotherapy. [51] *Level of evidence:1*

- A double-blind randomized trial, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, compared the changes in carotid IMT in 720 patients with familial hypercholesterolemia treated with simvastatin alone or with ezetimibe. It examined carotid IMT as a marker for atherosclerosis regression during LDL-C lowering. After 2 years, there was no significant difference in carotid IMT between the two groups ($P=.29$), despite a significant difference in reduction of serum cholesterol levels between the combined therapy and simvastatin groups ($P<.01$). [52] *Level of evidence:2*

References

Bile acid-binding resins

Indication

- Adjunctive therapy to diet for the reduction of elevated serum cholesterol levels in patients with primary hypercholesterolemia who do not respond adequately to diet

Dose information

Cholestyramine (granules):

- Oral (adult): 4 to 24 g/d, given in 1 to 2 divided doses
- Recommended starting dose: 4 g once or twice a day
- Oral (children): 240 mg/kg/d, given in 3 divided doses

Colestipol (tablets):

- Oral: 2 to 16 g/d, given in 1 to 2 divided doses
- Recommended starting dose: 2 g once or twice a day

Colesevelam (tablets):

Oral: 3.8 g (6 tablets) per day, given in 1 to 2 divided doses

Colesevelam (oral suspension):

- Oral (adult): 3.75-g packet once per day or 1.785-g packet twice per day
- Oral (children aged 10 to 17 years): 3.75-g packet once per day or 1.785-g packet twice per day

Major contraindications

- Cholestyramine
 - Biliary obstruction
- Colestipol
 - None
- Colesevelam
 - GI obstruction
 - Hypertriglyceridemia
 - Pancreatitis

Comments

- Treatment with statins is generally preferred over treatment with bile acid-binding resins. However, resins can lower LDL-C and decrease the risk of coronary atherosclerosis. They are additive in lowering LDL-C when used with other cholesterol-lowering drugs, and they lack systemic toxicity
- Evidence for the use of resins in people with low risk of coronary heart disease events (<0.6% per year) is lacking, however

- Use caution in patients with hepatic impairment; may aggravate malabsorption in primary biliary cirrhosis
- Use caution in patients with renal impairment; prolonged use may cause hyperchloremic acidosis (cholestyramine)
- Colesevelam improves glycemic control in adults with type 2 diabetes
- Colesevelam is FDA pregnancy category B
- Gastrointestinal adverse effects (bloating, constipation) are the main limiting factor in the use of bile acid sequestrants
- May decrease absorption of fat-soluble vitamins and folic acid. Long-term use may result in increased bleeding tendency due to vitamin K deficiency. Supplement dietary intake or prescribe a vitamin supplement containing fat-soluble vitamins (such as A, D, E, and K) during therapy, if necessary
- Monitor the following laboratory parameters periodically:
 - Serum lipid levels (periodically)
 - Liver function tests (prolonged therapy)
 - Serum electrolyte levels (prolonged therapy)
 - Activated partial thromboplastin time
- Bile acid resins interact with numerous medications, especially levothyroxine
- Expected lipid responses to bile acid resins:
 - LDL-C level decreases 15% to 30%
 - HDL-C level increases 3% to 5%

- Triglycerides are usually not affected but may increase (and they may increase markedly)

Evidence

- An RCT, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), evaluated the effect of lowering serum cholesterol using cholestyramine resin versus placebo on risk of CHD in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia. After more than 7 years, compared with the placebo group, the cholestyramine group experienced both a significant drop in average plasma total cholesterol and LDL-C and a 19% reduction in risk ($P < .05$) of definite CHD death or definite nonfatal myocardial infarction. The rates for new positive exercise tests, angina, and coronary bypass surgery were likewise reduced in the same group. In contrast, the risk of death from all causes in the cholestyramine group was not significantly reduced. [53] *Level of evidence:1*
- An RCT of 1,351 patients after coronary artery bypass graft compared aggressive reduction of LDL-C to <100 mg/dL with lovastatin (plus cholestyramine if required) versus a more moderate reduction to 132 to 136 mg/dL using the same drugs. Aggressive treatment significantly reduced the risk of need for repeat revascularization at 4 years. After another 3 years, aggressive cholesterol reduction significantly reduced the risk of revascularization and cardiovascular death compared with moderate reduction. [23] *Level of evidence:1*
- An analysis of three double-blind RCTs that compared intensive lipid therapy with placebos regarding effect on coronary stenosis progression (as determined by quantitative coronary angiography) and on major cardiovascular events combined the data of a total of 445 patients with coronary atherosclerosis and elevated apoB. The analysis showed that the combination of lovastatin with colestipol or niacin with colestipol significantly decreased coronary stenosis progression. [54] *Level of evidence:2*

References

Fibrates

Indication

- Treatment of hypertriglyceridemia
- Also indicated for treatment of high cholesterol; however, some experts believe there is inadequate evidence to support its use for hypercholesterolemia in patients with normal triglyceride levels

Dose information

Fenofibrate :

- Antara:
 - 43 to 130 mg/d orally initially
 - Maximum: 130 mg/d
- Lofibra:
 - 67 to 200 mg/d orally initially
 - Maximum: 200 mg/d
- Tricor:
 - 48 to 160 mg/d orally initially
 - Maximum: 160 mg/d
- Triglide:
 - 50 to 160 mg/d orally initially
 - Maximum: 160 mg/d

- Trilipix (delayed release):
 - 45 to 135 mg/d orally
 - Maximum: 135 mg/d; 45 mg/d for renally impaired patients

Gemfibrozil :

- 600 mg orally twice a day

Major contraindications

- Fenofibrate
 - Biliary cirrhosis
 - Breastfeeding
 - Dialysis
 - Gallbladder disease
 - Hepatic disease
 - Renal failure
- Gemfibrozil
 - Biliary cirrhosis
 - Gallbladder disease
 - Hepatic disease
 - Renal failure

Comments

- Fibrates are the most effective medication for lowering triglyceride levels. They can be used in combination with other classes to treat mixed dyslipidemias; however, there is an increased risk of myopathy when they are used concomitantly with statins. Gemfibrozil is metabolized by CYP450 and interferes with and competes with statins, so it should be avoided in combination. Fenofibrate is considered a preferred fibric acid derivative when used in combination with statins
- Fenofibrate and gemfibrozil are the only fibric acid derivatives available in the U.S.
- Reports of myopathy and rhabdomyolysis have occurred. More common than frank myopathy, but still fairly rare, myalgias have been reported. Use caution in patients with risk factors for the development of renal failure secondary to rhabdomyolysis (*eg*, severe acute infection, hypotension, major surgery, trauma; severe metabolic, endocrine, or electrolyte disorders; uncontrolled seizures). Discontinue therapy if markedly elevated serum CPK levels occur or myositis is diagnosed
- Reports of hepatotoxicity and elevated levels on liver function test results. Monitor hepatic function during therapy
- Increased risk of cholelithiasis and cholecystitis requiring surgery
- Fibrates interact with several medications, and the physician should review the patient's current medication list. The two commercially available fibrates in the U.S., gemfibrozil and fenofibrate (or its derivatives), are metabolized differently and have different rates and expectations for drug interactions

Evidence

The effect of fibrate therapy on lipid profiles:

- A meta-analysis of data from 53 trials (16,802 participants) using fibrates and 30 trials (4,749 participants) using niacin was completed; 53 RCTs using fibrates showed an 11% reduction in total cholesterol level, a 36% reduction in triglyceride

level, an 8% reduction in LDL-C level, and an 11% increase in HDL-C level, with a 25% reduction in the risk for major coronary events. [55] *Level of evidence:1*

- A multicenter, double-blind, double-dummy, parallel-group study involved 248 patients on pravastatin who were randomly assigned to fenofibrate-pravastatin combination therapy versus pravastatin monotherapy. After 12 weeks, compared with pravastatin alone, the combination therapy group had a significantly greater decrease in non-HDL-C, HDL-C, LDL-C, triglyceride, and apoB levels. [56] *Level of evidence:2*
- A systematic review and meta-analysis considered 10 studies (n=16,869) evaluating the efficacy and safety of fibrate therapy in people with chronic kidney disease. In patients with mild-to-moderate chronic kidney disease, fibrates lowered total cholesterol levels ($P=.05$) and triglyceride levels ($P=.03$) and increased HDL-C levels ($P=.001$), but LDL-C levels were unchanged ($P=.83$). In the fibrate group there was a reduced risk of major cardiovascular events (RR, 0.70; 95% CI, 0.54-0.89; $P=.004$) and cardiovascular death (RR, 0.60; 95% CI, 0.38-0.96; $P=.03$) but not of all-cause mortality. In people with diabetes, fibrates reduced the risk of progression in albuminuria (RR, 0.86; 95% CI, 0.76-0.98; $P=.02$); serum creatinine was elevated and calculated glomerular filtration rate was reduced, but there was no change in progression to end-stage kidney disease (RR, 0.85; 95% CI, 0.49-1.49; $P=.575$). [57] *Level of evidence:1*

Fibrates for primary prevention of coronary heart disease:

- A systematic review and meta-analysis of 18 studies evaluated the effects of fibrates on major clinical outcomes in 45,058 participants, including 2,870 major cardiovascular events, 4,552 coronary events, and 3,880 deaths. With fibrate therapy there was a barely significant reduction in major cardiovascular events ($P=.048$) and a trend in reduced coronary events ($P=.69$) but no significant effect on all-cause mortality, cardiovascular mortality, sudden death, or nonvascular

mortality. Fibrates also reduced the progression of albuminuria by 14% (2-25; $P=.028$). [7] *Level of evidence: 1*

- The Helsinki Heart Study was an RCT of 4,081 asymptomatic middle-aged men with primary dyslipidemia who were randomized to receive 600 mg of gemfibrozil twice daily versus placebo. After 5 years, the incidence of coronary heart disease events in the gemfibrozil group was reduced by 34% (95% CI, 8.2-52.6; $P<.02$; two-tailed test). [8] *Level of evidence: 1*

Fibrates for secondary prevention of coronary heart disease:

- A systematic review of the literature from 1971 to 1999 assessed the available clinical trial data for dietary intervention and fibric acid derivatives for survival and cost effectiveness. Neither dietary interventions nor fibric acid therapy were felt to have significant evidence for benefit in primary or secondary prevention of coronary heart disease for either survival or cost effectiveness. [58] *Level of evidence: 2*
- An RCT compared bezafibrate (n=42) with placebo (n=39) regarding the effect on progression of coronary artery disease in young men after acute myocardial infarction or stable angina. The cumulative coronary event rate was significantly lower among bezafibrate-treated patients than among placebo-treated patients (3 vs 11 patients; $P=.02$). [59] *Level of evidence: 3*
- An RCT of 3,090 young male patients after myocardial infarction, the Bezafibrate Infarction Prevention (BIP) study, examined the effect of bezafibrate on fatal or nonfatal myocardial infarction or sudden death. The frequency of the primary end point was 13.6% on bezafibrate versus 15.0% on placebo ($P=.26$). In a post hoc analysis, the subgroup with high baseline triglyceride levels (≥ 200 mg/dL) showed a reduction in the cumulative probability of the primary end point by bezafibrate (39.5%; $P=.02$). [60] *Level of evidence: 1*
- An RCT compared fluvastatin plus placebo versus fluvastatin plus fenofibrate in people with type 2 diabetes, dyslipidemia, and a history of coronary heart disease.

The fibrate-statin combination was found to significantly improve lipid levels versus statin therapy alone. [61] *Level of evidence:2*

Fibrate use in people with diabetes improves triglyceride levels but may not have significant effect on risk for coronary events:

- The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, an RCT, compared incidence of cardiovascular events in patients on fenofibrate therapy versus placebo in 9,795 patients with type 2 diabetes who were not taking statin therapy at the time of enrollment in the clinical trial. Over an average of 5 years, relative to placebo, the fenofibrate group had a 24% reduction in nonfatal myocardial infarction (HR, 0.76; 95% CI, 0.62-0.94; $P=.010$), and total cardiovascular disease events were likewise significantly reduced from 13.9% to 12.5% (HR, 0.89; 95% CI, 0.80-0.99; $P=.035$), including a 21% reduction in coronary revascularization (HR, 0.79; 95% CI, 0.68-0.93; $P=.003$). There was a significantly decreased progression in albuminuria ($P=.002$) and fewer episodes of retinopathy-related laser treatment (5.2% vs 3.6%, $P=.0003$) in the fenofibrate group. [62] *Level of evidence:1*
- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, an RCT, compared combination therapy with a statin plus a fibrate versus statin monotherapy in 5,518 patients with type 2 diabetes. There were no significant differences between the two study groups with respect to primary or any secondary outcome regarding cardiovascular risk. [63] *Level of evidence:1*

Fibrates for stroke prevention:

- An RCT of men with coronary heart disease and low HDL-C compared gemfibrozil with placebo over approximately 5 years. Gemfibrozil increased HDL-C level and reduced triglyceride and total cholesterol levels. Gemfibrozil significantly reduced the incidence of coronary heart disease but did not significantly reduce the risk of stroke. [64] *Level of evidence:1*

References

Nicotinic acid

Indications

- Nicotinic acid (also called niacin or vitamin B₃) is used to treat hypertriglyceridemia
- It is also used to modify the other lipid levels in dyslipidemia

Dose information

Immediate-release niacin:

- 250 mg orally once a day initially
- Dose may be increased every 4 to 7 days until desired LDL-C and triglyceride levels are achieved
- Usual effective dose is 1.5 to 2 g/d, given in 2 to 3 divided doses
- If dyslipidemia is not adequately controlled after 2 months at this level, the dose may be increased to 3 g/d, given in divided doses
- Maximum: 6 g/d

Extended-release niacin:

- 500 mg orally once a day at bedtime for 4 weeks
- Dose may be increased in 500-mg-per-week increments every 4 weeks until desired LDL-C, non-HDL-C, and triglyceride levels are achieved or until maximum dose is reached
- Maximum FDA-approved dose: 2,000 mg/d

Sustained-release niacin:

- Available as an over-the-counter formulation
- Dosed at 500 mg orally daily and increased by 500-mg increments to a typical maximum dose of 1,000 mg orally twice daily

No-flush niacin:

- Very poor bioavailability and limited or no lipid-modifying response; not recommended for clinical use

Major contraindications

- Bleeding
- Hepatic disease

Comments

- Nicotinic acid use is supported as an adjunct for lipid modification and for atherosclerosis regression; however, there are limited data supporting its use for reduction of major cardiovascular events and mortality
- There are data from randomized placebo-controlled trials supporting the benefits of nicotinic acid (immediate-release niacin) as monotherapy for reducing cardiovascular events and even improvement in late mortality from this approach
- Data on decreased atherosclerosis as measured by quantitative coronary angiography and carotid IMT support the use of nicotinic acid as add-on therapy to statins. The lipid modifying results and atherosclerosis findings on the background of a single randomized placebo-controlled trial finding that immediate-release niacin reduces cardiovascular events and mortality (>10 years after completion of the study) has been the justification for niacin use

- More recent clinical trials assessing extended-release niacin as an add-on to statin (±ezetimibe) in patients with ASCVD and well-controlled LDL-C found no benefit in cardiovascular morbidity/mortality at <5 years
- Nicotinic acid may be a useful adjunct when used with other lipid-modifying medications for severe dyslipidemia. Cutaneous flushing, with or without pruritus, may reduce adherence to therapy. Restarting with a more gradual increase in dose may prove to be more acceptable. Other ways to lessen these symptoms include pretreatment with aspirin, other nonsteroidal antiinflammatory medicines, or laropiprant (not available in the U.S.); taking nicotinic acid with food; avoiding alcohol and spicy foods; and taking hot showers after administration
- Immediate-release niacin tends to cause worse flushing than the sustained-release and extended-release forms, but it is less likely to cause hepatotoxicity
- Reports of severe hepatotoxicity, including fulminant hepatic necrosis, have been described, and it appears to be more common when a sustained-release preparation is substituted for an immediate-release preparation at equivalent doses
- Rare reports of rhabdomyolysis are associated with concomitant administration of statins
- Use caution in patients with diabetes or insulin resistance syndrome, a history of peptic ulcer, unstable angina, the acute phase of myocardial infarction, hepatic impairment, and gout, as well as those at risk for myopathy (especially if they are already taking statin therapy)
- Monitor the levels of serum lipids, liver enzymes, blood glucose, and serum uric acid
- Expected lipid responses to nicotinic acid at doses ranging from 2 to 6 g/d (1-2 g/d of the sustained-release preparation) are as follows:
 - Decrease LDL-C levels by 10% to 25%

- Increase HDL-C levels by 15% to 35%
- Decrease triglyceride levels by 20% to 50%

Evidence

Adding nicotinic acid to augment the lipid-modifying properties of other medication:

- An RCT, involving 3,414 patients pretreated with statin with or without ezetimibe to an LDL-C level between 40 and 80 mg/dL, evaluated the effect of two preparations of niacin (sustained release, 1,500-2,000 mg vs immediate release, 50-150 mg) on cardiovascular events. At 2 years, compared with pretreatment alone, the addition of niacin therapy resulted in increased HDL-C level (median from 35 to 42 mg/dL) and decreased triglyceride level (164 to 122 mg/dL) and LDL-C level (74-62 mg/dL), but there was no significant change in the incidence of cardiovascular events. [65] *Level of evidence:1*
- A prospective, randomized, open-label, blinded end-point study found that, in patients with mixed dyslipidemia whose conditions did not respond to standard-dose statins, treatment with high-intensity rosuvastatin 40 mg plus extended-release nicotinic acid with laropiprant resulted in improved lipid blood test results compared with rosuvastatin 40 mg plus fenofibrate. [66] *Level of evidence:2*
- A meta-analysis considered 4 studies (n=407) on the effect of niacin on serum glucose level, progression of coronary artery stenosis, and cardiovascular events. The use of niacin for 3 years was associated with an increase in serum glucose level and increased risk of developing impaired fasting glucose (but not diabetes mellitus). Use of niacin was associated with a significantly reduced incidence of coronary stenosis progression and major cardiovascular events. [67] *Level of evidence:2*
- An RCT evaluated the safety and efficacy of combination ezetimibe-simvastatin with and without extended-release niacin in 942 patients with type IIa/IIb dyslipidemia.

After about 15 months, the increased incidence of clinical adverse effects was largely attributed to niacin-associated flushing and pruritus. With respect to changes in blood lipid levels, the ezetimibe-simvastatin plus niacin group had significant increases of HDL-C levels and drops in triglyceride, non-HDL-C, LDL-C, and apoB levels (all values of $P \leq .004$). [68] *Level of evidence: 2*

- The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan trial (AVENT) compared nicotinic acid 1 g versus 1.5 g versus placebo in people with type 2 diabetes at high risk of macrovascular events. At 16 weeks, both doses of nicotinic acid significantly increased HDL-C levels versus placebo, whereas only the higher dose of 1.5 g resulted in a significant reduction in triglyceride levels. The higher dose also reduced levels of total cholesterol and LDL-C, but these results did not reach significance. [69] *Level of evidence: 2*
- A meta-analysis of 30 RCTs (n=4,749) on niacin use for dyslipidemia. Random-effects model showed 10% reduction in total cholesterol, 20% reduction in triglycerides, 14% reduction in low-density lipoprotein cholesterol, and 16% increase in HDL-C for niacin. Apart from flushes in the niacin group, both fibrates and niacin were shown to be well-tolerated and safe. [55] *Level of evidence: 2*
- A double-blind RCT of 160 patients with coronary disease, low HDL-C levels, and normal LDL-C levels randomized participants to receive one of four regimens: simvastatin plus niacin versus vitamins versus simvastatin-niacin plus antioxidants versus placebo. Compared with placebo, the average stenosis decreased 0.7% with simvastatin-niacin plus antioxidants ($P = .004$) and regressed by 0.4% with simvastatin-niacin alone ($P < .001$). The frequency of the cardiovascular clinical end point was 24% with placebo; 3% with simvastatin-niacin; 2% in the antioxidant-therapy group; and 14% in the simvastatin-niacin-plus-antioxidants group. [70] *Level of evidence: 2*

Use of nicotinic acid associated with reduction in atherosclerosis and cardiac events:

- A meta-analysis of 23 randomized lipid trials suggested that patients with vascular disease benefit comparably and additively from LDL-C reduction and HDL-C elevation. The statistically most effective LDL-C and HDL-C composite predictor of fractional in-treatment risk relative to placebo is 1 plus the fractional treatment-induced reduction of LDL-C level minus the fractional elevation of HDL-C level. [71] *Level of evidence:2*
- A combined analysis of three angiographic trials showed that patients with metabolic syndrome have significantly more rapid coronary stenosis progression and a higher frequency of clinical cardiovascular events. Greater stenosis progression rate is significantly associated with a higher rate of clinical events independent of patient risk factors and study therapy. LDL-C-lowering and HDL-C-raising therapies independently and significantly decrease coronary stenosis progression and reduce cardiovascular events. [54] *Level of evidence:2*
- An RCT studied the effect of once-daily extended-release niacin, added to background statin therapy, on the change in common carotid IMT. Participants with known coronary heart disease and low levels of HDL-C were included in the trial. After 12 months, the addition of extended-release niacin to statin therapy slowed the progression of atherosclerosis; the mean carotid IMT increased significantly in the placebo group but was unchanged in the niacin group. [72] *Level of evidence:2*
- The HDL and LDL Treatment Strategies (HALTS) in Atherosclerosis study, an RCT, compared the effect of extended-release niacin added to a statin with that of ezetimibe plus a statin on carotid IMT. Patients in the statin-niacin group showed a significant regression in carotid IMT. [73] *Level of evidence:2*
- An RCT (the Coronary Drug Project) comparing the effect of niacin versus placebo in patients with prior myocardial infarction showed that patients receiving niacin had a significantly lower rate of nonfatal myocardial infarction or stroke. [74] *Level of evidence:1*

Adverse effects of nicotinic acid:

- The Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial evaluated the efficacy of extended-release niacin/laropiprant versus placebo in 42,424 patients with preexisting atherosclerotic vascular disease who were all receiving simvastatin 40 mg daily (plus, if indicated, ezetimibe 10 mg daily). After a median of 3.9 years, 25% of participants allocated extended-release niacin and laropiprant versus 17% allocated placebo had discontinued study treatment owing to adverse effects. Compared with placebo, extended-release niacin and laropiprant plus statin increased the risk of definite myopathy (RR, 4.4; 95% CI, 2.6-7.5; $P < .0001$). There was no statistical difference in major cardiovascular events between the two groups. [75] *Level of evidence: 1*

References

Omega-3 fatty acids

Indication

- Prescription-strength omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) are used as an adjunct to diet to reduce hypertriglyceridemia for patients with triglyceride levels >500 mg/dL

Dosing information

- Lovaza: capsules, each containing 1 g of omega-3-acid ethyl ester concentrate consisting of eicosapentaenoic acid 465 mg and docosahexaenoic acid 375 mg
- Vascepa: 1-g eicosapentaenoic acid capsule, either as a single 4-g dose by mouth once per day or as 2-g doses by mouth twice daily

Major contraindications

- None

Comments

- Potential clinical benefits include lower triglyceride levels, a reduction in ventricular dysrhythmias, antithrombotic effects, improved endothelial function, antiinflammatory effects, and a slight reduction of blood pressure
- Eicosapentaenoic acid and docosahexaenoic acid are also prevalent in oily fish (salmon, tuna, mackerel, sardines) and some legumes (flax, walnuts)
- Omega-3 fatty acids appear to be particularly useful in lowering triglyceride levels. They have also been shown to lower the risk of sudden death in patients with coronary artery disease, presumably by an antiarrhythmic effect

Evidence

- A randomized, multicenter, double-blind control study evaluated the efficacy of prescription omega-3-acid ethyl esters on lipid levels in 245 atorvastatin-treated patients with elevated non-HDL-C and triglyceride levels. After 16 weeks, compared with statin alone, the omega-3 plus statin group significantly reduced median non-HDL-C levels (50.4% vs 46.3%; $P < .001$) but not LDL-C, apoA-I, or apoB levels. [76] *Level of evidence:2*
- A systematic review comparing cholesterol-lowering therapies found that statins, but not other therapies, reduced coronary heart disease mortality and that statins and omega-3 fatty acids reduced all-cause mortality. [77] *Level of evidence:1*
- An RCT (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) compared fish oil supplementation (1 g of omega-3 polyunsaturated fatty acids daily) versus no fish oil in patients after a myocardial infarction. Fish oil reduced the likelihood of death within 3.5 years. [78] *Level of evidence:1*
- A systematic review including 48 RCTs and 41 cohort analyses compared omega-3 intake versus dietary advice. It found no clear evidence that dietary or supplemental omega-3 fats alter total mortality, combined cardiovascular events, or cancers in patients with, or at high risk of, cardiovascular disease or in the general population. [79] *Level of evidence:1*

- A systematic review including 23 RCTs (n=1,075) evaluated the use of fish oils (mean dose of polyunsaturated fatty acids, 3.5 g/d) versus placebo for 12 weeks in patients with type 2 diabetes. Triglyceride levels in the treated group were lowered by 0.45 mmol/L (95% CI, -0.58 to -0.32; $P < .00001$), VLDL-C levels were lowered by -0.07 mmol/L (95% CI, -0.13 to 0.00; $P = .04$), and LDL-C levels were raised by 0.11 mmol/L (95% CI, 0.00-0.22; $P = .05$), although the latter was nonsignificant in subgroup analysis. No significant changes in total or HDL cholesterol, hemoglobin A1c, fasting glucose, fasting insulin, or body weight were observed. [80] *Level of evidence:1*

References

Lomitapide

Indication

- Lomitapide is an adjunct to diet to lower LDL-C, total cholesterol, and apoB levels in adults (persons older than 18 years) judged to have HoFH

Dosing information

- Available in capsules (5 mg, 10 mg, and 20 mg). Administered under the FDA's Risk Evaluation and Mitigation Strategies program. Initial dose is 5 mg orally daily, titrated up to a maximum dose of 60 mg daily

Major contraindications

- Hepatic disease
- Pregnancy

Comments

- Lomitapide was approved by the FDA as an orphan drug, on the basis of results from a single-arm open-label study of efficacy and tolerability in 29 participants with HoFH

- There are significant precautions regarding safety and tolerability because of relatively limited data and use for this rare disease and in light of documented development of fatty liver and steatorrhea as mechanistic consequences of using the medication
- Should not be administered if pregnancy is known, suspected, or contemplated
- Dose limitation is necessary in renal or hepatic disease
- Dose limitation and precautions are necessary if the drug is coadministered with drugs metabolized by cytochrome P450-3A4
- A low-fat diet and gradual dose titration are necessary to minimize steatorrhea
- Fatty liver is expected as a consequence of use. It is not known whether progression of fatty liver as a result of use of this medicine will result in significant liver dysfunction
- Dose modification is required if hepatotoxicity is suspected

Mipomersen

Indication

- Mipomersen is an adjunct to lipid-lowering medications and diet to reduce LDL-C, apoB, total cholesterol, and non-HDL-C levels in adults (persons older than 18 years) with HoFH
- It is available under the FDA's Risk Evaluation and Mitigation Strategies monitored program

Dosing information

- 200 mg subcutaneous injection weekly

Major contraindications

- Hepatic disease

Comments

- Mipomersen was approved by the FDA as an orphan drug for HoFH on the basis of the results from a multinational, randomized, placebo-controlled clinical trial of efficacy and tolerability involving 45 already-treated patients with clinical diagnosis or genetic confirmation of HoFH
- Mipomersen is an antisense oligonucleotide that targets the messenger RNA for apoB
- There are significant precautions regarding safety because of relatively limited data in developing this medicine for a rare disease
- Should not be administered if the patient is pregnant or if pregnancy is suspected or contemplated
- Dose limitation is necessary in renal or hepatic disease
- Fatty liver is expected as a consequence of use. It is not known whether progression of fatty liver as a result of use of this medicine will result in significant liver dysfunction
- Dose modification is required if hepatotoxicity is suspected
- Injection site reactions are common

Summary of evidence

Evidence

Preventive measures

Statin drugs in primary prevention:

- A meta-analysis considered 27 trials to evaluate the role of higher-dose statins in 174,149 people at low risk for vascular events. Statin therapy reduced the risk of major vascular events (relative risk [RR], 0.79; 95% CI, 0.77-0.81, per 1.0 mmol/L). This reduction was confirmed even in persons with 5-year risk of major vascular events lower than 10%. [1] *Level of evidence:1*
- A systematic review of statin drugs for primary prevention of cardiovascular events included a total of 18 clinical trials and 56,934 participants. Compared with placebo, statin use was associated with a reduction in all-cause mortality (odds ratio [OR], 0.86; 95% CI, 0.79-0.94), combined fatal and nonfatal cardiovascular disease (RR, 0.75; 95% CI, 0.70-0.81), combined fatal and nonfatal coronary heart disease (CHD) events (RR, 0.73; 95% CI, 0.67-0.80), combined fatal and nonfatal stroke (RR, 0.78; 95% CI, 0.68-0.89), and reduction of revascularization rates (RR, 0.62; 95% CI, 0.54-0.72). [2] *Level of evidence:1*
- The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is an RCT that compared lovastatin with placebo in a total of 5,608 men and 997 women with average total cholesterol and LDL-C levels, below-average HDL-C levels, and medium risk of coronary heart disease (0.6%-1.4% annual coronary heart disease risk). After about 5 years and compared with placebo, lovastatin, 20 to 40 mg daily, reduced the incidence of first acute major coronary events (RR, 0.63; 95% CI, 0.50-0.79; $P < .001$), myocardial infarction (RR, 0.60; 95% CI, 0.43-0.83; $P = .002$), unstable angina (RR, 0.68; 95% CI, 0.49-0.95; $P = .02$), coronary revascularization procedures (RR, 0.67; 95% CI, 0.52-0.85; $P = .001$), coronary events (RR, 0.75; 95% CI, 0.61-0.92; $P = .006$), and cardiovascular events (RR, 0.75; 95% CI, 0.62-0.91; $P = .003$). [3] *Level of evidence:1*
- The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), an RCT that studied people at moderate risk (*ie*, hypertension and one other risk factor plus an LDL-C level of 120-189 mg/dL), found no difference at 4.8 years between pravastatin 40 mg daily ($n=5170$) and usual care ($n=5185$) with regard to all-cause mortality (primary outcome) or a combined outcome of nonfatal

myocardial infarction or coronary heart disease death (secondary outcome).

However, 30% of those patients receiving usual care switched to active treatment during the study period, which may have contributed to the lack of significant findings in this study. [4] *Level of evidence:1*

- The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) randomized 10,305 hypertensive, high-risk middle-aged and elderly patients to atorvastatin 10 mg or placebo. The study was halted after about 3 years, owing to highly significant benefit of treatment on primary events after the first year of follow-up (100vs154 events; hazard ratio [HR], 0.64 [95% CI, 0.50-0.83]; $P=.0005$). [5] *Level of evidence:1*
- The JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) investigated the benefit of lowering both LDL-C and high-sensitivity C-reactive protein (hsCRP) using 20 mg of rosuvastatin versus placebo in 15,548 initially healthy men and women. In participants who achieved LDL-C <1.8 mmol/L and hsCRP <1 mg/L, there was a 79% reduction in cardiovascular events (event rate 0.24 per 100 person-years; HR, 0.21; 95% CI, 0.09-0.52). Regardless of the lipid end point used, hsCRP concentrations were predictive of event rates. [6] *Level of evidence:1*

Fibrates in primary prevention:

- A systematic review and meta-analysis of 18 studies evaluated the effects of fibrates on major clinical outcomes in 45,058 participants, including 2,870 major cardiovascular events, 4,552 coronary events, and 3,880 deaths. With fibrate therapy there was a barely significant reduction in major cardiovascular events ($P=.048$) and a trend in reduced coronary events ($P=.69$) but no significant effect on all-cause mortality, cardiovascular mortality, sudden death, or nonvascular mortality. Fibrates also reduced the progression of albuminuria by 14% (2-25; $P=.028$). [7] *Level of evidence:1*

- The Helsinki Heart Study was an RCT of 4,081 asymptomatic middle-aged men with primary dyslipidemia who were randomized to receive 600 mg of gemfibrozil twice daily versus placebo. After 5 years, the incidence of coronary heart disease events in the gemfibrozil group was reduced by 34% (95% CI, 8.2-52.6; $P < .02$; two-tailed test). [8] *Level of evidence:1*

Treatment

Medications

Statin drugs' effect on lipid profile and safety:

- The STELLAR trial (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) is a multicenter, open-label randomized trial comparing the efficacy and safety of rosuvastatin with those of atorvastatin, pravastatin, and simvastatin. Rosuvastatin reduced LDL cholesterol significantly more than simvastatin and pravastatin in all 14 pairwise comparisons analyzed. The best LDL cholesterol reduction (55%) was achieved in the rosuvastatin 40-mg group and was not significantly different ($P = .006$) from the next highest LDL cholesterol reduction (51%) observed in the atorvastatin 80-mg group. Drug tolerability was similar across treatments. [9] *Level of evidence:2*
- A systematic review of 8 randomized placebo-controlled trials (897 participants; period, 1996-2005) evaluated the LDL-C lowering efficacy and safety of statin drugs (lovastatin, pravastatin, simvastatin, or atorvastatin) in a pediatric population with heterozygous familial hypercholesterolemia. After an average of 6 months, as compared with placebo group, the pooled estimate of the difference in mean relative reductions of LDL-C in the statin group was -32.15% (95% CI, -34.90% to -29.40%), and there was no significant elevation of transaminase levels or CPK levels in the statin group. [10] *Level of evidence:1*
- A randomized, placebo-controlled clinical trial of pravastatin 20 or 40 mg daily vs placebo in Dutch children with diagnoses of familial hypercholesterolemia

found that pravastatin use resulted in a change in carotid IMT when used for 2 years. Compared with placebo, the mean change in IMT was 0.014 [SD=.046] mm ($P=.02$), and the mean reduction in LDL-C levels was +.03% and -24.1%, respectively ($P<.001$). [11] *Level of evidence:2*

- A meta-analysis of 49 clinical trials evaluated 14,236 patients for the safety of atorvastatin 10 mg or 80 mg, used for between 2 weeks and 54 months. Compared with placebo, there was no difference in incidence of treatment-associated adverse events in the two treatment groups. [12] *Level of evidence:2*

Statin drugs reduce overall mortality, cardiovascular mortality, and nonfatal cardiovascular events in patients with coronary heart disease who are at high risk for ischemic coronary events.

- A systematic review of 18 studies ($n=14,303$) was undertaken to assess safety and effect of statins in patients with acute coronary syndrome. Compared with patients on no statins, at 4 months there was a significant reduction in the number of unstable angina episodes (RR, 0.76; 95% CI, 0.59-0.96). Myopathy, defined as creatinine kinase levels more than 10 times the reference upper limit, was found in nine (0.13%) statin-treated patients, compared with one (0.015%) in the control groups. Serious muscle toxicity was primarily found with higher-dose (80-mg) simvastatin. [13] *Level of evidence:1*
- A randomized double-blinded controlled trial evaluated the efficacy of simvastatin versus placebo in 4,444 patients with angina or previous myocardial infarction and elevated serum cholesterol. All patients were instructed on a low-fat diet. After about 5 years, simvastatin produced mean changes in total cholesterol of -25%, LDL-C of -35%, and HDL-C of +8% compared with the control group, with few adverse effects. The relative risk of death in the simvastatin group was 0.70 (95% CI, 0.58-0.85; $P=.0003$). In the placebo-versus-simvastatin group, there were 189 versus 111 coronary deaths (RR, 0.58; 95% CI, 0.46-0.73) and 622 versus 431 with one or more

major coronary events (RR, 0.66; 95% CI, 0.59-0.75; $P < .00001$). [14] *Level of evidence:1*

- The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study is an RCT involving 1,600 people with coronary heart disease that compared atorvastatin with 'usual care' (management without statins). During this study, 196 (24.5%) of the usual care patients had a CHD recurrent event or died, compared with 96 (12%) of the patients on atorvastatin (RR, 0.49; 95% CI, 0.27-0.73; $P < .0001$), with a significant decrease in total mortality, coronary mortality, and stroke. [15] *Level of evidence:1*
- The West of Scotland Coronary Prevention Study (WOSCOPS) is an RCT that evaluated the efficacy of pravastatin 40 mg in 6,595 middle aged men with elevated cholesterol (mean level, about 270 g/dL). After an average of about 5 years, compared with placebo, in the treatment group there was a decrease in definite coronary events (RR, 31%; 95% CI, 17-43%; $P < .001$). nonfatal definite myocardial infarctions (RR, 31%; $P < .001$), death from coronary heart disease (definite cases alone: RR, 28%; $P = .13$; definite plus suspected cases: RR, 33%, $P = .042$); and death from all cardiovascular causes (RR, 32%; $P = .033$). [16] *Level of evidence:1*
- A subsequent RCT, the Heart Protection Study Collaborative Group (MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin) compared simvastatin with placebo in 20,536 high-risk people with and without coronary heart disease. All-cause mortality was significantly lower in the simvastatin group, primarily owing to 18% proportional reduction in the coronary death rate. There were also significant reductions in the first event rate for nonfatal myocardial infarction or coronary death (8.7% vs 11.8%; $P < .0001$), for nonfatal or fatal stroke (4.3% vs 5.7%; $P < .0001$), and for coronary or noncoronary revascularization (9.1% vs 11.7%; $P < .0001$). [17] *Level of evidence:1*

Elderly patients at high risk of cardiovascular disease appear to benefit from cholesterol-lowering therapy.

- The PROSPER study (Prospective Study of Pravastatin in the Elderly at Risk) was an RCT designed to evaluate the efficacy of pravastatin 40 mg on cholesterol serum levels and mortality in 5,804 patients aged 70 to 82 years with a history of, or risk factors for, vascular disease. Compared with placebo, LDL-C was decreased by 34% in the treated group, and the number of primary–end point events was 473 versus 408, respectively (HR, 0.85; 95% CI, 0.74-0.97; P =.014). Coronary death and nonfatal myocardial infarction risk was also reduced (HR, 0.81; 95% CI, 0.69-0.94; P =.006), as was the hazard ratio for transient ischemic attack (HR, 0.75; 95% CI, 0.55-1.00; P =.051), but the risk for stroke was unaffected. [18] *Level of evidence:*1

Aggressive cholesterol lowering in high-risk patients appears to be beneficial, and evidence suggests that target LDL-C should be lower than that suggested by current national guidelines.

- The Treating to New Targets (TNT) study evaluated the effect in 10,001 participants randomly assigned to treatment with atorvastatin 80 mg versus 10 mg in the period after the occurrence of a first cardiovascular event. This is a post hoc time-to-next-event analysis that concluded that treatment with atorvastatin 80 mg continued to significantly decrease the risk of any cardiovascular event over time compared with atorvastatin 10 mg in patients who had survived previous events; follow-up lasted 4.9 years on average. [19] *Level of evidence:*1
- The IDEAL trial (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) was an RCT comparing the secondary prevention provided by high-dose versus standard-dose statin therapy. Intensive lowering of LDL-C level with atorvastatin 80 mg daily (mean LDL-C level, 81 mg/dL) or simvastatin 20 mg daily (mean LDL-C level, 104 mg/dL) did not result in a significant difference in reduction of major coronary events, cardiovascular mortality, or all-cause mortality but did reduce the risk of nonfatal acute myocardial infarction and several composite secondary end points. [20] *Level of evidence:*1

- A post hoc analysis of the IDEAL trial assessed the efficacy of high-dose atorvastatin versus usual-dose simvastatin for secondary prevention. Compared with simvastatin, the atorvastatin group had a relative risk reduction of first through fifth cardiovascular event by 17% ($P < .0001$), 24% ($P < .0001$), 19% ($P = .035$), 24% ($P = .058$), and 28% ($P = .117$), respectively. [21] *Level of evidence: 2*
- A meta-analysis considered 26 large, long-running (<2 years) RCTs comparing varying degrees of statin regimens against placebo (21 trials) or each other (5 trials) in 169,138 patients. With each 1-mmol/L reduction in LDL-C level, the annual rate of myocardial infarction, revascularization, or ischemic stroke was reduced by just over a fifth. There was no evidence of threshold, which suggested that reduction of LDL-C by 2 to 3 mmol/L would reduce risk by about 40% to 50%. [22] *Level of evidence: 1*
- The Post Coronary Artery Bypass Graft Trial was designed to compare the effects of 2 lipid-lowering regimens and low-dose anticoagulation versus placebo on progression of atherosclerosis in saphenous vein grafts after coronary artery bypass graft surgery. A total of 1,351 patients were randomized to receive either aggressive reduction of cholesterol levels with lovastatin (plus cholestyramine if required) to goal LDL-C <100 mg/dL or more moderate reduction with the same drugs (achieving a mean LDL-C of 132-136 mg/dL) after coronary artery bypass graft. At 4 years, aggressive treatment significantly reduced the need for repeat revascularization. At 7.5 years of follow-up, there was a 30% reduction in revascularization procedures and a 24% reduction in patients assigned to the aggressive strategy compared with patients assigned to the moderate strategy ($P = .0006$ and 0.001 , respectively). [23] *Level of evidence: 1*
- The PROVE IT-TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators) compared standard therapy of 40 mg of pravastatin daily versus intensive therapy with 80 mg of atorvastatin daily in 4,162 patients whose study treatment started within 10 days of an acute coronary syndrome. The median LDL-C level achieved during treatment

was 95 mg/dL in the standard-dose pravastatin group and 62 mg/dL in the high-dose atorvastatin group ($P < .001$). The event rate in high-intensity treatment was 22.4%, compared with 26.3% in the standard treatment arm, representing a 16% reduction in the hazard rate for the primary end point, a composite of death from any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, and stroke. [24] *Level of evidence: 1*

- In a follow-up of the PROVE IT-TIMI 22 study, the authors conducted an analysis of high-intensity versus standard-dose statin therapy for the prevention of recurrent events. In results similar to those of the prevention-of-events analysis previously published, they concluded that additional events were also reduced by 19% with atorvastatin 80 mg ($n=275$ vs $n=340$, respectively; $P=.009$). [25] *Level of evidence: 1*
- The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial is a multinational double-blind RCT comparing a moderate lipid-lowering regimen consisting of 40 mg of pravastatin versus an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin in 654 patients for changes in atheroma burden as measured by intravascular ultrasonography. Comparing the moderate-dose versus intensive-dose groups after 18 months, there was a significant decrease in serum LDL-C levels (110 mg/dL vs 79 mg/dL; $P < .001$) and percentage drop in C-reactive protein levels (5.2% vs 36.4%; $P < .001$). There was a significantly lower end point and progression rate in atheroma volume in the atorvastatin (intensive) group. Compared with baseline, progression of coronary atherosclerosis occurred in the pravastatin group (2.7%; 95% CI, 0.2%-4.7%; $P=.001$) but not in the atorvastatin group (-0.4%; 95% CI, -2.4% to 1.5%; $P=.98$). [26] *Level of evidence: 2*

Statins are effective in reducing cardiovascular outcomes in patients with diabetes at higher risk of macrovascular complications. Although patients with diabetes are at higher cardiovascular risk whether or not they have other risk factors, trial data on statins in patients with diabetes with a low 10-year cardiovascular risk are lacking.

- A meta-analysis of 5 RCTs (n=32,752) evaluated the association of intensive-dose versus moderate-dose statin therapy with new-onset diabetes. The incidence of diabetes after about 5 years was 1,449 in intensive-dose therapy and 1,300 in moderate-dose therapy. After about 5 years, cardiovascular events were 3,134 and 3,550, respectively, representing 6.5 fewer cases in the intensive-dose group per 1,000 patient-years. Odds ratios were 1.12 (95% CI, 1.04-1.22; $I^2=0\%$) for new-onset diabetes and 0.84 (95% CI, 0.75-0.94; $I^2=74\%$) for cardiovascular events for participants receiving intensive therapy compared with moderate-dose therapy, respectively. [27] *Level of evidence:1*
- A meta-analysis involving 13 statin trials with 91,140 participants evaluated the relationship between statin use and development of diabetes. After an average of 4 years, statin therapy was associated with a 9% increased risk for incident diabetes (OR, 1.09; 95% CI, 1.02-1.17), with little heterogeneity ($I^2=11\%$) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants. [28] *Level of evidence:1*
- A systematic review of statin benefit for composite cardiovascular outcomes (cardiovascular mortality, myocardial infarction, stroke, revascularization, and unstable angina) in patients with treated diabetes was undertaken. Risks were significantly reduced with statins versus placebo in people with diabetes in both primary prevention (6 studies) and secondary prevention (8 studies), with similar relative risk reduction (0.78 and 0.76, respectively). [29] *Level of evidence:1*
- A large RCT compared simvastatin 40 mg with placebo, and subgroup analysis was performed for 5,963 participants with diabetes. At 4.8 years, major cardiovascular events were significantly reduced in patients receiving statin therapy, including participants without established cardiovascular disease or a raised LDL-C level. [30] *Level of evidence:1*
- Subgroup analysis considered the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, which measured the effects of pravastatin therapy,

40 mg/d over 6 years, on the risk of CHD death or nonfatal myocardial infarction and other cardiovascular outcomes in 1,077 patients with diabetes and 940 patients with impaired fasting glucose. Compared with placebo, the treatment group had a reduction of a major CHD event from 15.9% to 12.3% (relative risk reduction [RRR], 24%; $P<.001$) and 23.4% to 19.6% in the diabetic group (RRR, 19%; $P=.11$). Treatment in patients with diabetes or impaired fasting glucose also reduced the risk of a cardiovascular event, from 52.7 to 45.2% (21%; $P<.008$) and from 45.7 to 37.1% (26%; $P=.003$), respectively, and the risk of stroke from 9.9 to 6.3% (RRR, 39%; 95% CI, 7%-61%; $P=.02$) and from 5.4 to 3.4% (RRR, 42%; 95% CI, -9% to 69%; $P=.09$), respectively. [31] *Level of evidence:1*

- An RCT (the Collaborative Atorvastatin Diabetes Study [CARDS]) compared primary prevention of atorvastatin 10 mg in 2,838 participants with type 2 diabetes but without cardiovascular disease. Compared with controls after about 4 years, the treated group had a significantly reduced number of cardiovascular events (rate reduction, 37%; 95% CI, -52 to -17%; $P=.001$). [32] *Level of evidence:1*

There is evidence that statins reduce the rates of stroke, compared with placebo.

- A meta-analysis of 27 studies evaluated statin therapy versus placebo in 113,148 participants for ischemic stroke outcome. Compared with placebo, at stroke onset, statin treatment resulted in good functional outcome at 90 days (pooled OR, 1.41; 95% CI, 1.29-1.56; $P<.001$) but not 1 year (OR, 1.12; 95% CI, 0.9-1.4; $P=.31$). Reduction in fatality was significant at both 90 days (pooled OR, 0.71; 95% CI, 0.62-0.82; $P<.001$) and 1 year (OR, 0.80; 95% CI, 0.67-0.95; $P=.01$). In one RCT reporting 90-day functional outcome, statin treatment was associated with good outcome (OR, 1.5; 95% CI, 1.0-2.24; $P=.05$), but no reduction in fatality was found in the 3 RCTs reporting such data ($P=.9$). In patients treated with fibrinolysis, there was no association between statin use and increased fatality at 90 days once data in the largest study were adjusted for age and stroke severity (adjusted OR, 1.14; 95% CI, 0.90-1.44; 4,012 patients). [33] *Level of evidence:2*

- A 2004 systematic review compared the effect of statins versus placebo on stroke and found that after a mean of 4.3 years, statin therapy significantly reduced the rate of stroke versus placebo or no treatment in >90,000 patients pooled in statin studies. The authors reported a 21% (OR, 0.79 [0.73 to 0.85]) relative risk reduction for stroke and no increase in hemorrhagic strokes (OR, 0.90 [0.65 to 1.22]). Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7-23.6) and carotid IMT by 0.73% per year (95% CI, 0.27-1.19). [34] *Level of evidence:2*
- A systematic review of eight studies on pharmacologic agents to lower cholesterol in about 10,000 people with a history of stroke showed that, of the cholesterol-lowering agents tested, only statins reduce subsequent risk for recurrent stroke (OR, 0.88; 95% CI, 0.77-1.00), but there was no effect (OR, 1.00; 95% CI, 0.83-1.20) on hemorrhagic stroke, mortality, or sudden death. Three statin trials showed a reduction in subsequent serious vascular events (OR, 0.74; 95% CI, 0.67-0.82). [35] *Level of evidence:2*

Patients with chronic kidney disease, dialysis, and kidney transplant who take statins have shown similar cholesterol reductions, but there is little or no effect on cardiovascular outcomes compared with the reduced outcomes found in the general population.

- A systematic review and meta-analysis investigated the effects of statins on major clinical outcomes. Thirty-one trials that include at least one mortality or major morbidity event were identified, providing data for 48,429 patients with chronic kidney disease, including 6,690 major cardiovascular events and 6,653 deaths. Statin therapy produced a 23% (95% CI, 16%-30%) RR reduction for major cardiovascular events ($P<.001$), an 18% (95% CI, 8%-27%) RR reduction for coronary events, and a 9% (95% CI, 1%-16%) reduction in cardiovascular or all-cause deaths, but no significant effect on stroke (21%; 95% CI, -12% to 44%) nor clear effect on kidney failure events (5%; 95% CI, -1% to 10%). [36] *Level of evidence:1*

- A systematic review on the efficacy and safety of statins in patients with end-stage renal disease on dialysis. Statins had little or no effect on major cardiovascular events (4 studies; 7,084 participants; RR, 0.95; 95% CI, 0.88-1.03), all-cause mortality (13 studies; 4,705 participants; RR, 0.96; 95% CI, 0.90-1.02), cardiovascular mortality (13 studies; 4,627 participants; RR, 0.94; 95% CI, 0.84-1.06), and myocardial infarction (3 studies; 4,047 participants; RR, 0.87; 95% CI, 0.71-1.07). [37] *Level of evidence:1*
- A systematic review of 14 RCTs comparing statins with placebo in 2,086 patients receiving hemodialysis, continuous ambulatory peritoneal dialysis, or both found that after 12 weeks of treatment, statins decreased cholesterol levels in dialysis patients with efficacy similar to that seen in the general population. In patients on hemodialysis and taking statins, nonfatal cardiovascular events were reduced, but cardiovascular and overall mortality were not decreased. [38] *Level of evidence:1*
- A systematic review of 16 studies compared the effect of statin versus placebo (15 studies) or statin versus statin (1 study) in 3,229 patients with renal impairment. Point estimates trended toward decreased cardiovascular mortality (13 studies; RR, 0.68; 95% CI, 0.46-1.03) and nonfatal cardiovascular events (1 study; RR, 0.70; 95% CI, 0.48-1.01) in patients who used statins. [39] *Level of evidence:1*
- A systematic review of 26 studies with more than 25,000 patients with chronic kidney disease but not requiring dialysis showed that statins decreased both the risk of all-cause mortality (21 RCTs; 18,781 patients; RR, 0.81; 95% CI, 0.74-0.89) and cardiovascular deaths (20 studies; 18,746 patients; RR, 0.80; 95% CI, 0.70-0.90). [40] *Level of evidence:1*
- The German Diabetes and Dialysis (4D) Study is an RCT comparing the effect from atorvastatin versus placebo in 1,255 patients with type 2 diabetes mellitus who were on maintenance hemodialysis. Atorvastatin treatment was not associated with a reduction in the relative risk of cardiovascular events or mortality irrespective of serum levels of C-reactive protein. [41] *Level of evidence:1*

- An RCT called AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects On Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events) evaluated the efficacy and safety of rosuvastatin 10 mg daily versus placebo in 2,776 patients, aged 50 to 80 years, who were undergoing maintenance hemodialysis. Rosuvastatin had no effect on individual components of the primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. There was also no significant effect on all-cause mortality (13.5 vs 14.0 events per 100 patient-years; hazard ratio, 0.96; 95% CI, 0.86-1.07; $P=.51$). [42] *Level of evidence:1*

Ezetimibe:

- An RCT compared ezetimibe versus placebo in patients with hypercholesterolemia over a period of 12 weeks. Ezetimibe significantly reduced direct LDL-C (mean reduction, 16.9%, compared with an increase of 0.4% with placebo; $P<.01$) compared with placebo in 892 patients with primary hypercholesterolemia. Ezetimibe effects on LDL cholesterol occurred early (2 weeks) and persisted throughout the 12-week treatment period. Compared with placebo, ezetimibe 10 mg also significantly improved levels of apoB, total cholesterol, triglycerides, HDL-C, and HDL₃cholesterol ($P<.01$). [43] *Level of evidence:2*
- A multicenter, 12-week, randomized, double-blind, parallel-group trial evaluated the efficacy and safety of various strengths of ezetimibe/simvastatin versus various strengths of atorvastatin in 1,289 patients with hypercholesterolemia aged 65 years or older with or without cardiovascular disease. Compared with atorvastatin, the ezetimibe/simvastatin group trended toward a significantly greater percentage decrease in LDL-C (-54.2% for ezetimibe/simvastatin 10/20 mg vs -39.5% for atorvastatin 10 mg and -46.6% for atorvastatin 20 mg; -59.1% for 10/40 mg vs -50.8% for atorvastatin 40 mg; $P<.001$ for all comparisons). [44] *Level of evidence:2*
- A multicenter, prospective, randomized, double-blind, placebo-controlled trial assessed the effect of ezetimibe versus placebo therapy on LDL-C levels in 108

patients with type 2 diabetes who had persistent albuminuria and elevated cholesterol levels despite long-term simvastatin use. After 2 months, adding ezetimibe to simvastatin therapy significantly decreased LDL-C levels and reduced total cholesterol and apoB levels; LDL-C levels were less than 70 mg/dL in only 17% of patients taking simvastatin plus placebo, compared with 72% of patients on simvastatin plus ezetimibe ($P<.0001$). [45] *Level of evidence:2*

- A multicenter, randomized, double-blind, active-controlled clinical trial in 1,437 hypercholesterolemic, high-risk patients compared multiple medical regimens with an intervening washout period. In all groups, ezetimibe plus atorvastatin was more effective at reducing LDL-C than higher-dose atorvastatin or rosuvastatin ($P<.001$). [46] *Level of evidence:2*
- An RCT in 769 patients with primary hypercholesterolemia who had not achieved adequate lipid reduction with dietary changes and statin monotherapy compared addition of ezetimibe with addition of placebo for 8 weeks. The group receiving ezetimibe had substantial reduction in LDL-C levels compared with the group receiving placebo. The combination of statin plus ezetimibe was well tolerated. [47] *Level of evidence:2*
- A RCT assessed the efficacy and safety of ezetimibe administered with simvastatin in patients with hypercholesterolemia, who were randomized to receive ezetimibe alone, simvastatin alone, ezetimibe plus simvastatin, or placebo for 12 weeks. Ezetimibe plus simvastatin versus simvastatin alone significantly reduced LDL-C levels and triglyceride levels and significantly increased HDL-C levels. The combination was well tolerated. [48] *Level of evidence:2*
- A double-blind RCT randomized participants with dyslipidemia to receive ezetimibe alone or with various dosages of atorvastatin compared with various doses of atorvastatin alone or placebo. After 12 weeks, ezetimibe plus atorvastatin significantly improved LDL-C, HDL-C, and triglyceride levels, total

cholesterol/HDL-C ratio, and high-sensitivity C-reactive protein level compared with atorvastatin alone. [49] *Level of evidence:2*

- An RCT compared ezetimibe 10 mg plus response-based atorvastatin titration versus response-based atorvastatin titration alone. Participants at high risk for coronary heart disease were started on a 6- to 10-week dietary stabilization and atorvastatin 10 mg/d open-label run-in period, and those with LDL-C levels >130 mg/dL at the end of this period were then randomized to receive ezetimibe 10 mg/d versus an additional 10 mg/d of atorvastatin. The atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal. The proportion of participants reaching their target LDL-C level (<100 mg/dL) was significantly higher in the group receiving combination therapy versus atorvastatin monotherapy. The addition of ezetimibe to the starting dose of 10 mg/d of atorvastatin provided a more effective means for reducing LDL-C than continued doubling of atorvastatin. [50] *Level of evidence:2*
- A meta-analysis of the lipid-modifying effect of ezetimibe looked at 14 randomized, double-blind clinical trials that compared the effectiveness of adding ezetimibe to simvastatin versus the use of rosuvastatin as monotherapy. The analysis used pooled data for LDL-C, HDL-C, total cholesterol, triglyceride, non-HDL-C, apoA-I, and apoB levels in patients treated with ezetimibe/simvastatin compared with rosuvastatin at all available doses. At comparable doses in the range tested, the combination of ezetimibe and simvastatin achieved slightly better reductions than rosuvastatin as monotherapy. [51] *Level of evidence:1*
- A double-blind randomized trial, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, compared the changes in carotid IMT in 720 patients with familial hypercholesterolemia treated with simvastatin alone or with ezetimibe. It examined carotid IMT as a marker for atherosclerosis regression during LDL-C lowering. After 2 years, there was no significant difference in carotid IMT between the two groups ($P=.29$), despite a significant difference in reduction of serum cholesterol levels

between the combined therapy and simvastatin groups ($P < .01$). [52] *Level of evidence:2*

Bile acid-binding resins:

- An RCT, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), evaluated the effect of lowering serum cholesterol using cholestyramine resin versus placebo on risk of CHD in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia. After more than 7 years, compared with the placebo group, the cholestyramine group experienced both a significant drop in average plasma total cholesterol and LDL-C and a 19% reduction in risk ($P < .05$) of definite CHD death or definite nonfatal myocardial infarction. The rates for new positive exercise tests, angina, and coronary bypass surgery were likewise reduced in the same group. In contrast, the risk of death from all causes in the cholestyramine group was not significantly reduced. [53] *Level of evidence:1*
- An RCT of 1,351 patients after coronary artery bypass graft compared aggressive reduction of LDL-C to <100 mg/dL with lovastatin (plus cholestyramine if required) versus a more moderate reduction to 132 to 136 mg/dL using the same drugs. Aggressive treatment significantly reduced the risk of need for repeat revascularization at 4 years. After another 3 years, aggressive cholesterol reduction significantly reduced the risk of revascularization and cardiovascular death compared with moderate reduction. [23] *Level of evidence:1*
- An analysis of three double-blind RCTs that compared intensive lipid therapy with placebos regarding effect on coronary stenosis progression (as determined by quantitative coronary angiography) and on major cardiovascular events combined the data of a total of 445 patients with coronary atherosclerosis and elevated apoB. The analysis showed that the combination of lovastatin with colestipol or niacin with colestipol significantly decreased coronary stenosis progression. [54] *Level of evidence:2*

The effect of fibrate therapy on lipid profiles:

- A meta-analysis of data from 53 trials (16,802 participants) using fibrates and 30 trials (4,749 participants) using niacin was completed; 53 RCTs using fibrates showed an 11% reduction in total cholesterol level, a 36% reduction in triglyceride level, an 8% reduction in LDL-C level, and an 11% increase in HDL-C level, with a 25% reduction in the risk for major coronary events. [55] *Level of evidence:1*
- A multicenter, double-blind, double-dummy, parallel-group study involved 248 patients on pravastatin who were randomly assigned to fenofibrate-pravastatin combination therapy versus pravastatin monotherapy. After 12 weeks, compared with pravastatin alone, the combination therapy group had a significantly greater decrease in non-HDL-C, HDL-C, LDL-C, triglyceride, and apoB levels. [56] *Level of evidence:2*
- A systematic review and meta-analysis considered 10 studies (n=16,869) evaluating the efficacy and safety of fibrate therapy in people with chronic kidney disease. In patients with mild-to-moderate chronic kidney disease, fibrates lowered total cholesterol levels ($P=.05$) and triglyceride levels ($P=.03$) and increased HDL-C levels ($P=.001$), but LDL-C levels were unchanged ($P=.83$). In the fibrate group there was a reduced risk of major cardiovascular events (RR, 0.70; 95% CI, 0.54-0.89; $P=.004$) and cardiovascular death (RR, 0.60; 95% CI, 0.38-0.96; $P=.03$) but not of all-cause mortality. In people with diabetes, fibrates reduced the risk of progression in albuminuria (RR, 0.86; 95% CI, 0.76-0.98; $P=.02$); serum creatinine was elevated and calculated glomerular filtration rate was reduced, but there was no change in progression to end-stage kidney disease (RR, 0.85; 95% CI, 0.49-1.49; $P=.575$). [57] *Level of evidence:1*

Fibrates for primary prevention of coronary heart disease:

- A systematic review and meta-analysis of 18 studies evaluated the effects of fibrates on major clinical outcomes in 45,058 participants, including 2,870 major

cardiovascular events, 4,552 coronary events, and 3,880 deaths. With fibrate therapy there was a barely significant reduction in major cardiovascular events ($P=.048$) and a trend in reduced coronary events ($P=.69$) but no significant effect on all-cause mortality, cardiovascular mortality, sudden death, or nonvascular mortality. Fibrates also reduced the progression of albuminuria by 14% (2-25; $P=.028$). [7] *Level of evidence:1*

- The Helsinki Heart Study was an RCT of 4,081 asymptomatic middle-aged men with primary dyslipidemia who were randomized to receive 600 mg of gemfibrozil twice daily versus placebo. After 5 years, the incidence of coronary heart disease events in the gemfibrozil group was reduced by 34% (95% CI, 8.2-52.6; $P<.02$; two-tailed test). [8] *Level of evidence:1*

Fibrates for secondary prevention of coronary heart disease:

- A systematic review of the literature from 1971 to 1999 assessed the available clinical trial data for dietary intervention and fibric acid derivatives for survival and cost effectiveness. Neither dietary interventions nor fibric acid therapy were felt to have significant evidence for benefit in primary or secondary prevention of coronary heart disease for either survival or cost effectiveness. [58] *Level of evidence:2*
- An RCT compared bezafibrate (n=42) with placebo (n=39) regarding the effect on progression of coronary artery disease in young men after acute myocardial infarction or stable angina. The cumulative coronary event rate was significantly lower among bezafibrate-treated patients than among placebo-treated patients (3vs11 patients; $P=.02$). [59] *Level of evidence: 3*
- An RCT of 3,090 young male patients after myocardial infarction, the Bezafibrate Infarction Prevention (BIP) study, examined the effect of bezafibrate on fatal or nonfatal myocardial infarction or sudden death. The frequency of the primary end point was 13.6% on bezafibrate versus 15.0% on placebo ($P=.26$). In a post hoc analysis, the subgroup with high baseline triglyceride levels (≥ 200 mg/dL) showed a

reduction in the cumulative probability of the primary end point by bezafibrate (39.5%; $P=.02$). [60] *Level of evidence: 1*

- An RCT compared fluvastatin plus placebo versus fluvastatin plus fenofibrate in people with type 2 diabetes, dyslipidemia, and a history of coronary heart disease. The fibrate-statin combination was found to significantly improve lipid levels versus statin therapy alone. [61] *Level of evidence: 2*

Fibrate use in people with diabetes improves triglyceride levels but may not have significant effect on risk for coronary events:

- The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, an RCT, compared incidence of cardiovascular events in patients on fenofibrate therapy versus placebo in 9,795 patients with type 2 diabetes who were not taking statin therapy at the time of enrollment in the clinical trial. Over an average of 5 years, relative to placebo, the fenofibrate group had a 24% reduction in nonfatal myocardial infarction (HR, 0.76; 95% CI, 0.62-0.94; $P=.010$), and total cardiovascular disease events were likewise significantly reduced from 13.9% to 12.5% (HR, 0.89; 95% CI, 0.80-0.99; $P=.035$), including a 21% reduction in coronary revascularization (HR, 0.79; 95% CI, 0.68-0.93; $P=.003$). There was a significantly decreased progression in albuminuria ($P=.002$) and fewer episodes of retinopathy-related laser treatment (5.2% vs 3.6%, $P=.0003$) in the fenofibrate group. [62] *Level of evidence: 1*
- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, an RCT, compared combination therapy with a statin plus a fibrate versus statin monotherapy in 5,518 patients with type 2 diabetes. There were no significant differences between the two study groups with respect to primary or any secondary outcome regarding cardiovascular risk. [63] *Level of evidence: 1*

Fibrates for stroke prevention:

- An RCT of men with coronary heart disease and low HDL-C compared gemfibrozil with placebo over approximately 5 years. Gemfibrozil increased HDL-C level and reduced triglyceride and total cholesterol levels. Gemfibrozil significantly reduced the incidence of coronary heart disease but did not significantly reduce the risk of stroke. [64] *Level of evidence:1*

Adding nicotinic acid to augment the lipid-modifying properties of other medication:

- An RCT, involving 3,414 patients pretreated with statin with or without ezetimibe to an LDL-C level between 40 and 80 mg/dL, evaluated the effect of two preparations of niacin (sustained release, 1,500-2,000 mg vs immediate release, 50-150 mg) on cardiovascular events. At 2 years, compared with pretreatment alone, the addition of niacin therapy resulted in increased HDL-C level (median from 35 to 42 mg/dL) and decreased triglyceride level (164 to 122 mg/dL) and LDL-C level (74-62 mg/dL), but there was no significant change in the incidence of cardiovascular events. [65] *Level of evidence:1*
- A prospective, randomized, open-label, blinded end-point study found that, in patients with mixed dyslipidemia whose conditions did not respond to standard-dose statins, treatment with high-intensity rosuvastatin 40 mg plus extended-release nicotinic acid with laropiprant resulted in improved lipid blood test results compared with rosuvastatin 40 mg plus fenofibrate. [66] *Level of evidence:2*
- A meta-analysis considered 4 studies (n=407) on the effect of niacin on serum glucose level, progression of coronary artery stenosis, and cardiovascular events. The use of niacin for 3 years was associated with an increase in serum glucose level and increased risk of developing impaired fasting glucose (but not diabetes mellitus). Use of niacin was associated with a significantly reduced incidence of coronary stenosis progression and major cardiovascular events. [67] *Level of evidence:2*
- An RCT evaluated the safety and efficacy of combination ezetimibe-simvastatin with and without extended-release niacin in 942 patients with type IIa/IIb dyslipidemia.

After about 15 months, the increased incidence of clinical adverse effects was largely attributed to niacin-associated flushing and pruritus. With respect to changes in blood lipid levels, the ezetimibe-simvastatin plus niacin group had significant increases of HDL-C levels and drops in triglyceride, non-HDL-C, LDL-C, and apoB levels (all values of $P \leq .004$). [68] *Level of evidence: 2*

- The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan trial (AVENT) compared nicotinic acid 1 g versus 1.5 g versus placebo in people with type 2 diabetes at high risk of macrovascular events. At 16 weeks, both doses of nicotinic acid significantly increased HDL-C levels versus placebo, whereas only the higher dose of 1.5 g resulted in a significant reduction in triglyceride levels. The higher dose also reduced levels of total cholesterol and LDL-C, but these results did not reach significance. [69] *Level of evidence: 2*
- A meta-analysis of 30 RCTs (n=4,749) on niacin use for dyslipidemia. Random-effects model showed 10% reduction in total cholesterol, 20% reduction in triglycerides, 14% reduction in low-density lipoprotein cholesterol, and 16% increase in HDL-C for niacin. Apart from flushes in the niacin group, both fibrates and niacin were shown to be well-tolerated and safe. [55] *Level of evidence: 2*
- A double-blind RCT of 160 patients with coronary disease, low HDL-C levels, and normal LDL-C levels randomized participants to receive one of four regimens: simvastatin plus niacin versus vitamins versus simvastatin-niacin plus antioxidants versus placebo. Compared with placebo, the average stenosis decreased 0.7% with simvastatin-niacin plus antioxidants ($P = .004$) and regressed by 0.4% with simvastatin-niacin alone ($P < .001$). The frequency of the cardiovascular clinical end point was 24% with placebo; 3% with simvastatin-niacin; 2% in the antioxidant-therapy group; and 14% in the simvastatin-niacin-plus-antioxidants group. [70] *Level of evidence: 2*

Use of nicotinic acid associated with reduction in atherosclerosis and cardiac events:

- A meta-analysis of 23 randomized lipid trials suggested that patients with vascular disease benefit comparably and additively from LDL-C reduction and HDL-C elevation. The statistically most effective LDL-C and HDL-C composite predictor of fractional in-treatment risk relative to placebo is 1 plus the fractional treatment-induced reduction of LDL-C level minus the fractional elevation of HDL-C level. [71] *Level of evidence:2*
- A combined analysis of three angiographic trials showed that patients with metabolic syndrome have significantly more rapid coronary stenosis progression and a higher frequency of clinical cardiovascular events. Greater stenosis progression rate is significantly associated with a higher rate of clinical events independent of patient risk factors and study therapy. LDL-C-lowering and HDL-C-raising therapies independently and significantly decrease coronary stenosis progression and reduce cardiovascular events. [54] *Level of evidence:2*
- An RCT studied the effect of once-daily extended-release niacin, added to background statin therapy, on the change in common carotid IMT. Participants with known coronary heart disease and low levels of HDL-C were included in the trial. After 12 months, the addition of extended-release niacin to statin therapy slowed the progression of atherosclerosis; the mean carotid IMT increased significantly in the placebo group but was unchanged in the niacin group. [72] *Level of evidence:2*
- The HDL and LDL Treatment Strategies (HALTS) in Atherosclerosis study, an RCT, compared the effect of extended-release niacin added to a statin with that of ezetimibe plus a statin on carotid IMT. Patients in the statin-niacin group showed a significant regression in carotid IMT. [73] *Level of evidence:2*
- An RCT (the Coronary Drug Project) comparing the effect of niacin versus placebo in patients with prior myocardial infarction showed that patients receiving niacin had a significantly lower rate of nonfatal myocardial infarction or stroke. [74] *Level of evidence:1*

Adverse effects of nicotinic acid:

- The Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial evaluated the efficacy of extended-release niacin/laropiprant versus placebo in 42,424 patients with preexisting atherosclerotic vascular disease who were all receiving simvastatin 40 mg daily (plus, if indicated, ezetimibe 10 mg daily). After a median of 3.9 years, 25% of participants allocated extended-release niacin and laropiprant versus 17% allocated placebo had discontinued study treatment owing to adverse effects. Compared with placebo, extended-release niacin and laropiprant plus statin increased the risk of definite myopathy (RR, 4.4; 95% CI, 2.6-7.5; $P < .0001$). There was no statistical difference in major cardiovascular events between the two groups. [75] *Level of evidence:1*

Omega-3 fatty acids:

- A randomized, multicenter, double-blind control study evaluated the efficacy of prescription omega-3-acid ethyl esters on lipid levels in 245 atorvastatin-treated patients with elevated non-HDL-C and triglyceride levels. After 16 weeks, compared with statin alone, the omega-3 plus statin group significantly reduced median non-HDL-C levels (50.4% vs 46.3%; $P < .001$) but not LDL-C, apoA-I, or apoB levels. [76] *Level of evidence:2*
- A systematic review comparing cholesterol-lowering therapies found that statins, but not other therapies, reduced coronary heart disease mortality and that statins and omega-3 fatty acids reduced all-cause mortality. [77] *Level of evidence:1*
- An RCT (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) compared fish oil supplementation (1 g of omega-3 polyunsaturated fatty acids daily) versus no fish oil in patients after a myocardial infarction. Fish oil reduced the likelihood of death within 3.5 years. [78] *Level of evidence:1*
- A systematic review including 48 RCTs and 41 cohort analyses compared omega-3 intake versus dietary advice. It found no clear evidence that dietary or supplemental

omega-3 fats alter total mortality, combined cardiovascular events, or cancers in patients with, or at high risk of, cardiovascular disease or in the general population.

[79] *Level of evidence:1*

- A systematic review including 23 RCTs (n=1,075) evaluated the use of fish oils (mean dose of polyunsaturated fatty acids, 3.5 g/d) versus placebo for 12 weeks in patients with type 2 diabetes. Triglyceride levels in the treated group were lowered by 0.45 mmol/L (95% CI, -0.58 to -0.32; $P < .00001$), VLDL-C levels were lowered by -0.07 mmol/L (95% CI, -0.13 to 0.00; $P = .04$), and LDL-C levels were raised by 0.11 mmol/L (95% CI, 0.00-0.22; $P = .05$), although the latter was nonsignificant in subgroup analysis. No significant changes in total or HDL cholesterol, hemoglobin A1c, fasting glucose, fasting insulin, or body weight were observed. [80] *Level of evidence:1*

Non-drug treatments

Dietary therapy:

- A systematic review and meta-analysis included 4 studies on low-glycemic-index diets' effects on lipid levels and found modest benefit. This meta-analysis suggests that a low-glycemic-index diet may help lower total cholesterol and LDL-C levels. [81] *Level of evidence:1*
- A systematic review of 11 RCTs assessed the effects of providing Mediterranean or Mediterranean-style dietary advice to 52,044 patients at increased risk of cardiovascular disease. In groups provided with dietary advice, there were small but significant reductions in total cholesterol levels (-0.16 mmol/L; 95% CI, -0.26 to -0.06; random-effects model) and LDL-C levels (-0.07 mmol/L; 95% CI, -0.13 to -0.01). However, heterogeneity precluded meta-analyses for primary prevention outcomes. [82] *Level of evidence:1*
- A systematic review considered 24 studies examining primary and secondary prevention of cardiovascular and cancer events and mortality related to dietary fat

intake. In men, specifically, after at least 2 years' duration, there were no clear effects of dietary fat changes on total mortality (RR, 0.98; 95% CI, 0.93-1.04; 71,790 participants) or cardiovascular mortality (RR, 0.94; 95% CI, 0.85-1.04; 65,978 participants), but specific reduction of saturated fat significantly reduced the risk of cardiovascular events by 14% (RR, 0.86; 95% CI, 0.77-0.96). [83] *Level of evidence:1*

- A systematic review of 44 RCTs involving 18,175 healthy adults compared physiologic changes after clinicians provided patients with general dietary advice versus no advice. Dietary advice resulted in increased fruit and vegetable intake, but only by 1.18 servings per day (95% CI, 0.65-1.71). Dietary fiber intake was likewise increased by 6.5 g/d (95% CI, 2.2-10.82), whereas total dietary fat as a percentage of total energy intake fell by 4.48% (95% CI, 2.47-6.48), and saturated fat intake fell by 2.39% (95% CI, 1.4-3.37). Dietary advice significantly reduced total serum cholesterol and LDL-C levels, but mean HDL-C and triglyceride levels were unchanged. Blood pressure was slightly but significantly reduced by 2.61 mm Hg systolic (95% CI, 1.31-3.91) and 1.45 mm Hg diastolic (95% CI, 0.68-2.22), and 24-hour urinary sodium excretion was reduced by 40.9 mmol (95% CI, 25.3-56.5). [84] *Level of evidence:1*
- In a randomized study, 83 HIV-positive patients on highly active antiretroviral therapy (HAART) were randomly assigned to dietary intervention versus no intervention. After 1 year, only 21% of the diet group had HAART-related dyslipidemia, compared with 68% of controls ($P < .001$). [85] *Level of evidence:2*
- Meta-analysis of 76,464 women in the Nurses' Health Study (1980-2010) and 42,498 men in the Health Professionals Follow-up Study (1986-2010) identified an inverse dose-related relationship between nut consumption and subsequent total and cause-specific mortality; the HRs were as follows: 0.93 (95% CI, 0.90-0.96) for consumption less than one 1.5-ounce serving per week; 0.89 (95% CI, 0.86-0.93) for 1 serving per week; 0.87 (95% CI, 0.83-0.90) for 2 to 4 servings per week; 0.85 (95% CI, 0.79-0.91) for 5 to 6 servings per week; and 0.80 (95% CI, 0.73-0.86) for >6 servings per week ($P < .001$ for trend). [86] *Level of evidence:2*

- A systematic review considered 78 RCTs involving 296,707 participants, most healthy, that evaluated the efficacy of oral antioxidants, alone or in combination with vitamins or other interventions as primary or secondary prevention for cardiovascular disease. Mean duration of treatment was 3 years (median duration, 2 years). Overall, there is no evidence supporting the use of antioxidant supplements as either primary or secondary prevention. However, in those trials with low risk of bias, the use of beta-carotene (RR, 1.05; 95% CI, 1.01-1.09) and vitamin E (RR, 1.03; 95% CI, 1.00-1.05) was associated with significantly increased mortality. In univariate meta-regression analysis, vitamin A was significantly associated with increased mortality (RR, 1.0006; 95% CI, 1.0002-1.001; $P=.002$). [87] *Level of evidence:1*

Garlic:

- A meta-analysis of 13 RCTs evaluated the efficacy of garlic to reduce total cholesterol in 796 patients. In the treatment group, the weighted mean difference was -15.7 mg/dL (95% CI, -25.6 to -5.7 mg/dL; $P<.01$). [88] *Level of evidence:2*

Dietary fiber:

- A randomized, double-blind, placebo-controlled crossover study evaluated the efficacy of plant sterol/psyllium cookie in modifying plasma lipid levels in 33 participants with LDL-C levels between 100 and 160 mg/dL. After 4 weeks, plasma total cholesterol level was significantly reduced ($P<.01$). These reductions were primarily in LDL-C ($P<.01$). [89] *Level of evidence: 3*
- A systematic review included one RCT, the Diet and Reinfarction Trial (DART), that compared the effects of dietary advice given to men younger than 70 years recovering from a myocardial infarction. All-cause or cardiac mortality was similar whether advice to increase fiber intake had been given or not. [90] *Level of evidence: 1*

Plant stanol esters:

- An RCT found that stanol esters reduced total cholesterol and LDL-C levels in a mildly hypercholesterolemic U.S. population. [91] *Level of evidence: 2*
- Another RCT found that 5.1 g/d of plant stanol esters reduced total cholesterol and LDL-C levels in participants on a stable regimen of a statin. [92] *Level of evidence: 2*

Soy protein:

- A systematic review found that soy protein was associated with modest reductions in serum cholesterol concentrations. [93] *Level of evidence: 3*
- A randomized, double-blind crossover trial was conducted in 51 women consuming isocaloric supplements containing 20 g of complex carbohydrates (comparison diet), 20 g of soy protein containing 34 mg of phytoestrogens given in a single dose, and 20 g of soy protein containing 34 mg of phytoestrogens split into two doses. After 5 weeks, there were significant declines in total cholesterol (6% lower) and LDL-C (7% lower) in both soy diets compared with the carbohydrate placebo diet. A significant decline in diastolic blood pressure (5 mm Hg lower) was also noted in the twice-daily soy diet, compared with the placebo diet. [94] *Level of evidence: 3*

Red yeast rice:

- An RCT involved 83 otherwise healthy middle-aged and elderly participants with any degree of dyslipidemia who were not being treated with lipid-lowering drugs and were treated with red yeast rice (2.4 g/d) versus placebo. All patients were instructed to follow a balanced diet. After 8 weeks, compared with placebo, the total cholesterol level in the treated group decreased significantly (254 ± 36 mg/dL to 208 ± 31 mg/dL; $P < .001$), but other lipid levels only trended downward. [95] *Level of evidence: 3*
- An RCT on 62 patients with dyslipidemia and a history of statin-related myalgias were assigned to either red yeast rice, 1,800 mg twice daily, or placebo. All patients were enrolled in a therapeutic lifestyle change program. After 24 weeks, compared

with placebo, LDL-C and total cholesterol levels were significantly lower ($P=.011$ and $P=.016$, respectively) in the red yeast rice group. Levels of HDL cholesterol, triglyceride, liver enzyme, or CPK; weight loss; and pain severity scores did not significantly differ between groups. [96] *Level of evidence:2*

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Guidelines

Diagnosis

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- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on

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- Grundy SM, Cleeman JI, Merz CN, et al; for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines . Circulation. 2004;110:227-39

The American Heart Association and the American College of Cardiology have issued the following scientific statement:

- Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines . Circulation. 2014;129:S49-73

The American Academy of Pediatrics has issued the following scientific guidelines:

- Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

Treatment

The National Heart, Lung and Blood Institute has produced the following guideline and subsequent amendment:

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The U.S. Department of Health and Human Services and the U.S. Department of Agriculture have produced the following guideline:

- Dietary Guidelines for Americans, 2010 . Washington, DC: U.S. Government Printing Office; 2010

The U.S. Department of Veterans Affairs and the U.S. Department of Defense , have jointly produced the following:

- VA/DoD Clinical Practice Guidelines: The Management of Dyslipidemia for Cardiovascular Risk Reduction . Washington, DC: Department of Veterans Affairs, Department of Defense; 2014

The Institute for Clinical Systems Improvement (ICSI) has issued the following guideline:

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The Canadian Medical Association has published the following:

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Screening and Prevention

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- Screening for Lipid Disorders in Adults . Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2008
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults : a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1-45

The U.S. Department of Veterans Affairs and the U.S. Department of Defense , have jointly produced the following:

- VA/DoD Clinical Practice Guidelines: The Management of Dyslipidemia for Cardiovascular Risk Reduction . Washington, DC: Department of Veterans Affairs, Department of Defense; 2014

The American Heart Association and the American College of Cardiology have issued the following scientific statements:

- Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines . *Circulation*. 2014;129:S49-73
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Codes

ICD-9 code

- 272 Disorders of lipid metabolism
- 272.0 Pure hypercholesterolemia
- 272.1 Pure hyperglyceridemia

- 272.2 Mixed hyperlipidemia
- 272.3 Hyperchylomicronemia
- 272.4 Other and unspecified hyperlipidemia

FAQ

(1.) If my patient presents with myocardial infarction or an acute coronary syndrome, when should I initiate statin therapy?

Trials indicate that statins started within 24 to 96 hours of hospital admission reduce recurrent ischemic events in the first 16 weeks and reduce mortality at 3 to 5 years. In short, the sooner the better. Statins should be considered a part of initial therapy in anyone presenting with acute myocardial infarction or acute coronary syndromes.

(2.) Should the age of my patient affect the course of statin therapy?

Even elderly patients have been shown to achieve significant short- and long-term benefits from therapy targeted to reduce serum LDL-C levels. Moreover, statin therapy is well-tolerated. Myalgias are more common in older patients, but the incidence of rhabdomyolysis is rare. In general, patient age should not be a significant factor in deciding whether, or how aggressively, to treat dyslipidemia, but given the risk differences and competing factors in elderly patients, high-dose statin therapy should be avoided and combination therapy should be selected carefully to minimize drug interaction.

(3.) What serum LDL-C target level should I aim for with lipid-lowering therapy?

Absolute answers await further studies, but all evidence suggests now that lower is better. Particularly in patients with known coronary artery disease or those at high risk for coronary artery disease, target levels of LDL-C <70 mg/dL appear to be efficacious and reasonable. In moderate-to-high-risk patients, levels below 100

mg/dL appear to be the best target. Even in low-risk patients, LDL-C <130 mg/dL may be a reasonable goal. The decision to use medicine to achieve particular LDL-C and non-HDL-C goals should be individualized to the patient needs.

(4.)Should children be screened and treated for hypercholesterolemia?

The American Academy of Pediatrics released expert guidelines on screening. Screening of the lipid profile is recommended for all children aged 8 to 10 years and in those as young as 2 years if they are at high risk for familial hypercholesterolemia.

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2013

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